2013 IACC Strategic Plan Update - Question 1 Draft – Volunteer drafters OARC and John Robison

"When should I be concerned?"

Introduction

The aspirational goal of the first Question is to identify children at risk for autism spectrum disorder (ASD) before behavioral symptoms of ASD fully manifest. When originally framed, Question 1 was directed toward identifying at-risk children by the age of 24 months to facilitate the greatest chance of successful early intervention. Scientific advances since then have shown that, in infants at high genetic risk for ASD due to having an older sibling with autism, symptoms of autism begin to emerge as young as 6 months of age in those who later develop ASD. These new findings suggest that it may someday be possible to screen for children at risk for ASD before the emergence of the full symptoms of autism and early enough to facilitate even more effective intervention. While recent findings have demonstrated this early screening potential in high-risk infant siblings, future challenges include determining whether the same potential for very early identification can be extended to other high risk populations (e.g. very low birthweight infants) and/or to the general population.

Many of the advances in the screening and diagnosis area have been in development and refinement of screening tests. Moving forward, more attention needs to focus on innovations in diagnostic tools. There also remains a great need for the development of efficient and cost effective screeners for use in children below 18 months of age, as well as more efficient methods of deploying developmental and ASD screening in community settings, including evaluation of effective parent-professional communication strategies for coping with concerns, referrals, follow-up evaluations for services and diagnosis, and linkage to appropriate services and supports. In addition, the development of culturally sensitive diagnostic tools that can be more easily used in both clinical and research settings is urgently needed. Finally, there has been a growing awareness of the need for better tools to diagnose adolescents and adults on the ASD spectrum and to provide meaningful assessments of functioning, which is an issue that is captured in an objective in Question 6 of the IACC Strategic Plan, but may involve adaptation of tools that are currently used to diagnose children.

Progress Toward the Strategic Plan Objectives

The 2011-2012 IACC ASD Research Portfolio Analysis reviewed projects funded by both government agencies and private foundations from 2008-2012. From 2008-2012, the total funding devoted to projects that address Question 1 was $186.771M, and if just the years since the publication of the first IACC Strategic Plan in 2009 are considered, the funding for Question 1 related projects was $157.65M. On average for each year from 2009-2012, the funding levels for this Question were 35% higher than the 2008 level ($29M) that preceded publication of the Strategic Plan. Also in years 2009-2012, 11% of the funding for this Question supported core/other research projects outside of the research gaps covered by the 9 objectives in Question 1.

Of the nine specific objectives under Question 1, four objectives addressing development of screening and diagnostic tools, identification of risk biomarkers and a workshop on ethical issues, met or exceeded the recommended budget and fulfilled the recommended number of projects. Three objectives, concerning determining the utility of genetic tests and developing measures of heterogeneity and symptom severity, partially met the recommended budget and had a number of projects underway. One objective, on understanding the reasons for disparities in screening and diagnosis, was far below the recommended budget and number of projects. The remaining objective, on studies to understand if early diagnosis leads to early intervention and better outcomes, did not have any dedicated funding or projects, though some aspects of this research topic are covered in projects that are categorized elsewhere, such as a project in Question 4 on early intervention (that was preceded by early diagnosis) that also partially addresses the issue of outcomes.

Progress in the Field

Over the past 5 years, good progress has been made toward developing tools and practices for more effective screening and diagnosis. New research suggests that existing screening tools, such as the Modified Checklist for Autism in Toddlers (M-CHAT with the follow-up interview, which is typically not utilized)[1] and the Infant-Toddler Checklist[2] can be effectively used by pediatricians and other community providers. The M-CHAT shows promise as a screen for communication and developmental delays, and as an ASD screen with the follow-up interview between 18 – 36 months of age, and the Infant-Toddler Checklist shows promise as a broadband screen for communication impairments that can identify children with autism between 12 and 24 months, and that has practical value as the basis of a 5-minute screen during the 1-year well-baby check-up[3]. New research suggests that with repeated screening at the ages of 6, 12, and 18 months, that it might be possible to identify as many as 95% of children with ASD by the age of 24 months. While this represents a remarkable scientific advance, validation and translation of this potential into reality in the general population and in community settings remains an enormous gap.

The clinical reality is that currently only about 20% of children with ASD are being identified early (by 3 years of age) [4]. Barriers to the broader deployment of advanced screening and diagnostic tools include cost and the expertise required to administer the tests. Also, repeat screenings at 6 month intervals beginning at 6 months of age are not being done in practice, despite demonstrated efficacy of such screenings in at-risk infants[5]. In addition, it appears that in practice, children who are identified in early screens are not always being referred for diagnosis and early intervention, even though there is now strong evidence to suggest the benefit of early intervention[6–8]. Thus, we need to better understand the barriers that are preventing caregivers from seeking a diagnostic evaluation after a child fails an autism screener and to identify strategies that will help caregivers navigate the pathway from screening to diagnosis to entry into early intervention. Until this gap between screening and intervention is closed, the potential impact of ASD screening on improving outcomes for individuals with ASD will not be realized.

More needs to be done to raise awareness in the practitioner community of the current capabilities and benefits of early, repeated screenings, early diagnosis and early intervention. Although not within the scope of a research plan, the severe lack of capacity of professionals to

both conduct screening and diagnosis and to provide services and supports remains a major stumbling block. Currently, in the U.S., over 1% of children are estimated to have an ASD and about 15% of children are identified with developmental disorders throughout childhood. Although not all developmental disorders are identifiable in the first three years of life, only 2.8% of infants and toddlers receive early intervention services, suggesting that many children who need early intervention services are not receiving them[9]. More complete data are needed to estimate the population and characteristics of children with ASD and other developmental delays that are likely to need early intervention services so that early identification leads to timely evaluation and access to services and supports.

Some progress has been made in understanding the prevalence of ASD in diverse communities, with recent results now suggesting that what initially appeared to be lower prevalence of ASD in some minority populations may instead be a reflection of how effectively ASDs are being diagnosed in those comunities[10,11]. There is still a gap, however, in understanding the reasons for disparities in access to screening, diagnosis, referral, and early intervention services. While this issue was targeted by the IACC in the 2009 Strategic Plan, much more work is needed to address this gap, and it should remain the subject of intense focus.

An area of groundbreaking research for Question 1 has been the detection of ASD risk in high risk infants (infant siblings) as young as 6 months of age. Among infant siblings, differences in both white-matter tracts and posture and have been observed in 6-month-olds who are later diagnosed with ASD[12,13]. Differences in the developmental trajectories of visual attention to social stimuli have also been identified as a marker of those infant siblings who later developed ASD. Eye tracking technology that gives children a choice between looking at moving geometric patterns or human faces was found to reliably distinguish children with ASD, who prefer to look at the geometric images, as young as 14 months[14], and a decline in a child's visual attention to the eyes of others during social interactions between when he/she is 2 to 6 months of age is another biomarker of infants who are later diagnosed with ASD[15a]. These exciting results suggest new potential screening tools based on eye tracking technology, like other existing tools, must now be validated in other high risk populations and the general population and, if proven efficacious, modified for broader use in order to be beneficial to the wider community.

At the molecular level, there has been significant progress in identifying genetic differences in ASD. Mutations associated with genetic risk for ASD can now be identified in about 30% of individuals diagnosed with ASD[16–23]. This increase in the capability to link genetic markers with ASD is substantially greater than 5 years ago, and further progress is anticipated. In order for these genetic markers to be useful from a screening perspective, they too will need to be validated in general populations. Such an advance could also help address the issue of adult diagnosis. It is noteworthy that the overwhelming majority of screening and diagnostic tools under research currently are being developed for and studied in infants and children, but there is a scarcity of tools that can be used effectively in adults. More effort needs to be focused on developing, adapting and validating screening and diagnostic tools for use across the lifespan.

Advances in capabilities to detect ASD early create a variety of legal, ethical, and social concerns, and the IACC Strategic Plan update of 2011 recommended that a workshop be held to address these issues. NIH, the Autistic Self Advocacy Network and Autism Speaks all held workshops that either directly or partially addressed this topic, fulfilling the original Strategic Plan objective. Still,

continued attention to this topic is warranted as the legal, ethical and social implications of ASD screening will continue to evolve in response to changing technologies.

In 2013, the Diagnostic and Statistical Manual of Mental Disorders (DSM) was revised, consolidating previous ASD diagnoses together into a single "autism spectrum disorder" category[24,25]. The new criteria in DSM-5 raised potential concerns in parts of the autism community that some people who would have previously met the criteria for diagnosis (and potentially benefitted from ASD-specific services), may no longer be diagnosed under the new criteria. Recent findings, however, on the whole suggest that this is not the case[26,27]. Moving forward, more research is needed to further assess the reliability and validity of DSM-5 ASD criteria, and to understand the impact of these new criteria on diagnosis, prevalence estimates and access to services. In addition, diagnostic instruments must be adapted to accommodate the new criteria.

Progress Toward the Aspirational Goal:
Children at Risk for ASD Will Be Identified Through Reliable Methods Before ASD Behavioral Characteristics Fully Manifest.

Within the past five years, tools and technologies have emerged that have the potential capability to detect children at risk for ASD before the full manifestation of behavioral symptoms, which is the aspirational goal of this Question. The challenges that remain are: to develop practical, cost effective tools that will be broadly accessible; validate and adapt these tools for use in a variety of diverse populations; support the development of the needed provider workforce; and deploy these tools so that this capability becomes a clinical reality across communities. Additionally, the link between screening and referral to intervention remains weak, but must be strengthened for the realization of the aspirational goal. Even when early screening takes place and at-risk children are identified in clinical and community settings, almost half the children are not progressing through the system to diagnosis and early intervention and face major roadblocks in the ultimate goal of accessing needed services and supports as early as possible. Future work should focus on identifying and removing the cultural and logistical impediments that may be preventing families and providers from following up on screening results that have identified a child with increased risk for ASD.

In the area of continued screening tool development, there is a need for increased investigation of risk factors in the 0-12 month age group. Currently there is no combination of genetic and behavioral markers in this age group that are reliable indicators of ASD risk. Also, the focus of the search for biomarkers has been on behavior and genetics, but this focus needs to be broadened to include a number of physiologic markers as well (e.g., sleep, autonomic measures, and neurological, metabolic, immune and gastrointestinal (GI) function measures). In addition, in the period prior to the development of language skills, biomarkers such as early motor tone, symmetry, and joint attention should be explored further. To improve accuracy of identification, emphasis should be placed on both direct observation and parent report.

In order to increase community usefulness of established tools, more investment is needed for community-based studies with larger sample sizes that will increase knowledge of disparities among various groups in access to screening and in applicability of screening tools. New technologies such as portable device applications (apps), Electronic Health Records (EHRs), and

video tasks will also be important for the development of innovative screening methods and screeners that could be used for diagnosis in children and adults. Finally, rigorous validation of existing tools is necessary so the community will know which ones are reliable in which populations.

True realization of the aspirational goal is dependent on progress on the other Questions of the Strategic Plan. While all the Questions are interrelated, the success of screening and diagnosis depends most heavily on the existence of effective interventions (Question 4) and services (Question 5) for all those identified, including those with mild or moderate levels of disability. In addition, while the aspirational goal of Question 1 focuses on early diagnosis in children, there is also a need to greatly strengthen efforts to develop and adapt diagnostic tools for use in adult populations, which is addressed in Question 6 of the Strategic Plan, in order to enhance the potential to reduce disability and improve quality of life across the lifespan.

References

1. Wright, K. & Poulin-Dubois, D. in *Comprehensive Guide to Autism* (Patel, V. B., Preedy, V. R. & Martin, C. R.) 2813–2833 (Springer New York, 2014). at <http://link.springer.com/10.1007/978-1-4614-4788-7_167>
2. Wetherby, A. M., Brosnan-Maddox, S., Peace, V. & Newton, L. Validation of the Infant--Toddler Checklist as a broadband screener for autism spectrum disorders from 9 to 24 months of age. *Autism* **12,** 487–511 (2008).
3. Pierce, K. *et al.* Detecting, studying, and treating autism early: the one-year well-baby check-up approach. *J. Pediatr.* **159,** 458–465.e1–6 (2011).
4. Autism and Developmental Disabilities Monitoring Network Surveillance Year 2008 Principal Investigators & Centers for Disease Control and Prevention. Prevalence of autism spectrum disorders--Autism and Developmental Disabilities Monitoring Network, 14 sites, United States, 2008. *MMWR Surveill Summ* **61,** 1–19 (2012).
5. Ozonoff, S. *et al.* A prospective study of the emergence of early behavioral signs of autism. *J Am Acad Child Adolesc Psychiatry* **49,** 256–266.e1–2 (2010).
6. Karanth, P. & Chandhok, T. S. Impact of early intervention on children with autism spectrum disorders as measured by inclusion and retention in mainstream schools. *Indian J Pediatr* **80,** 911–919 (2013).
7. Peters-Scheffer, N., Didden, R., Korzilius, H. & Sturmey, P. A meta-analytic study on the effectiveness of comprehensive ABA-based early intervention programs for children with Autism Spectrum Disorders. *Research in Autism Spectrum Disorders* **5,** 60–69 (2011).
8. Rogers, S. J. Empirically supported comprehensive treatments for young children with autism. *J Clin Child Psychol* **27,** 168–179 (1998).
9. Rosenberg, S. A., Robinson, C. C., Shaw, E. F. & Ellison, M. C. Part C Early Intervention for Infants and Toddlers: Percentage Eligible Versus Served. *PEDIATRICS* **131,** 38–46 (2012).
10. Mandell, D. S., Ittenbach, R. F., Levy, S. E. & Pinto-Martin, J. A. Disparities in Diagnoses Received Prior to a Diagnosis of Autism Spectrum Disorder. *Journal of Autism and Developmental Disorders* **37,** 1795–1802 (2006).
11. Begeer, S., Bouk, S. E., Boussaid, W., Terwogt, M. M. & Koot, H. M. Underdiagnosis and referral bias of autism in ethnic minorities. *J Autism Dev Disord* **39,** 142–148 (2009).
12. Wolff, J. J. *et al.* Differences in white matter fiber tract development present from 6 to 24 months in infants with autism. *Am J Psychiatry* **169,** 589–600 (2012).

13. Nickel, L. R., Thatcher, A. R., Keller, F., Wozniak, R. H. & Iverson, J. M. Posture Development in Infants at Heightened vs. Low Risk for Autism Spectrum Disorders. *Infancy* **18,** 639–661 (2013).
14. Pierce, K., Conant, D., Hazin, R., Stoner, R. & Desmond, J. Preference for Geometric Patterns Early in Life as a Risk Factor for Autism. *Archives of General Psychiatry* **68,** 101 (2011).
15. Jones, W. & Klin, A. Attention to eyes is present but in decline in 2–6-month-old infants later diagnosed with autism. *Nature* (2013). doi:10.1038/nature12715
16. Itsara, A. *et al.* De novo rates and selection of large copy number variation. *Genome Research* **20,** 1469–1481 (2010).
17. Sanders, S. J. *et al.* De novo mutations revealed by whole-exome sequencing are strongly associated with autism. 237–241 (2012).
18. Neale, B. M. *et al.* Patterns and rates of exonic de novo mutations in autism spectrum disorders. 242–245 (2012).
19. Iossifov, I. *et al.* De Novo Gene Disruptions in Children on the Autistic Spectrum. 285–299 (2012).
20. Lim, E. T. *et al.* Rare Complete Knockouts in Humans: Population Distribution and Significant Role in Autism Spectrum Disorders. 235–242 (2013).
21. Poultney, C. S. *et al.* Identification of Small Exonic CNV from Whole-Exome Sequence Data and Application to Autism Spectrum Disorder. 607–619 (2013).
22. Krumm, N. *et al.* Transmission Disequilibrium of Small CNVs in Simplex Autism. 595–606 (2013).
23. O'Roak, B. J. *et al.* Sporadic autism exomes reveal a highly interconnected protein network of de novo mutations. 246–250 (2012).
24. American Psychiatric Association, American Psychiatric Association & DSM-5 Task Force. *Diagnostic and statistical manual of mental disorders: DSM-5.* (American Psychiatric Association, 2013).
25. American Psychiatric Association. Query. at <http://iacc.hhs.gov/subcommittees/basic-translational-research/dsm-5/dsm5-diagnostic-criteria.shtml#autism-spectrum-disorder>
26. Huerta, M., Bishop, S. L., Duncan, A., Hus, V. & Lord, C. Application of DSM-5 criteria for autism spectrum disorder to three samples of children with DSM-IV diagnoses of pervasive developmental disorders. *Am J Psychiatry* **169,** 1056–1064 (2012).
27. Regier, D. A. *et al.* DSM-5 field trials in the United States and Canada, Part II: test-retest reliability of selected categorical diagnoses. *Am J Psychiatry* **170,** 59–70 (2013).