2013 IACC Strategic Plan Update - Question 7 Draft

What Other Infrastructure and Surveillance Needs Must Be Met? - Volunteer drafter – Alison Singer

Introduction:

The aspirational goal for Question 7 is to "develop and support infrastructure and surveillance systems that advance the speed, efficacy and dissemination of ASD research". The original *IACC Strategic Plan*, launched in 2009, was structured around only six Questions. In 2010, the IACC recognized that grouping the topics of research infrastructure and workforce, as well as ASD surveillance, into a separate chapter would highlight these issues that are critically important to research success and help the committee track investments and evaluate progress in this area in the same organized, rigorous manner that is used in the rest of the plan. Over the past 5 years, a total of $158M dollars has been invested in building and maintaining the ASD research infrastructure to support needed research and surveillance efforts. Many of the original infrastructure needs identified in 2009 have been accomplished, but continued investment is critical in order to develop, maintain, and build on these valuable new resources.

Progress Toward the Strategic Plan Objectives:

The *IACC ASD Research Portfolio Analyses* reviewed projects funded by both government agencies and private foundations from 2008-2012. From 2009-2012, the total funding devoted to projects pertaining to Question 7 was $158.03M. On average for each year from 2010-2012, the funding levels for this Question were doubled from the 2009 level ($15.8M) and the number of funded projects was also more than twice as high. Additionally, in years 2009-2012, 27% of the total funding went toward core research projects that were not aligned with the research gaps covered by the 16 objectives in Question 7.

Of the 16 specific objectives under Question 7, 8 objectives addressing basic and clinical data sharing and dissemination, workforce expansion, and model-systems resources met or exceeded the recommended budget and fulfilled the recommended number of projects. Four objectives, concerning documenting the services available in each state, expanding biobanks, and expanding surveillance infrastructure partially met the recommended budget and had a number of projects underway. Four more objectives did not have any funding or projects. Two of these objectives, focused on a needs assessment for database linkage and a funding mechanism for rapid replication of research results, remain high-priority. The objective concerning development of a web tool for prevalence estimates was fulfilled through several projects outside the autism portfolio, and the intent of the objective to disseminate best practices in service provision through "Promising Practices" papers was not completed, but may

have been superseded by other types of best practice dissemination methods, so the objective in its current form was not viewed by the committee as a high priority to continue.

Infrastructure:

Over the past five years there has been a significant rise in data sharing among researchers, increased availability of biological samples, expanded surveillance efforts, substantial investment in building the ASD research workforce and major improvement in dissemination of research results to the community.

Databases have been developed to house and provide researchers with access to valuable research data collected from those affected by autism as well as neurotypical subjects. In addition, in 2011 the NIH Office of Autism Research Coordination developed and launched a new database, the *IACC Portfolio Analysis Web Tool*, that gathers data on federal and non-profit supported ASD research-related projects together into one place, enabling broad public access to detailed information about these projects, as well as searching, sorting and graphics to facilitate further analysis and monitoring of progress over time.

The Interactive Autism Network (IAN), developed by the Kennedy Krieger Institute, is a tool designed to match scientists with research subjects to enhance the pace of research. The IAN network has also greatly facilitated rapid research on issues of symptom severity and intervention. For example, in 2011 when concerns about the impacts of autistic wandering behavior were brought to the IACC's attention, a study involving over 1,200 children was completed in only 3 months utilizing the IAN database; results of the study indicated that almost 50% of children with ASD had wandered[1]. (In conjunction with this rapid study, a new ICD-9 code to track wandering in conjunction with autism or other conditions in health records was almost immediately implemented and the American Academy of Pediatrics issued new guidelines that included wandering in patient-family anticipatory guidance, alerting parents of children with ASD to the prevalence of wandering so that they could take preventative measures[2].

The National Database for Autism Research (NDAR) funded by the NIH is a rich resource that includes genomic data and imaging studies as well as other types of data for use in ASD research. NDAR has become the standard data repository for the ASD research community. In January 2010, the NIH began including an expectation for data sharing in most of its awards, requiring that human subject data be deposited in a broadly accessible database. In 2012, 81% of NIH-funded human subjects grants were contributing data to NDAR. NDAR also supports data sharing from other funders of autism research including the Autism Science Foundation, the Centers for Disease Control, the Department of Defense, and the State of New Jersey. NDAR has also now linked to IAN and the Autism Speaks supported Autism Genetic Resource

Exchange (AGRE) and Autism Tissue Program (ATP), enabling researchers access to data in those repositories.

To date, NDAR has facilitated the sharing of data on 70,000 research subjects with much more expected in the next 24 months. Also, the rich "omics" (genomics, proteomics, transcriptomics, metabolomics, etc.) and imaging datasets have been de-identified and protected in the computational cloud, enabling an unprecedented array of resources, techniques and computational software to be used collaboratively by the research community. The results of such efforts along with categorization of data into common concepts like IQ, language and executive function enable users to query and pull down data from across multiple sources and disciplines, maximizing the utility of the data and driving scientific discovery. NDAR data have been cited in publications, and access requests have been substantial. Over 300 researchers at 75 laboratories from 10 countries have applied and been granted access to NDAR in 2013.

Aggregated data in NDAR, among its federated partners and the labs sharing data are available to the general public (see NDAR Query[3]). NDAR now supports harmonized receipt of all human subjects research data with clinical, imaging, genomics, proteomics, EEG, eye tracking, and task-based fMRI specifically supported. Table 1 provides a summary of the data now available in NDAR.

Number of Research Subjects Shared

	2009*	2013
Total	4,000	70,000
"Omics" Data (Genomes, proteomes, etc.)	3,200	18,500
Imaging Data	0	2,400

Table 1.* *Essentially all data being shared within the community in 2009 were contained in the Autism Speaks AGRE and ATP data repositories. By 2013, NDAR had dramatically expanded the data available in all categories.*

The NIMH Repository and Genomics Resource (NIMH-RGR) is another key resource that has played an important role in supporting research by providing access to biological samples from over 150,000 well characterized, high quality patient and control samples from a wide-range of mental disorders, including autism. The number of samples in the NIMH Genomics Repository has increased to more than 27,000, many with extensive phenotype/genotype information. The NIMH repository has also started collecting induced pluripotent stem cell (iPS) lines and fibroblasts. In terms of DNA, this represents a two-fold increase since 2008.

NIMH Genetics Repository Sample Summary (2008-2013)

Phenotypic category	# Subjects with DNA/LCL/CPL[1] samples	#Subjects with samples and phenotypic[2] data in distribution[3] (% non-caucasian[4])	# Total affected cases in distribution (independent cases[5])	#Multiplex families (Trios)	# Subjects with fibroblast lines (iPSC[6]) in distribution
Autism (2013)	28,288	15,676 (17%)	6,278 (4,222)	1,553 (3,387)	21 (25)
Autism (2012)	27,240	14,628 (17%)	5,938 (3,906)	1,530 (3,179)	0 (0)
Autism (2011)	25,890	9,822 (24%)	4,252 (2,479)	1,431 (1,860)	0 (0)
Autism (2010)	23,421	8,601 (20%)	3,842 (2,128)	1,386 (1,630)	0 (0)
Autism (2009)	19,824	6,434 (19%)	3,001 (1,598)	1,125 (1,209)	0 (0)
Autism (2008)	14,887	6,434 (19%)	3,001 (1,598)	1,125 (1,209)	0 (0)

Table 3. Summary of sample number and type for Autism specific samples included in the NIMH Genomics Repository. [1] LCL, Lymphoblastoid Cell Line; CPL, Cryopreserved Lymphoblasts [2] Phenotypic data includes clinical interviews, DIGS (Diagnostics Interview for Genetics Studies) & DSM variables. Samples include unaffected family members. [3] Distributions are NIMH sample collections with phenotypic data available for distribution to authorized investigators. [4] Non-Caucasians include Black, Hispanic, American Indian and Asian. [5] Subjects are unrelated. [6] Induced pluripotent stem cell lines produced by NIMH Genomics Repository Stem Cell facility.

In addition to genomics and cell line samples, brain tissue is another critically important resource needed to further autism research. Unfortunately, brain tissue samples have actually declined in number over the past five years due to a freezer malfunction in 2012 that resulted in the loss of more than half of the existing samples from the largest autism brain repository in the U.S. The brains lost have not yet been replaced in terms of numbers, and it may take several years to fully recover. In 2013, only 9 new ASD brains were added to existing repositories. Despite these challenges and setbacks, there is a concerted effort both publicly and privately to increase the number of brain tissue samples. In 2013, NIH launched a new NIH Neurobiobank initiative. This repository will collect and standardize brain tissue samples for research on ASD as well as other brain disorders. The initiative includes a publication to increase awareness of brain donation, "Why Brain Donation? A Legacy of Hope." In addition, a group of private funders including the Autism Science Foundation, the Simons Foundation, Autism Speaks, and the Nancy Lurie Marks Foundation recently launched the Autism BrainNet, a multi-site effort to increase the numbers of ASD-specific brain samples. Their efforts will also include an ASD-specific outreach and education plan to encourage tissue donation.

Surveillance:

Updated estimates published in 2012 from the Centers for Disease Control and Prevention's ASD and Developmental Disability Monitoring Network (ADDM) indicate that 1 in 88 children is identified with an ASD spectrum disorder, based on an average taken across multiple ADDM network study sites across the U.S. [4]. The ADDM network, which uses a methodology based on records review, has been the CDC's primary U.S. surveillance initiative, currently including 12 sites, and data are now available over multiple years, which enables researchers to examine prevalence trends as well as characteristics that are changing in the population and average age at diagnosis. The ADDM infrastructure has laid the foundation to expand surveillance to younger children in 6 ADDM sites. In addition, ADDM investigators have initiated data linkage and analytic projects to better understand characteristics of the population of children with identified ASD. These include evaluations of perinatal characteristics, parental age, medication use, participation in the juvenile justice system, hazardous air pollutant exposures, phenotypic characteristics, and changes in prevalence over time, among others. The ADDM Network has established a system to provide updated ASD prevalence estimates and has enabled a better understanding of the needs of the community. In addition to ADDM, the National Survey of Children's Health (NSCH), using telephone survey methodology, reported ASD prevalence estimates that were consistent with ADDM estimates[5] .The 2009-2010 National Survey of Children with Special Healthcare Needs infrastructure was used for the 2010 follow-up study on Pathways to Diagnosis to better understand identification of children with ASD[6]. A workshop

was held in 2011 to summarize the state of the science and needs in evaluating trends in ASD prevalence.

There are also private organizations, and groups outside the United States monitoring prevalence and service data. Autism Speaks has supported a population-based screening effort at an ADDM Network site to evaluate how many children with ASD are potentially being missed by current ascertainment methods. Autism Speaks has also initiated the Global Autism Public Health Initiative (GAPH) to support awareness and epidemiologic studies of ASD in sites around the world. There have also been efforts in the United Kingdom to examine the prevalence of ASD. A study in children using a comprehensive diagnostic assessment method found a prevalence of 1.16 in 100, and a study in adults using a population based survey and diagnostic assessment approach found a similar prevalence of .98 in 100.[7,8,9]. In South Korea, a population based study that used diagnostic assessments found a prevalence in children of 1 in 38, and that two-thirds of cases of ASD identified were unrecognized and untreated, highlighting a need for improved screening, diagnosis and services[10a].

There is increasing international focus on surveillance of prevalence and services. In 2012, the United Nations General Assembly unanimously passed a resolution calling on governments to monitor and report as well as improve access to healthcare, education, training, and intervention programs for persons with ASD and other developmental disabilities[10b-c]. In 2013, the executive board of the World Health Assembly adopted a complementary resolution, "Comprehensive and Coordinated Efforts for the Management of Autism Spectrum Disorders."[10c-d] These resolutions indicate growing commitment to address ASD on a global level.

Health disparities are another area of high interest within the field of surveillance. ADDM Network study results initially showed autism prevalence in some minority groups were lower than in in whites, but more recent data have begun to close the gaps with prevalence in minorities and whites becoming more similar, suggesting that the difference is not in actual prevalence but instead may reflect differences in diagnosis (e.g, later diagnosis, missed diagnosis, etc. in minority communities)[11,12,13,4]. More research is needed to understand the role of cultural issues, access to services and other issues in this phenomenon.

ASD is also being studied in immigrant populations to learn more about ASD in diverse populations. In 2013, results from a study of ASD prevalence among diverse populations of children in Minneapolis, Minnesota, collaboratively supported by CDC, NIH, Autism Speaks, and the Association of University Centers on Disabilities (AUCD), showed that while Somali children had a similar prevalence of autism to white children and a higher prevalence than in non-Somali black children or Hispanic children, that the prevalence of intellectual disability among children with ASD was much higher in Somalis[14]. Additional studies will be needed to understand the

reasons for these differences. A study by Swedish researchers investigated the relationship between parental immigration status and risk of ASD, taking into consideration the importance of region of origin, timing of immigration and autism subtypes[15]. They found that children of immigrant parents were at increased risk of low-functioning ASD, especially when parents' immigrated from countries with a low human development index, and that risk was higher when immigration occurred around pregnancy, but elucidation of the reasons for these differences will require further research.

Despite tracking of the age of diagnosis and other changes over time, the average age of diagnosis has remained relatively constant. This has been the case because as diagnostic criteria and community awareness improve, more cases are being identified when they were initially missed. As the prevalence of ASD has increased, a greater number of children have been identified with ASD — specifically those with ASD without intellectual disability and, as mentioned earlier, among racial and ethnic minority groups. Children without intellectual disability or with fewer ASD characteristics tend to be identified at later ages. Thus, while more children are being identified, much work needs to be done to identify children with ASD and other developmental delays earlier and more equitably so that all of those in need of services can be connected to appropriate services and supports as early as possible. Additionally, there is a need to increase awareness of adults on the autism spectrum and to include adults in future surveillance and prevalence monitoring. A future challenge to the accuracy of trends in prevalence may result from the implementation of DSM 5 clinical criteria. Because ADDM has collected detailed descriptions of the clinical findings for each child, the system is poised to evaluate how prevalence estimates may be influence by these updated criteria.

The surveillance infrastructure may present opportunities for more in depth data collection related to services, treatment, and co-occurring conditions to complement data currently collected and identify opportunities for improving diagnosis and treatment of children with ASD. A future challenge to the accuracy of trends in prevalence may result from the implementation of DSM 5 clinical criteria. Because ADDM has collected detailed descriptions of the clinical findings for each child, the system is poised to evaluate how prevalence estimates may be influence by these updated criteria.

Future efforts must focus on encouraging more families from diverse backgrounds to participate in ASD research, join registries, and donate biological samples. Also, as the ability to collect and link data grows, it is crucial to also pay greater attention to issues of privacy, security and ethical use of data.

Progress Towards the Aspirational Goal:

Progress towards the Question 7 aspirational goal to "develop and support infrastructure and surveillance systems that advance the speed, efficacy and dissemination of ASD research" has been rapid over the past 5 years. As demonstrated by the above tables, the numbers of shared subjects and samples have doubled at minimum, and in some cases increased by orders of magnitude. This increase in resources to study advances the speed and efficacy of ASD research. The sharing of these resources through initiatives such as NDAR, IAN, and AGRE demonstrate effective dissemination of resources, and fuel the cycle of increased research speed and efficacy. In terms of research infrastructure, the aspirational goal will be met as long as current support is continued and current momentum is maintained.

Surveillance systems have also progressed over the past 5 years, with tracking of the age of diagnosis and other changes over time. As awareness of ASD has grown in the community and diagnostic criteria have changed, more children have been identified with ASD, especially those without intellectual disability and among racial and ethnic minority groups. Children without intellectual disability or with fewer ASD characteristics tend to be identified at later ages. Thus, while more children are being identified, much work needs to be done to identify children with ASD and other developmental delays earlier and more equitably so that all of those in need of services can be connected to appropriate services and supports as early as possible. The surveillance infrastructure may present opportunities for more in depth data collection related to services, treatment, and co-occurring conditions to complement data currently collected and identify opportunities for improving diagnosis and treatment of children with ASD.

The progress towards meeting the goal of dissemination and communication of autism research findings has been significant. Many organizations and groups including Simons Foundation, Autism Speaks, Autism Science Foundation, Interactive Autism Network, NIH and the CDC regularly share lay-audience friendly summaries of recent research findings and new interventions to raise community awareness. Future efforts must focus on encouraging more families from diverse backgrounds to participate in ASD research, join registries, and donate biological samples. As the ability to collect and link data grows, it is crucial to also pay greater attention to issues of privacy, security and ethical use of data. The initial steps toward the aspirational goal of "developing and support infrastructure and surveillance systems that advance the speed, efficacy and dissemination of ASD research" have begun, but continued investment and broader outreach will be needed to ensure that the benefits of ASD research and access to the highest quality interventions, services and supports are attainable for all communities across the U.S. and around the globe.

References

1. Anderson, C. *et al.* Occurrence and family impact of elopement in children with autism spectrum disorders. *Pediatrics* **130,** 870–877 (2012).

2. American Academy of Pediatrics. *Autism: Caring for children with autism spectrum disorders*. **CD-ROM,** (2013).
3. National Database for Autism Research. Query. at <http://ndar.nih.gov/query_instructions.html>
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. *Morb. Mortal. Wkly. Rep. Surveill. Summ. Wash. DC 2002* **61,** 1–19 (2012).
5. Van Naarden Braun, K. *et al.* Evaluation of a methodology for a collaborative multiple source surveillance network for autism spectrum disorders--Autism and Developmental Disabilities Monitoring Network, 14 sites, United States, 2002. *Morb. Mortal. Wkly. Rep. Surveill. Summ. Wash. DC 2002* **56,** 29–40 (2007).
6. Schieve, L. A. *et al.* Parent-reported prevalence of autism spectrum disorders in US-born children: an assessment of changes within birth cohorts from the 2003 to the 2007 National Survey of Children's Health. *Matern. Child Health J.* **16 Suppl 1,** S151–157 (2012).
7. Baird, G. *et al.* Prevalence of disorders of the autism spectrum in a population cohort of children in South Thames: the Special Needs and Autism Project (SNAP). *Lancet* **368,** 210–215 (2006).
8. Brugha, T. S. *et al.* Epidemiology of autism spectrum disorders in adults in the community in England. *Arch. Gen. Psychiatry* **68,** 459–465 (2011).
9. Brugha, T. S. *et al.* Validating two survey methods for identifying cases of autism spectrum disorder among adults in the community. *Psychol. Med.* **42,** 647–656 (2012).

10a. Kim, Y. S. *et al.* Prevalence of autism spectrum disorders in a total population sample. *Am. J. Psychiatry* **168,** 904–912 (2011).

10b. http://www.autismspeaks.org/about-us/press-releases/un-passes-unanimous-resolution-expressing-deep-concern-over-long-term-challe

10c.Placeholder for link to text of UN Resolution

10d. http://www.autismspeaks.org/science/science-news/who-adopts-autism-resolution

10e.Placeholder for link to text of WHO resolution

11. Centers for Disease Control and Prevention. Prevalence of autism spectrum disorders—Autism and Developmental Disabilities Monitoring Network. *MMWR Surveill Summ* **58,** (2009).
12. Centers for Disease Control and Prevention. Prevalence of autism spectrum disorders—Autism and Developmental Disabilities Monitoring Network, Six Sites. *MMWR Surveill Summ* **56,** (2007).
13. Centers for Disease Control and Prevention. Prevalence of autism spectrum disorders—Autism and Developmental Disabilities Monitoring Network, 14 Sites. *MMWR Surveill Summ* **56,** (2002).
14. Hewitt, A. *et al.* Minneapolis Somali autism spectrum disorder prevalence project: Community report 2013. (2013).
15. Magnusson, C. *et al.* Migration and autism spectrum disorder: population-based study. *Br. J. Psychiatry J. Ment. Sci.* **201,** 109–115 (2012).