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 18 MONTHS?

National Database for Autism Research (NDAR)

Most public and private funders of autism research have made data sharing within NDAR an integral component for funding. Autism Speaks' Autism Genetic Research Exchange (AGRE) and Autism Tissue Program (ATP), and the Interactive Autism Network (IAN) are now linked with NDAR. Collectively, 40,000 consenting de-identified research participants are available for secondary analysis.

Additionally, more than 78,000 research participants have been registered with such an identifier. All data is harmonized (e.g., uses the same variable names) 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 projects are expected to include these terms.

Biobanking

Domestic Brain and Tissue Banks - 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. Balancing this loss, the Autism Tissue Program (ATP) has added 15 brains and the NICHD repository has added 10 brains in the past 18 months. 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 18 months, 278 individuals have been added to this donor registry. The NIH has created the NIH Neurobiobank, a brain bank federation linking the banks it supports and providing information about brain and tissue donation for research to the public, advocates, and researchers including links to brain banks and their consent policies.

Comment [A1]: Discussion Point: A clear statement about how many brains are available should be added – this should be evident from ATP and University of Maryland.

Autism Speaks, the Simons Foundation, and several academic leaders in the field have been developing a network model to bring together existing brain banks, centralize, and standardize brain banking efforts. The network model is focused on enhanced outreach to promote brain donation and use of refined operating procedures for brain (and other tissues) acquisition, processing, and access.

Comment [A2]: Discussion Point: What is the relationship to the aforementioned Neurobiobank? Is there coordination?

Induced Pluripotent Stem Cells (iPSC) – Major advances in recent iPSC technology include 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), and these lines can be

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

differentiated into functioning neurons. While still early in the development of this approach, more than 50 fibroblast lines have been collected from people with ASD for iPSC derivation.

Comment [A3]: Discussion Point: Is this the correct number?

Comment [A4]: Discussion Point: If this number is so low, then we may consider moving it to an emerging gap area.

Genetics

As noted in Question 2, whole exome and genome sequencing have emerged as high throughput approaches to power discovery. The existing infrastructure of stored DNA samples have 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, Simons Foundation, and the NIH developed partnerships to increase the amount and diversity of genetic data available through the AGRE and NDAR by co-funding the phenotype and DNA collection on several unique cohorts.

Comment [A5]: Discussion Point: Should the table be kept or just a listing of the collections without the data?

Table X Cohorts of DNA Collection

Newly established cohorts for DNA collection			
Collection	Total amount of available DNA expected	Estimated timeline for availability	Funder
Autism Speaks Treatment Network Biorepository	456	2014	Autism Speaks and NIH
EARLI high risk infant cohort	775	2015	Autism Speaks and NIH
IBIS high risk infant cohort	1,360	2015	Autism Speaks and NIH
Baby Siblings Research Consortium	1,780	2015	Autism Speaks and Simons Foundation

Furthermore, AGRE expanded its Multiplex Family Collection more than 28% by making DNA available for an additional 383 pedigrees (653 probands).

TABLE XX: Newly available DNA on AGRE multiplex autism families

Total Number of Pedigreed Families	1,736
Total number of Probands	3,348
Total number of DZ Twins	204
Total number of MZ Twins	118

Comment [A6]: Discussion Point: Should this table be included? Should the data be presented differently?

As a result of its ongoing partnership with NDAR, all participants currently available through AGRE are also assigned GUIDs (globally unique identifiers) and federated through the NDAR portal.

The NIMH-funded Center for Collaborative Genomics Studies on Mental Disorders (CCGSMD) at Rutgers University currently distributes samples from almost 11,500 subjects.

Comment [A7]: Discussion Point: Is this the number of subjects with ASD?

Clinical Trials

Two new networks have been established for clinical trials. 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. The NIMH launched the Fast Fail Trials in Autism Spectrum Disorder (FAST-AS) to test treatments via an accelerated contract mechanism.

Autism Speaks convened two workgroups comprised of academic and industry leaders, and staff from Autism Speaks and the Simons Foundation to evaluate existing outcome measures and support medicines development for 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. Papers summarizing the outcome are in preparation.

A major effort, EU-AIMS (http://www.eu-aims.eu/), supported by the Innovative Medicines Initiative in Europe – was launched, involving 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 Autism and Developmental Disabilities Monitoring (ADDM) Network confirm just over 1% of children identified with an ASD (range: 4.8–21.2 per 1,000 children aged 8 years in 2008, with an average of 1 in 88) (CDC, 2012). Of great concern is the average increase in ASD prevalence of 78% from 2002 to 2008 in multiple areas of the United States covered by the ADDM Network (CDC, 2012). While some of the increase was attributed to improved identification of particular subgroups, a true increase in risk is possible (CDC, 2012).

The ADDM Network infrastructure has been expanded to include six sites evaluating prevalence among younger children, one site funded by Autism Speaks to include direct screening and evaluation to records-based surveillance, and to provide the foundation for methods used to determine the prevalence of Somali children in Minneapolis. Findings from the 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 participation by families in autism research shows it still lags behind other diseases. Results from a 2005 national online survey reported that only 15% of adults have ever 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 the IAN continues to corroborate that finding, reporting that only 16% of respondents say they have participated in autism research.

Several advocacy groups, such as Autism Speaks and the Autism Science Foundation, have projects and programs specifically targeted to improving research dissemination and enhancing communication between scientists and stakeholders.

Research Workforce Development and Support

The NIH, Autism Speaks and the Autism Science Foundation have launched post-doctoral training, collectively supporting 16 new trainees each of the past two years. 100% of the Autism Science Foundation fellows and 73% of the Autism Speaks fellows reported that the award was their first autism research grant. Over 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 over 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. The elimination of ARRA funding means that even with an unchanged NIH budget appropriation, autism research will experience a real decline.

WHAT GAPS HAVE EMERGED IN THE PAST 18 MONTHS?

NDAR

Timeliness –Researchers are expected to share data every 6 months and results at the time of publication, but there are cases where this has been delayed. *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. *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. *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 now recommended.

Brain and Tissue Bank

The continued lack of availability of brain tissue from donors with ASD and those with co-existing 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, made worse by the 2012 freezer failure. Programs would benefit from enlisting parent advisors 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: (1) facility to store data, (2) means to serve the dataset to the broader scientific

community, and (3) cost-effective computational resources for the research community to easily access and analyze the dataset. None of these is unique to ASD research and all are being addressed by the broad genomics community.

Clinical Trials

The support for trials to treat core symptoms of autism, associated co-occurring conditions (i.e., sleep), and comparative effectiveness trials are needed. Recruitment of patients 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). For trials to be successful there should be infrastructure for supporting small and large scale ASD trials from pre-clinical studies, to trial and analysis of data.

Surveillance

Recent findings demonstrate the need for enhanced surveillance 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 expected in the fifth edition of Diagnostic and Statistical Manual of Mental Disorders (DSM-5). Continued support of international surveillance activities and epidemiologic research is important to compare prevalence estimates and characteristics across countries. Further, surveillance among ethnic minorities and underserved populations afford opportunities to understand risk factors and barriers to services.

Communication and Dissemination

Productivity measures need to move beyond the publications accounting and should focus on valued outcomes. New ways to broadcast and communicate the types of trials and research available for participation must be considered. Communication about the prevalence of autism and the manner by which prevalence data are collected need to be expressed to the stakeholder community in clear, lay language.

Research Workforce Development and Support

Continued focus on developing the work force through investment in young investigators at levels of pre- and postdoctoral training is key. There is a need to focus on developing an early career award mechanism to bridge the gap between postdoctoral training and assistant professorship. Retention of investigators in active research and investment in ongoing vital autism research will be affected by the loss of ARRA funding. 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 scientists.

Word count: 2025

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