Question 7 Draft Updates for the IACC 2011 Strategic Plan

This document does not reflect decisions of the IACC and is for discussion purposes only

What other Infrastructure and Surveillance Needs Must be Met?

What is new in this research area and what have we learned this past year?

Data sharing

This year, the Autism Informatics Consortium (AIC) was formed with the goal of accelerating scientific discovery by making informatics tools and resources more useful to, and usable by, autism researchers. The consortium is charged with identifying information technology solutions, harmonizing major informatics frameworks, and developing standards in the field for working with research data. The consortium is comprised of representatives from both public and private institutions that are responsible for the development of major autism informatics tools and resources. Current members include Autism Speaks (Autism Genetic Resource Exchange), Kennedy Krieger Institute (Interactive Autism Network), Simons Foundation and Prometheus Research (Simons Foundation Autism Research Initiative), and the National Institutes of Health (National Database for Autism Research). The AIC held its first workshop on August 26-27, 2010 at the NIMH offices in Rockville, MD. In attendance were representatives from 12 major research institutions. The objective of the meeting was to explore short term (1-2 years) and intermediate term (2-5 years) priorities for increasing the utility and harmonization of major autism research informatics resources, identify ways to best pursue those priorities, and determine ways to measure progress toward achieving them.

Considerable progress has been made on the input of data to the National Database for Autism Research created by the NIH. Data are now available to researchers from over 10,000 participants enrolled in studies of ASD. Access to the data is through a NDAR supported web portal which supports queries from multiple databases simultaneously.

Biobanking

There has been considerable progress in the growth of a number of major biobank repositories:

The Autism Treatment Network (ATN), a program of Autism Speaks funded in part through grants from HRSA and NIMH, is a collaboration among 14 academic medical centers that provide clinical services for children with ASD and collect and store common, extensive phenotypic data on children with autism in a central patient registry. The NIMH is supporting ATN efforts to collect DNA, plasma, and urine from four of the 14 sites as a beginning step toward establishing a comprehensive biorepository for the ATN. One goal of establishing the repository is to provide a platform for conducting comparative effectiveness research that can utilize biomarkers to predict response to treatments.

Deleted: This year the ATN was funded by the National Institute of Mental Health

The Simons Simplex Collection, supported by the Simons Foundation Autism Research Initiative (SFARI), was established to develop a permanent research repository of detailed phenotypic and genetic information on 3000 simplex families with a child with an ASD. Nearly 2000 families have been enrolled as of November 2010 with the goal of completing enrollment by the summer of 2011. (Fischbach and Lord, 2010)

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The Autism Genome Project, a collaborative effort between Autism Speaks and a number of other organizations is focusing on identifying genes associated with the risk for ASD. The AGP consists of 120 scientists from more than 60 institutions representing 11 countries. The biobank now contains 23,101 total samples including 5,814 probands, which are individuals who are the first member within their family identified as having an ASD.

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The Autism Genetic Resource Exchange (AGRE) is a program of Autism Speaks to advance genetic research in autism spectrum disorders. Genetic biomaterials and clinical data are obtained from multiplex families (i.e., families with more than one member diagnosed with an ASD). The biological samples, along with the accompanying clinical data, are made available to AGRE-approved researchers. There are over 10,000 samples in the AGRE repository on individuals with ASD and their family members (including 4,240 probands). About half of the samples in AGRE are also represented in the AGP.

Through the Center for Collaborative Genetic Studies on Mental Disorders, the NIMH supports the NIMH Genetics Repository, a collection of DNA, cell culture lines, and clinical data from individuals with complex mental disorders, including ASD. From these materials, researchers can discover gene variants, epigenetic signals, and biomarkers that identify disease risk, aid in diagnosis, and predict response to treatments. Beginning in 2008 and continuing through 2013, the NIMH is sponsoring the Human Genetics Initiative to expand the number of samples in the NIMH Genetics Repository, and the current biobank collection consists of 589 trios (ASD-affected individual and both parents), 513 partial trios with biomaterials from one parent, and 972 independent cases. In addition, over 1,400 ASD samples are being processed and are expected to be available shortly. The Human Genetics Initiative works collaboratively with AGRE and offers access to much of the AGRE collection as well as samples from the NIMH Genetics Repository. In the coming years, NIMH will focus on increasing the number of samples, particularly from parents and first degree relatives, and linking the ASD-relevant data with the National Database for Autism Research.

The *Eunice Kennedy Shriver* National Institute on Child Health and Human Development (NICHD/NIH) supports the Brain and Tissue Bank for Developmental Disorders program, which collects, stores, and distributes brain and other tissues for biomedical research. The bank was expanded in 2009 and is currently funded through 2014. To date, researchers can request tissue samples donated by ~60 ASD individuals, as well as tissues from autism-related disorders like Fragile X (20 cases), Tuberous Sclerosis (33 cases), Neurofibromatosis (18 cases), and Rett Syndrome (10 cases). The use of this tissue has resulted in 77 scientific papers on autism and 42 papers on the other disorders. While efforts to recruit donors have had positive impact, there is still a great unmet need for ASD tissue collection and distribution across the ASD research community.

The Autism Tissue Program (ATP), a clinical program of Autism Speaks, is dedicated to supporting scientists worldwide in their efforts to understand autism, autism related disorders and the human brain. The ATP makes post-mortem brain tissue available to as many qualified scientists as possible to advance research on autism and other related neurological conditions. Towards that end, the ATP has acquired a total of 150 whole brain donations from individuals with autism, autism related disorders,

their relatives and controls while making all tissue and comprehensive phenotype data available to the research community.

Surveillance

One area which has progressed is the establishment of systems to identify and monitor the prevalence of ASDs in the US. The ADDM Network (CDC, 2009) and report from the National Survey of Children's Health (Kogan et al., 2009) reported ASD prevalence of around 1% of children. Of great concern was the average increase of 57% from 2002 to 2006 in 10 areas of the US covered by the ADDM Network (CDC, 2009) with 45% of the children ever having an autistic disorder diagnosis in 2002 and 47% in 2006. While some of the increase was attributed to improved identification of particular subgroups such as Hispanic children and children without cognitive impairment; a true increase in risk is also possible. (CDC, 2009) Several other recent studies have also indicated that multiple identification factors contribute to, but do not fully explain the rising ASD prevalence (Hertz-Picciotto and Delwiche, 2009; Saemundsen, 2010; King and Bearman, 2009; Rice et al., 2010; Van Meter et al., 2010; Mazumdar et al., 2010). Concerted efforts are now needed to evaluate the reasons behind these changes.

Information and Communication Dissemination

Of particular importance is the rapid translation of research findings as they apply to intervention and the dissemination to families and practitioners in the community in a way that is easy to access and understand. There have been several reviews of intervention quality and effectiveness (http://www.impaqint.com/files/4-content/1-6-publications/1-6-2-project-reports/finalasdreport.pdf) (Lang et al., 2010) and several states have formed task forces or councils for ASD and other DD services and have compiled service plans based on the current state of knowledge. http://www.aucd.org/template/event.cfm?event_id=2456&id=547&parent=547

Research Workforce Development

In 2009, NIH supported 60 trainees (graduate students and postdoctoral fellows) through individual NIH training and fellowship grants to study autism. These are in addition to a large number of trainees supported in by NIH in 2009 on over 200 traditionally-funded NIH research project grants focused on autism, as well as over 100 new autism-related research projects funded under the American Recovery and Reinvestment Act. Private research organizations such as Autism Speaks and the Autism Science Foundation also supported several research training awards in 2009 and 2010.

In addition, in 2010 NIH used ARRA funds to launch a new program called the Director's Pathfinder Award to Promote Diversity in the Scientific Workforce to support research on innovative strategies, programs and tools to increase diversity within the biomedical research workforce. NIH awarded six grants, totaling approximately $12 million, for research projects to develop approaches for improving the retention of graduate students, postdocs, and faculty from diverse backgrounds, including women faculty, underrepresented racial and ethnic groups, individuals from socially, culturally, economically, or educationally disadvantaged backgrounds, and individuals with disabilities, in the research workforce.

Comment [OARC1]: Please note this initiative is not specific to autism research or individuals with autism – it includes all types of underrepresented groups in all fields of biomedical research

Another area of research workforce growth in 2010 was the pharmaceutical industry, which has increased its investment in drug-related research for ASD. One large company has efforts specifically devoted to drug discovery for autism and other major pharmaceutical companies have active trials or are in the research planning phase. There are also some smaller biotech/pharmaceutical companies that have active trials (phase I-IV) in clinicaltrials.gov specifically for autism or fragile-x and autism.

Comment [OARC2]: Is this last paragraph on pharma more relevant to Chapter 7 or chapter 4?

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What gap areas have emerged since last year?

Data sharing

The AIC identified several short term and long term priorities for increasing the utility and harmonization of major autism research informatics resources, identifying ways to best pursue those priorities, and determining ways to measure progress toward achieving them. Examples of gap areas identified include the need for improved options for data federation, query interfaces and languages, genetic visualization tools, file and data set management, data quality and validation rules and algorithms, data dictionaries and ontologies, standardizing GUID usage. procedures for maintaining phenotype resources with associated biospecimens (imaging, genetics, etc) , defining a core (clinical) phenotype battery, working with publishers of copyrighted assessments, and addressing concerns about intellectual property.

During 2010, the Affordable Care Act was passed with an unprecedented call to transition record keeping to Electronic Health Records (EHRs). The development of EHRs provides an opportunity to consider the use of EHRs for data collection and analyses related to the service needs of people with ASDs. Of course, important privacy issues need to be considered and addressed before these types of data could be more routinely collected and utilized as part of EHRs.

Biobanking

In the absence of biological markers, current approaches for stratification of individuals with ASD into clinically meaningful subgroups have relied on behavioral characteristics. However, the variability of behavioral, medical, and developmental concerns that affect individuals with ASD has made it extremely difficult to predict which treatments work best for which individuals. The integration of biologic information into phenotype selection algorithms can help to guide the development and evaluation of more targeted and effective therapeutics and significantly improve the prediction of a therapeutic response. To this end, there is a need for the establishment of a robust network of clinical research sites offering clinical care in real-world settings that can collect and coordinate standardized and comprehensive diagnostic, biological (e.g. genotype), medical, and treatment history data that would provide a platform for conducting comparative effectiveness research and clinical trials of novel autism treatments. Currently, there is a need high-throughput screening tools to quickly evaluate gene-environment interactions relevant to ASD. Lack of progress in this area has made identification of potential exposures of interest difficult and driven by anecdotal evidence.

Surveillance

Moving forward, there is a need to maintain the sites so that early prevalence and population characteristics can be compared over time. A particular challenge is keeping consistency in the number of sites with four-year funding cycles and different numbers of sites funded based on availability of funds. In addition, completeness of data collection is hindered in some sites by the lack of access to educational records for surveillance purposes. Despite these challenges, the ADDM Network has maintained a core of approximately 12 sites with multiple prevalence years completed. There is now a need to go further to understand how multiple identification and potential risk factors have influenced

the increasing estimates of ASD prevalence. Further analyses of existing datasets are needed to examine any relationship between changes in ASD prevalence and changes in potential risk factors in the population. Surveillance cohorts also provide the opportunity for communities and policy makers to use these data for resource allocation in addition to characterizing population-based identification patterns and gaps. Surveillance data can also be used to better characterize the population of children identified with an ASD by select characteristics such as level of cognitive impairment, subtypes as diagnosed by community professionals, diagnostic features, associated conditions, degree of impairment by clinician rating. Expansion of surveillance efforts are to improve early identification and to understand functioning and outcome of individuals with an ASD as adults.

Communication and Information Dissemination

There have been several reviews of intervention quality and effectiveness and several states or agencies (Governor's councils, task forces, Department of Education, etc.) have developed plans for ASD and other DD services based on the current state of knowledge. This information and these plans should be easily accessible to other communities. Right now, there are many public and private resources which work to compile services and supports information; however, finding this information can be challenging.

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Focusing more on the issue of translating research into practice, the IACC Services Subcommittee Workshop on November 8, 2010 called for research that is meaningful to teachers and family members, and conducted in non-clinical settings to better simulate the settings in which children with ASD are being served. This will help to ensure that students with ASD receive high quality special education services.

The Agency for Health Research and Quality (AHRQ) has ongoing efforts to related to translation of research into practice. This work includes identifying sustainable and reproducible strategies (1) to help accelerate the impact of health services research on direct patient care and (2) to improve the outcomes, quality, effectiveness, efficiency, and/or cost effectiveness of care through partnerships between health care organizations and researchers. To further address the challenges around dissemination of research findings, AHRQ developed a "knowledge transfer framework" which encompasses three major stages—knowledge creation and distillation, diffusion and dissemination and end user adoption, implementation and institutionalization. While this work is not specific to autism, it may provide a useful framework to guide autism research translation efforts.

Research Workforce Development

Ongoing investment in developing research expertise and facilitating careers in autism research is needed, especially in the emerging areas of health services research, translational research, and international collaborative studies. In addition, continued efforts to enhance diversity in the research workforce are needed.

What new research opportunities and research objectives have emerged?

Revise Objective B: Conduct an annual "State of the States" assessment of existing state programs and supports for people and families living with ASD by 2011. *IACC Recommended Budget: $300,000 each year.* Revise Objective D: Establish and maintain an international network of biobanks for the collection of brain, fibroblasts for pluripotent stem cells, and other tissue or biological material, by acquisition sites that use standardized protocols for phenotyping, collection, and regulated distribution of limited samples by 2011. This includes support for post-processing of tissue such as genotyping, RNA expression profiling, and MRI. Protocols should be put into place to expand the capacities of ongoing large-scale children's studies to collect and store additional biomaterials, including newborn bloodspots, promoting detection of biological signatures. Support should also be provided to develop an international web-based digital brain atlas that would provide high resolution 3D images and quantitative anatomical data from tissue of patients with ASD and disease controls across the lifespan, which could serve as an online resource for quantitative morphological studies by 2014.

IACC Recommended Budget for establishing biobanks by 2011: $10,500,000 over 2 years. IACC Recommended Budget for maintaining biobanks: $22,200,000 over 5 years.

Research Resources

New Objective:

A. Establish a robust network of clinical research sites offering clinical care in real-world settings that can collect and coordinate standardized and comprehensive diagnostic, biological (e.g. DNA, plasma, fibroblasts, urine), medical, and treatment history data that would provide a platform for conducting comparative effectiveness research and clinical trials of novel autism treatments by 2012.

B. Create an information resource for ASD researchers (e.g. PHEN-X Project) to share information to facilitate data sharing and standardization of methods across projects. This includes common protocols, instruments, designs and other procedural documents and should include updates on new technology and links to information on how to acquire and utilize technology in development. This can serve as a bidirectional information reference, with autism research driving the development of new resources and technologies, including new model systems, screening tools, and analytic techniques by 2013.

C. Provide resources to centers or facilities which develop promising vertebrate and invertebrate model systems and make these models more easily available or expand the utility of current model systems, and support new approaches to develop high throughput screening technologies to evaluate the validity of model systems by 2013.

D. Create an information resource for ASD service providers, researchers, families, and people with an ASD which serves as a portal to obtain the most recent evidence-based reviews and plans for intervention, services, and support by 2012.

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Comment [c3]: Existing obj K

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Deleted: <#> programs and funding mechanisms that expand the research workforce, enhance interdisciplinary research training, and recruit early career scientists into the ASD field by 2013. *IACC Recommended Budget: $5,000,000 over 3 years.* ¶

Comment [c4]: How does NDAR and AIC fit into this?

Comment [c5]: Offered as a revision to Obj E

E. Conduct a meeting in 2011 that will establish standards for data collection on phenotyping and imaging protocols (other aspects??)

References

Centers for Disease Control and Prevention. Prevalence of autism spectrum disorders – Autism and Developmental Disabilities Monitoring Network, United States, 2006. MMWR 2009;58(SS10);1-20.
Kogan MD, et al. Prevalence of parent-reported diagnosis of autism spectrum disorder among children in the U.S., 2007. Pediatrics DOI: 10.1542/peds.2009-1522.

Lang R, Regester A, Lauderdale S, et al. Treatment of anxiety in autism spectrum disorders using cognitive behaviour therapy: A systematic review. Dev Neurorehabil.2010 Oct; 13(1):53-63.