2012 INTERAGENCY AUTISM COORDINATING COMMITTEE STRATEGIC PLAN UPDATE: QUESTION 7 WHAT OTHER INFRASTRUCTURE AND SURVEILLANCE NEEDS MUST BE MET?

WHAT IS NEW IN THIS RESEARCH AREA, AND WHAT HAVE WE LEARNED IN THE PAST TWO YEARS?

Data Sharing

Most public and private funders of autism research have now made data sharing with the National Database for Autism Research (NDAR) an integral part of funding new research projects, which will in turn make future data available to other researchers. In addition, the Autism Genetic Research Exchange (AGRE), the Autism Tissue Program (ATP), and the Interactive Autism Network (IAN) are now linked with NDAR. Collectively, this means that 40,000 consenting de-identified research participants are available for secondary analysis by other scientific researchers. Data sharing requires a global universal identifier to track subjects in different studies, and to-date, more than 78,000 research participants have been registered with such an identifier. All data within NDAR is harmonized (e.g., uses the same names for each piece of data collected) and validated (e.g., reported values are consistent with other projects) to a community-established common data definition. At the NIH, 80% of newly awarded human subject grants related to autism have an expectation for data sharing[1]; by 2015, virtually all NIH-funded human subjects research is expected to include these terms.

Biobanking

The loss of more than 50 brains after a freezer malfunction in June 2012 was a tragic blow to the slowly developing ASD biobank effort, as nearly one third of the largest autism brain repository was destroyed in this accident. While this loss will lead to delays in research due to reduced access to samples, other programs have started to move forward with brain banking efforts. The Autism Tissue Program (ATP) has established a donor registry in which 5,976 individuals have registered to donate brain tissue and carry a card designating their wishes. In the last two years, the ATP has received 15 brains and 278 individuals have been added to the registry. In addition, Autism Speaks, the Simons Foundation, and several academic leaders in the field have developed a network model to bring together existing biobanks and to centralize and standardize brain banking efforts.

Brains that are donated to the ATP are analyzed and the data are made available through the ATP informatics portal, which now has 297 neuropathology reports on donor brains. These data are central to the Brain Atlas Project, which began 13 years ago to create a three-dimensional map of the human brain that integrates anatomic and gene expression data throughout the adult human brain. Brain repositories contributed 40 brain hemispheres to the original project, and an additional 53 hemispheres have now been processed. During the past 18 months, the final 10 brain hemispheres were analyzed.

[1] Training and Fellowship grants are excluded from this calculation in 2012, but will be included in 2013.

The NIH has created the NIH Neurobiobank, a federation linking the biobanks it supports and providing information about donation to the public, advocates, and researchers. A total of 4,082 subjects have now registered to donate brain and/or tissue samples to the biobank with 174 self-identified as having ASD (24 deceased and donated; 150 registered for future donation). Of these, 51 confirmed ASD cases are registered, and nine registrants are pending diagnostic confirmation.

Genetics

As noted in Question 2, whole genome and whole exome sequencing, in which an organism's entire genome or the entire coding portion of their DNA is sequenced at one time, have emerged as high throughput approaches to accelerate gene discovery. The existing infrastructure of stored DNA samples has enabled both the NIH-funded Autism Sequencing Consortium's exome sequencing efforts (with 7,600 DNA samples from unrelated ASD patients) as well as several whole genome sequencing initiatives, including the collaboration between Beijing Genomics Institute and Autism Speaks. Additionally, Autism Speaks, the Simons Foundation, and the NIH developed partnerships to increase the amount and diversity of genetic data available through AGRE and NDAR by co-funding the phenotype and DNA collection on several unique cohorts. Newly established cohorts for collecting DNA include those funded by Autism Speaks and the NIH, such as the Autism Speaks Autism Treatment Network (ATN) Biorepository, Early Autism Risk Longitudinal Investigation (EARLI) high risk infant cohort, and Infant Brain Imaging Study (IBIS) high risk infant cohort. These cohorts expect to have accrued an estimated 456,775, and 1,360 DNA samples respectively (by 2014 for the Biorepository and 2015 for the others). Additionally, Autism Speaks and the Simons Foundation jointly fund the Baby Siblings Research Consortium with an estimated 1,780 DNA samples expected by 2015.

Furthermore, AGRE expanded its Multiplex Family Collection more than 28% by making DNA available for an additional 383 families (including 653 probands, or individuals with ASD). The total DNA available from AGRE includes 1,736 families with a documented pedigree, or ancestry. The total number of probands is 3,348, while the number of fraternal twins is 204 and the number of identical twins is 118 in the AGRE collection. The NIMH-funded Center for Collaborative Genomics Studies on Mental Disorders (CCGSMD) at Rutgers University has increased the power to detect rarer genetic causes of autism. The CCGSMD currently distributes samples from almost 11,500 subjects from children with autism and their families.

Induced Pluripotent Stem Cells (iPSCs)

A major advance in ASD research has been the development of iPSC technology, including the proof-of-principle that iPSC lines can be derived from somatic cells of patients with syndromic forms of autism (i.e., fragile X, Rett and Timothy syndromes) (Kim et al., 2012). To-date, more than 50 fibroblast lines have been collected from people with ASD for iPSC derivation.

Clinical Trials

Two new networks have been established for clinical trials. First, the Network for Excellence in Neuroscience Clinical Trials (NeuroNEXT), was created to conduct treatments studies (Phase 2 or biomarker studies) through partnerships with academia, private foundations, and industry. The network is designed to expand the National Institute of Neurological Disorders and Stroke's

(NINDS) capability to test therapies, increase the efficiency of clinical trials before embarking on larger studies, and respond quickly as opportunities arise to test treatments. Second, the National Institute of Mental Health (NIMH) launched the Fast Fail Trials in Autism Spectrum Disorder (FAST-AS), a contract-based initiative which uses an experimental medicine paradigm to quickly test pharmacologic treatments and rule out ineffective ones, enabling more rapid identification of promising therapeutic approaches.

Autism Speaks convened two workgroups comprised of academic and industry leaders as well as representatives from Autism Speaks and the Simons Foundation to evaluate existing outcome measures and support the development of medicines to improve social communication, repetitive behaviors, and anxiety associated with autism. The workgroups met with the FDA to help develop consensus around appropriate outcome measures for autism clinical trials, and papers summarizing the outcome are in preparation.

A major effort, EU-AIMS— supported by the Innovative Medicines Initiative in Europe—was launched in 2012 and involves a 5-year $55 million effort to accelerate discovery and development of medicines for ASD.

Surveillance

Updated estimates from the Centers for Disease Control and Prevention's (CDC) Autism and Developmental Disabilities Monitoring (ADDM) Network—based on a cohort that were eight years old in 2008—confirmed that just over 1% of children (one in 88) in the U.S. are diagnosed with ASD (CDC, 2012). This figure ranged from 4.8 to 21.2 per 1,000 children across ADDM collection sites. Of particular concern is the average increase in ASD prevalence of 78% from 2002 to 2008 in multiple areas of the U.S. covered by the ADDM Network. While some of the increase was attributed to improved identification of particular subgroups, a true increase in the number of individuals affected is possible. In concert with recommendations from a workshop on factors contributing to the increasing ASD prevalence held by CDC and Autism Speaks in 2011 (CDC, 2011), several studies have highlighted the role of changes in identification (Keyes et al., 2012; Miller et al., 2012) as well as the limited role of some perinatal risk factors on changes in ASD prevalence (Schieve et al., 2011).

The CDC ADDM Network infrastructure has now been expanded to include six sites evaluating prevalence among younger children. Additionally, one site funded by Autism Speaks will include direct screening and evaluation to compare to records-based surveillance, which will provide the foundation for methods used in a project co-funded by CDC, Autism Speaks and NIH to determine the prevalence of ASD among Somali children in Minneapolis, Minnesota. Findings from the CDC and HRSA's National Survey of Children's Health (NSCH) led to the development of the Pathways to Diagnosis and Services Survey, a population-based study of the diagnostic and service experiences of children with autism (CDC, 2012).

Communication and Dissemination

Direct studies of family involvement in autism research shows participation still lags behind that for other diseases. Results from a 2005 national online survey reported that only 15% of adults

in the general population have had the opportunity to participate in a clinical research study (Gullo, 2005). Similar results were found in a 2007 market research survey on autism research attitudes and behavior, where only 14% of respondents reported having participated in an autism-related research study, though 90% reported that they would like to participate (Patchwork Consulting LLC, 2004). Unfortunately, 2012 data from IAN continues to corroborate that finding, reporting that only 16% of respondents say they have participated in autism research.(Reference?)

Research Workforce Development and Support

As the ASD research effort has expanded in recent years, so too has investment in the ASD research workforce. For instance, in 2011, the NIH supported 27 individual postdoctoral trainee awards (in addition to the large number of postdoctoral researchers funded through larger grants awarded to Principal Investigators), compared to 15 in 2010. Autism Speaks and the Autism Science Foundation have now also launched support for post-doctoral training, collectively supporting 16 new trainees each of the past two years (2011 and 2012). All of the Autism Science Foundation fellows and 73% of the Autism Speaks fellows reported that the award was their first autism research grant, and more than 90% of the fellows reported that they planned to stay in the field.

The American Recovery and Reinvestment Act (ARRA), enacted by Congress in February 2009, included funds that were awarded to autism research grantees during a two-year period from 2009 to 2010. Over the two-year time period, $123,916,638 or 22% of federal funds for autism research came from ARRA. Now that ARRA funding has ended, even with an unchanged NIH budget appropriation, autism research funding will experience a real decline.

WHAT GAPS HAVE EMERGED IN THE PAST TWO YEARS?

NDAR

The NDAR program has identified several areas critical data sharing issues that must be addressed as the field continues to move forward: (1) Timeliness – Researchers are currently expected to share data updates every six months and share full results at the time of publication. However, this process is frequently delayed, which is an issue that must be remedied. (2) Data Quality – While provisions have been made to include the cost to share data within a project's budget, further support is needed to ensure data are professionally maintained and shared throughout the life of a project. (3) Culture – Offering funding opportunities for secondary use of existing data is needed to demonstrate and improve the utility of the investment made in data sharing infrastructure. (4) Data Storage and Computational Approaches – Costs associated with the storage and processing of data may overwhelm existing infrastructure. Establishing the mechanisms for efficient data storage and use of available emerging computational pipelines is recommended.

Brain and Tissue Bank

The continued dearth of available brain tissue for research from donors with ASD and from those with co-occurring conditions and disorders, such as epilepsy, as well as unaffected 'control' tissue, continues to be one of the great challenges for research on the neurobiology of ASD, intensified by the 2012 freezer failure. Tissue donation recruitment programs would benefit from enlisting parent advisors who would be able to be sensitive to patient perspectives and responsive to expectations of this unique group of advocates who wish to support research in this most personal way.

Genetics

The scale and volume of data being generated (~1 terabyte/genome) could easily overwhelm even the most robust computational storage and analytic systems. There are three emerging major gaps that must be addressed: (1) Adequate facilities to store data. (2) The means to serve the dataset to the broader scientific community. (3) Cost-effective computational resources for the research community to easily access and analyze the dataset. None of these issues are unique to ASD research, and all are being addressed by the broad genomics community.

Infrastructure Support and Redundancies

The amount of tissue that has been collected and data that have been generated has increased in recent years. In order to ensure continued integrity of the tissue and data, both physical and virtual back up support methodology and systems must be built into the processes of collection and storage. Physical hardware and virtual software systems must be developed to protect and ensure the integrity and longevity of the samples.

Induced Pluripotent Stem Cells (iPSCs)

The development of iPSC technology has created both new research opportunities and new research needs. Among the needs is standardization of methodology and generation of a variety of fibroblast lines from patients with different diagnoses in order to understand the heterogeneity and natural history of ASD.

Clinical Trials

Support continues to be needed for trials to treat core symptoms of autism and co-occurring conditions such as sleep disturbances, as well as for comparative effectiveness trials. Difficulty in recruiting research participants restricts progress; therefore, access to large, well-characterized patient populations must be addressed, and a centralized registry for re-contact of patients for further research would assist in this endeavor. Collection of data with well-characterized populations should be systematic and standardized (tissue samples, blood, microarray data analysis, etc.). For trials to be successful there should be infrastructure for supporting small and large scale ASD trials throughout the process, from pre-clinical studies to clinical trials and data analysis.

Surveillance

Recent findings demonstrate the need for enhanced surveillance and monitoring of ASD prevalence among younger children and the incorporation of direct-screening and case confirmation components into the current ADDM methodology to analyze ASD prevalence estimates and improve understanding of the identified disparities. It is important to investigate the impact of changes to ASD diagnostic criteria in the fifth edition of Diagnostic and Statistical Manual of Mental Disorders (DSM-5). Continued support for international surveillance activities and epidemiologic research is important, enabling comparison of prevalence estimates and characteristics across countries. Further, surveillance among ethnic minorities and underserved populations will be critically important in understanding risk-factors and barriers to services in these groups.

Communication and Dissemination

At present, research productivity is often measured by the number of publications produced. However, there is a need to develop new measures that focus on valued outcomes such as improvement in quality of life. In order to boost participation in research studies, new outreach approaches to effectively disseminate information about the types of trials and research available for participation, and to encourage participation, must also be considered. Finally, information about the prevalence of autism and the methods used to collect prevalence data need to be expressed to the stakeholder community in clear, lay language in order to raise awareness and promote understanding of the meaning and limitations of the data.

Research Workforce Development and Support

Continued focus on developing the research workforce through investment in young investigators at levels of pre- and postdoctoral training is a high priority. Similarly, there is a need to focus on developing a funding mechanism to support early-career investigators, to bridge the gap between postdoctoral training and assistant professorship. Retention of investigators in active research and investment in vital ongoing autism research efforts will be affected by the loss of ARRA funding, a situation that needs to be monitored. The decline in federal spending post-ARRA has raised significant concerns about the sustainability of research progress and the possible loss of well-trained, productive autism researchers. Active efforts must be made to maintain and continue enhancing the research workforce needed to address the many research needs and challenges presented by ASD.

References:

Centers for Disease Control and Prevention (CDC); Autism and Developmental Disabilities Monitoring Network - Surveillance Year 2008 Principal Investigators. Prevalence of Autism Spectrum Disorders - Autism and Developmental Disabilities Monitoring Network, 14 Sites, United States, 2008. *MMWR Surveill Summ.* 2012 Mar; 61(3):1-19. [PMID: 22456193]

Centers for Disease Control and Prevention (CDC). Workshop on U.S. Data to Evaluate Changes in the Prevalence of Autism Spectrum Disorders (ASDs). 2011 February 1; Atlanta, Georgia. Available at: http://www.cdc.gov/NCBDDD/autism/documents/EvaluatingChanges_WorkshopSummary.pdf

Gullo K. New survey shows public perception of opportunities for participation in clinical trials has decreased slightly from last year. *Harris Interactive Health Care News*. 2005;5:6-1-14.

Kim KY, Jung YW, Sullivan GJ, Chung L, Park IH. Cellular reprogramming: a novel tool for investigating autism spectrum disorders. *Trends Mol Med*. 2012 Aug;18(8):463-71. [PMID: 22771169]

Keyes KM, Susser E, Cheslack-Postava K, Fountain C, Liu K, Bearman PS. Cohort effects explain the increase in autism diagnosis among children born from 1992 to 2003 in California. *Int J Epidemiol*. 2012 Apr;41(2):495-503. [PMID: 22253308]

Miller JS, Bilder D, Farley M, Coon H, Pinborough-Zimmerman J, Jenson W, Rice CE, Fombonne E, Pingree CB, Ritvo E, Ritvo RA, McMahon WM. Autism Spectrum Disorder Reclassified: A Second Look at the 1980s Utah/UCLA Autism Epidemiologic Study. *J Autism Dev Disord*. 2012 Jun 13. [Epub ahead of print] [PMID: 22696195]

Patchwork Consulting LLC. Market Research Analysis for Interactive Autism Network. 2007, 1, 56-57, Baltimore, MD.

Schieve LA, Rice C, Devine O, Maenner MJ, Lee LC, Fitzgerald R, Wingate MS, Schendel D, Pettygrove S, van Naarden Braun K, Durkin M. Have secular changes in perinatal risk factors contributed to the recent autism prevalence increase? Development and application of a mathematical assessment model. *Ann Epidemiol*. 2011 Dec;21(12):930-45. [PMID: 22000328]