1. WHEN SHOULD I BE CONCERNED?

- **What are the early signs of ASD?**
- **Are there typical characteristics that are part of an ASD diagnosis?**
- **How do variations in symptoms and severity create challenges in early diagnosis of ASD?**

What do we know?

A child's caregivers are often first to identify the signs of ASD. In the classic case, there may be delays or plateaus in a child's attainment of developmental milestones, such as the use of gestures, responding to name, or the onset of speech and pretend play. In other cases, the first signs of ASD occur in young children who appear to regress after they seem to have been developing normally. Current diagnostic criteria and classifications of ASD represent progress in identifying a core set of developmental symptoms that, in the past, might have been attributed to other disorders because of more narrowly defined ASD evaluation criteria.

The diagnosis of ASD can be reliably made by age three, because the core symptoms emerge by that time. However, most children eventually diagnosed with ASD exhibit signs of abnormal development well before the age of two. Recent studies of children at high risk because of the presence of a sibling with ASD suggest that many cases of autism can be detected by 12 months of age using simple behavioral tests, such as response to calling the child's name or ease of engaging the child in jointly looking at an object (Landa, Holman, & Garrett-Mayer, 2007). Nevertheless, the average age of diagnosis is 5 years (Wiggins, Baio, & Rice, 2006). A number of screening tools have been developed for detecting autism for children of varied ages and different levels of clinical variability. There are tools available for parents and caregivers, including a video glossary of early "red flags" of ASD in young children developed to help families and professionals learn how to identify subtle differences in development that may indicate areas of concern (Wetherby et al., 2007). In terms of diagnosis, there is emerging evidence that tools can be developed with sufficiently high sensitivity and specificity to support epidemiologic and risk factor studies.

Nationwide, there has been an effort to improve early identification of children with ASD to improve their functioning and outcomes. A recently published randomized, controlled trial demonstrated how a comprehensive developmental behavioral intervention for toddlers with ASD led to improvements in cognitive and adaptive behavior, thereby emphasizing the importance of early identification of and intervention for young children with ASD (Dawson et al., 2010). Various public campaigns, including the CDC's "Learn the Signs. Act Early," have been initiated in recent years to raise awareness about the importance of early identification of developmental delays, including those associated with ASD. The American Academy of Pediatrics (AAP) recommends screening children for ASD at 18 and 24 months with a standardized screening tool.

What do we need?

Most cases of autism and related disorders are not diagnosed until after a child's third birthday and sometimes not until adulthood, yet early intervention can have a critical influence on the future course of ASD. Moreover, many children from culturally, linguistically, and other diverse groups may have limited access to assessment services leading to delays in diagnosis (Mandell et al., 2009). Several issues have limited the use of early interventions. It remains difficult to diagnose ASD in very young children because there is considerable healthy variation in the age at which infants and toddlers reach typical developmental milestones (e.g., speech) and delays do not always indicate the presence of a disorder. The diagnosis of an ASD in a person of any age is currently based on behavioral and cognitive signs, reflecting abnormal brain development, but not on detection of brain or other biological differences that may be present before the emergence of the behavioral or cognitive signs. The discovery of reliable biomarkers could potentially identify people with ASD, or infants who will subsequently develop or are already developing subtle signs of ASD.

Children with ASD develop along different trajectories, some show abnormal behavior soon after birth, others develop normally for the first year or longer and then regress while others appear to later improve significantly. Greater clarity is needed in identifying these different trajectories and greater consistency is needed in applying their definitions. Healthcare and other early care and education providers may not have received training in recognizing the early warning signs of ASD. Pediatricians may not have received training on using existing screening tools at well check-ups as recommended by the American Academy of Pediatrics and some caregivers may be unaware of the early warning signs of ASD or where to access services, leading to delays in diagnosis.

Although families are eager for guidance, more research is needed to better answer the question of when developmental variation should become cause for concern. Studies that test both new and current diagnostic and screening methods and that integrate both developmental and biologic approaches in community-based settings are needed. In particular, studies need to be designed to validate methods in underrepresented minorities and disadvantaged populations. Such studies could increase the understanding of barriers to diagnosis and access to services. Taken together, earlier identification coupled with increased access to interventions and services could reduce disparities in health care and service provision, and ultimately improve outcomes for people with ASD.

Scientific studies of ASD require the reliable diagnosis of participants but this can be a time consuming and labor intensive process. Therefore, streamlined diagnostic approaches that facilitate the enrollment of research participants are needed. Researchers also need ASD measures that are easy to administer and are sensitive to changes in clinical status. With regard to heterogeneity, identifying characteristics that are specific to certain ASD subpopulations could potentially identify neurobiological and genetic markers and improve our understanding of more global causal and intervention mechanisms.

2011 Addendum to Question 1: When Should I Be Concerned?

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

The prevalence of autism continues to rise according to the most recent data gathered by the Autism and Developmental Disabilities (ADDM) Network, supported by the Centers for Disease Control and Prevention (CDC), indicating that nearly 1% of children in the U.S. have an ASD diagnosis. This reflects an increase of 57% over a four year period. Importantly, the mean age at diagnosis did not change significantly over this time period with most children not diagnosed until age 3 to 5 years. A second study from the large National Survey of Children's Health, sponsored by the Health Resources and Services Administration (HRSA), used very different study methods from those use in the ADDM project, but also reported a prevalence of ASD of approximately 1% of children (Kogan et al., 2009).

Research from three important studies over the past year has pointed to the importance of factors that place children at increased risk for ASD. Findings indicate the role of underlying genetic disorders and prenatal risk factors that when present, may warrant screening and early follow up and in some instances, more specific medical work up. First, an evidence-based review of a large clinical series of people with ASD and with other developmental disorders concluded that chromosomal microarray resulted in considerably higher diagnostic sensitivity for genetic testing than did G-banded karyotyping, particularly for submicroscopic deletions and duplications (Miller et al., 2010). Second, a study by Johnson et al., found that very preterm birth (<26 weeks gestational age) was associated with a much higher risk of developing ASD, with a prevalence of 8% diagnosed by age 11. While early gestational age has been identified as a risk factor for ASD, previous studies have lacked the power to examine children born at such vulnerable gestational ages. A third study of 7.9 million children in California showed that older fathers and mothers were more likely to have a child with autism as compared to younger parents (Grether et al., 2009). Evidence is also accumulating on the developmental trajectory for autism. A 2010 prospective study showed little deviation between children who eventually developed autism and typically developing children up to age 6 months, after which time measurable differences emerged (Ozonoff et al., 2010). Importantly, while a decrease in developmental trajectory of skills was found in the majority of children, it was not identified by most parents, suggesting current limitations in the use of parent-identified early markers of ASD in the first year of life. Also, Klin et al., found that as compared with typically developing toddlers, toddlers with ASD paid more attention to stimuli in which sound and motion were synchronous. This difference in sensory processing may be connected to the tendency for people with ASD to focus on the mouth over the eyes in conversation.

Two important studies highlighted work on the barriers to early screening and diagnosis. Evaluation of the implementation of the AAP recommendations for developmental surveillance was conducted in 17 diverse

pediatric practices and demonstrated reasonable success in implementing ongoing screening (85% of practices screened children at recommended screening ages), but that pediatric practices experienced challenges in referral for medical subspecialty care and early intervention (King et al., 2010b). A second study evaluated the diagnostic sensitivity of the various parent/care-giver autism Level 2 screening scales for children older than 3 years—beyond the AAP-recommended screening ages—and concluded that even in this older age group, while some tests performed well, overall, more scientific evidence is needed for these instruments (Norris & Lecavalier, 2010).

What gaps have emerged since last year?

Recent data show that girls are diagnosed with ASD at a later age than are boys (Giarelli et al., 2010; Shattuck et al., 2009). Examination of the *2009 IACC ASD Research Portfolio Analysis* shows that studies in girls and minority racial/ethnic/socioeconomically disadvantaged populations remains a gap area. While possible reasons for this disparity, including different clinical manifestations of ASD by gender and cultural differences in accepted or anticipated behaviors in girls relative to boys, are unclear, gender should be included as an important disparity factor in studies examining barriers to early screening and diagnosis.

There are important ethical, legal and social issues implications resulting from the study by Miller et al., particularly relating to screening for genetic and other markers for autism and other developmental disorders. There is a diverse range of opinions in the autism community on early screening for autism ranging from strong support for developing biologic prenatal screening methods to concerns that such efforts may lead to selected terminations of fetuses showing genetic or other biomarkers of increased risk. It is imperative that autism research proceed with the appropriate precautions and safeguards and that the concerns of the autism community are reflected in this process. At this point, the state of the science is focused on improving early screening in the first years of life to identify risk for ASD in order to initiate early intervention to reduce or prevent the development of disabling symptoms and promote positive skill development.

The study by King et al. highlights the need for a clearer understanding of the challenges and barriers to screening and referral. Studies are needed to determine the factors that lead to implementing screening and referral programs that successfully serve children with ASD and their families. Studies should include factors relating to the clinical practice, availability and collaboration among community-based services, and information needs of parents, other caregivers, and early educators.

There is a lack of reliable and valid screening and diagnostic tests for use in international, resource-poor settings. Early screening and diagnosis when coupled with inexpensive, parent-guided interventions is an important potential prevention strategy in such settings.

Research is needed to identify effective methods for identifying children at higher

risk for ASD, such as extremely preterm children and children with a sibling with ASD, in community screening efforts. Although the AAP recommends ongoing developmental and autism-specific screening in the first few years of life, establishing risk profiles indicating the need for heightened monitoring of development among some children warrants investigation as an additional tool to improve early identification.

***ASPIRATIONAL GOAL*: CHILDREN AT RISK FOR ASD WILL BE IDENTIFIED THROUGH RELIABLE METHODS BEFORE ASD BEHAVIORAL CHARACTERISTICS FULLY MANIFEST.**

Research Opportunities

- Valid and reliable ASD screening instruments and approaches, including general developmental screening instruments for use in community settings to identify a wide range of people, including younger children, adolescents, adults, people with co-occurring medical conditions, and people with subtle characteristics, who require diagnostic evaluation.
- Sensitive and efficient clinical diagnostic tools for diagnosing ASD in widely diverse populations, including underrepresented racial and ethnic groups, females, younger, older age groups, people with co-occurring medical conditions.
- ASD measures that are easy to administer and sensitive to incremental changes in both core and associated ASD characteristics. Such measures can be used to help track the clinical course of people with ASD, monitor responses to interventions, and provide information about the broader autism phenotype.
- Detailed criteria for specific ASD sub-types in order to better describe the variations in characteristics and severity and study how these variations relate to underlying pathology, intervention strategies, and outcomes.
- ASD subpopulations and associated biobehavioral markers that provide early indication of ASD risk and opportunities for appropriate early intervention.
- Protocols for genetic testing in routine clinical practice in order to identify people at risk for ASD. Identification of people with genetic variations associated with ASD will facilitate intensive studies of ASD subpopulations with shared genetic risk factors to characterize common phenotypic and biological features.
- Inclusion of ethical considerations into the diagnosis and screening processes, including consideration of the implications of genetic testing.
- Addressing barriers to the use of screening and diagnostic tools in minority populations and in community settings, including training programs for professionals.

Short-Term Objectives

2009

A. Develop, with existing tools, at least one efficient diagnostic instrument (e.g., briefer, less time intensive) that is valid in diverse populations for use in large-scale studies by 2011. *IACC Recommended Budget: $5,300,000 over 2 years.*

2009
Revised in 2011

B. Validate and improve the sensitivity and specificity of new or existing screening and diagnostic tools, including comparison of general developmental screening versus autism-specific screening tools, in both high risk and population-based samples through studies of the following community populations, including resource-poor international settings, that are diverse in terms of age, socio-economic status, race, ethnicity, gender, characteristics of ASD, and general level of functioning by 2012. *IACC Recommended Budget: $5,400,000 over 3 years.* **(no recommended budget change resulting from revisions to the objective in 2011) (Provided by NIH)**

2010
Revised in 2011

C. Conduct at least three studies to identify reasons for the health disparities in accessing early screening and diagnosis services, including identification of barriers to implementation of and access to screening, diagnosis, referral and early intervention services among diverse populations, as defined by socio-economic status, race, ethnicity, and gender of the child, by 2012. *IACC Recommended Budget: $2,000,000 over 2 years.* **(no recommended budget change resulting from revisions to the objective) (Provided by NIH)**

2010

D. Conduct at least two studies to understand the impact of early diagnosis on choice of intervention and outcomes by 2015. *IACC Recommended Budget: $6,000,000 over 5 years*.

2011

E. Conduct at least one study to determine the positive predictive value and clinical utility (e.g., prediction of co-occurring conditions, family planning) of chromosomal microarray genetic testing for detecting genetic diagnoses for ASD in a clinical setting, by 2012. **IACC Recommended Budget: $9,600,000 over 5 years. (Provided by NIH)**

2011

F. Convene a workshop to examine the ethical, legal, and social implications of ASD research by 2011. The workshop should define possible approaches for conducting future studies of ethical, legal, and social implications of ASD research, taking into consideration how these types of issues have been approached in related medical conditions. **IACC Recommended Budget $35,000 over 1 year. (Provided by NIH)**

Long-Term Objectives

2009
Revised in 2011

A. Identify behavioral and biological markers that separately, or in combination, accurately identify, before age 2, one or more subtypes of children at risk for developing ASD and evaluate whether these risk markers or profiles can improve early identification through heightened developmental monitoring and screening by 2014. *IACC Recommended Budget: $33,300,000 over 5 years.* **(no recommended budget change resulting from revisions to objective) (Provided by NIH)**

2009

B. Develop at least five measures of behavioral and/or biological heterogeneity in children or adults with ASD, beyond variation in intellectual disability, that clearly relate to etiology and risk, treatment response and/or outcome by 2015. *IACC Recommended Budget: $71,100,000 over 5 years.*

2009

C. Identify and develop measures to assess at least three "continuous dimensions" (i.e., social reciprocity, communication disorders, and repetitive/restrictive behaviors) of ASD symptoms and severity that can be used by practitioners and/or families to assess response to intervention for people with ASD across the lifespan by 2016. *IACC Recommended Budget: $18,500,000 over 5 years.*

2. HOW CAN I UNDERSTAND WHAT IS HAPPENING?

- **What is happening early in development?**
- **Are there known biological differences that help explain ASD symptoms?**
- **Can subgroups of people with ASD help us understand the etiology of ASD symptoms?**

What do we know?

Researchers, clinicians, and families have long posed questions about the possible biological bases of ASD. Clinicians classify ASD as a developmental brain disorder based on the behavioral features required for diagnosis. Little evidence exists, however, for a specific neurological abnormality beyond reports of an exuberant and transient pattern of brain or head growth (Akshoomoff, Pierce, & Courchesne, 2002; Dawson et al., 2007; Hazlett et al., 2005). While much of the current science suggests that the behavioral features of ASD result from atypical brain structure, wiring or connections, there is no proven neural variance associated with ASD. Nevertheless, there are some promising leads, and projects are underway that have the potential to provide biological signatures of some forms of ASD.

The development of sophisticated imaging methods has enabled researchers to accurately visualize many aspects of brain structure and functioning. For example, many children and adults with ASD perceive and analyze the visual information conveyed by facial expression differently than do other people (Spezio et al., 2007). Other researchers have employed magnetic resonance imaging (MRI) methods to investigate differences in brain anatomy between people with and without ASD, and have found differences in the density of white and gray matter, in some cases linked to specific symptoms of ASD (Craig et al., 2007).

Subsets of people with ASD have been reported to have experienced regression (i.e., the loss of previously acquired language, social, and developmental skills). The phenomenon is poorly understood and may co-occur with medical conditions common to people with ASD such as epilepsy. Recent studies have sought to understand the relationship between regressive symptoms, co-occurring disorders such as epilepsy, and the etiology of ASD.

Regression is not unique to people with ASD and the loss of language skills (acute language regression) can occur in people without the disorder. In one study, researchers found that children with acute language regression (who did not have ASD) were more likely to have associated seizures or epilepsy than were children with regressive autism (which includes language regression, as well as the loss of other social and developmental skills). This suggests that there are different subtypes of language regression and may help to understand the phenomenon and its relationship to ASD (McVicar, et al., 2005).

Currently, the frequency of language regression is unknown in either children with ASD or the general population. Previous studies of regression have been hampered by delayed referral for

evaluation after the onset of regressive symptoms (McVicar, et al., 2005).

A few hypotheses regarding how disruptions of the immune system might contribute to ASD and other neurodevelopmental disorders have emerged in recent years. Some recent findings suggest that the immune system differences of parents and their children may affect early brain development and the onset and fluctuation of symptoms in some children with ASD (Pardo, Vargas, & Zimmerman, 2005). For example, some research indicates that maternal autoantibodies directed at fetal brain tissue could interfere with normal brain development (Braunschweig et al., 2008). While such medical symptoms may not be entirely specific to ASD, treating may have significant impact on quality of life, symptom severity, and level of functioning.

Better understanding of the biology of genes linked to ASD and their functions can also provide insight. Recent studies have shown that the MeCP2 gene (mutations in which can cause Rett Syndrome) is involved in forming connections at the synapse. Genes regulated by the Fragile X syndrome gene, FMR1, also directly affect synapse function by controlling signaling of the neurotransmitter glutamate. In addition, a 2008 study found that the two genes that cause tuberous sclerosis complex (TSC) impair the formation of axons. Recently, several groups reported remarkable success with targeted therapies in animal models of these disorders showing the ability to reverse the underlying neuroanatomical and even behavioral deficits in the adult (Dolen et al., 2007; Ehninger et al., 2008; Guy et al., 2007). Understanding how MeCP2, TS1, FMR1, TSC1 and TS2TSC2 regulate the growth and function of neurons may help scientists understand related disorders like autism.

What do we need?

Exploring the biological basis of ASD requires access to biospecimens of people with and without ASD. Some progress has been made to establish the necessary infrastructure for the collection and preservation of post-mortem tissue from people with ASD. Nevertheless, the tissues currently available are insufficient for the needs of researchers. Educational campaigns, through contact with healthcare providers and the internet, may be useful to increase public awareness. New technology is expanding biological research beyond post-mortem tissue. For example, it is now possible to create pluripotent stem cells from skin fibroblasts of individual patients to create neuronal cell lines for study.

One of the greatest barriers to progress in determining the biological bases of ASD has been the heterogeneity of the spectrum. A clear need exists to advance understanding of the many phenotypes of ASD, including studies that link genotype to phenotype, investigations of natural and treated history, analyses of genetic interaction with environmental exposures, and studies of co-occurring behavioral and medical conditions. Different autism phenotypes may have different etiologies. There is a need to combine genotyping and functional analysis to better understand the contribution of specific genotypes with functional or structural subtypes. To determine the earliest discernable onset of ASD, experts have expressed the need for an intensive, multidisciplinary study

starting at early ages that examines biomedical, neurodevelopmental, and behavioral trajectories of children with ASD. A parallel multidisciplinary analysis of typically developing children and children with non-ASD developmental disorders would be especially enlightening, as limited normative information is currently available. An evaluation of differences in the interplay of biology and environmental exposures for children with and without ASD is also needed. Understanding early trajectories may lead to targeted interventions aimed at mitigating behavioral and medical challenges and improving outcomes through adulthood.

Another understudied arena of ASD research is gender differences. Many studies of autism preferentially enroll males, which, due to a 4:1 increased prevalence, are easier to recruit. Without additional information about the biological features of ASD in females, it remains unclear whether the course of ASD is similar and whether currently used interventions are appropriate for females. It is critical to determine how sex is related to etiology, protective factors, diagnosis, and trajectory. In addition, many studies of autism preferentially enroll higher functioning individuals who do not have cognitive impairment, because of their ability to cooperate and participate in study related tasks. However, these individuals represent only a subset of all individuals with autism and lessons learned from them may or may not be generalizable to all individuals with ASD. Priority must be made to develop studies looking at the underlying etiology of non verbal individuals and to understand the impact of and etiology of co-occurring language and cognitive impairment.

2011 Addendum to Question 2: How Can I Understand What Is Happening?

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

Over the past year, a group of notable studies advanced what is known about the underlying biology of ASD with respect to neuropathology, symptoms, and cellular metabolism/signaling. In recent years, researchers have noted abnormalities in brain growth, structure and connectivity in ASD, and numerous 2010 studies strengthen the idea that the brains of people with ASD develop and connect in atypical ways (Anderson et al., 2010; Groen et al, 2010; Lai et al., 2010., Qiu, et al, 2010; von dem Hagen, et al., 2010).

Researchers published results of the first longitudinal study of early brain growth in toddlers aged 1 ½ to 5 (Schumann et al., 2010). They found evidence of cerebral gray and white matter overgrowth in all regions by age 2.5. After correcting for age and gender, they found almost all brain regions developed at an abnormal rate in ASD and that this trend was more pronounced in girls. Other studies uncovered differences in the volume and structure of the brain's white matter, the component of the brain that carries signals from one region to another and allows communication between the two hemispheres (Kumar et al., 2010; Zikopoulos & Barbas, 2010). It was recently discovered that such structural abnormalities are found not only in children with ASD, but their unaffected siblings, as well (Barnea-Goraly,

Lotspeich, & Reiss, 2010). New advances in the use of magnetic resonance imaging (MRI) suggest that structural differences in the cortex of the brain could be used as a potential biomarker for ASD (Ecker, 2010).

Important research advances continue to improve the understanding of how changes in the brain might lead to unique characteristics of ASD. Researchers have recently found abnormalities in underlying neural circuits linked to characteristic traits such as atypical eye gaze and difficulties processing visual information, facial expressions, and biological motion (Akechi et al., 2010; Brieber et al., 2010; Dinstein et al., 2010; Dziobek et al., 2010; Kliemann et al., 2010; Koh, Milne, & Dobkins, 2010; Loth, Gomez, & Happe, 2010; New et al., 2010). A recent study of biological motion perception suggests that the distinct brain response in ASD may provide a neural endophenotype for the disorder (Kaiser et al., 2010a; Kaiser et al., 2010b). Another notable study is the first to identify a specific gene that can be associated with a neural endophenotype of ASD (Scott-van Zeeland et al., 2010). Using brain imaging, researchers found that variations in the known risk gene CNTNAP2 are associated with differences in functional connectivity in the frontal cortex and can predict performance on a rewards task.

In addition, the Committee has noted the importance of a consensus report about evaluation, diagnosis, and treatment of gastrointestinal disorders in children with ASD in the journal *Pediatrics* (Buie et al., 2010b). While the panel concluded that it was too early to make evidence-based recommendations, the consensus expert opinion was that people with ASD deserve the same thoroughness and standard of care in treating gastrointestinal symptoms as all patients, and that problem behaviors in ASD may stem from gastrointestinal problems. Of note, a study conducted in Minnesota found that children with ASD did not experience any greater frequency of gastrointestinal symptoms than the general population (Ibrahim et al., 2009). The Committee has also discussed reports of ASD symptoms diminishing during periods of fever and noted that this phenomenon, described in a 2009 review article (Mehler & Purpura, 2009) and discussed at a 2010 Simons Foundation conference (Simons Foundation, 2010) warrants further study.

Committee members have pointed to the new focus on metabolic and immune system interactions in ASD through studies of immune molecules, mitochondria, oxidative stress, and viral infections. In 2010, a team of researchers examined oxidative stress in Egyptian children with autism (Mostafa, et al., 2010). They found oxidative stress in close to 90% of these children and that this was related to an index of autoimmunity. They suggest that oxidative stress may play a role in autoimmunity, and that this represents a potential treatment target. In other notable work, a literature review suggests that extant energy metabolism deficits in ASD are not systematically related to specific genetic or genomic defects (Palmieri & Persico, 2010).

Researchers also examined gray matter from post-mortem brains of individuals with ASD and found increased levels of oxidized mitochondrial proteins in over half of subjects that was related to high calcium levels (Palmieri et al., 2010).

They concluded that interactions between the mitochondrial aspartate/glutamate carrier gene and altered calcium homeostasis may play a role in autism. In another 2010 study, researchers investigated activation in microglia, cells which offer the first line of immune defense in the central nervous system. Marked activation was observed in five of the 13 people with ASD included in the study; researchers are continuing to study how neuroimmune abnormalities may be associated with ASD (Morgan et al., 2010). There is also evidence that autoimmune factors may play a role. A study of 690,000 Danish children found that those with ASD were significantly more likely to have families with a history of rheumatoid arthritis, type 1 diabetes, or celiac disease (Atladottir et al., 2009).

Another notable study in 2010 explored how vertical viral transmission, or the transmission of a virus from mother to child just before or after birth, may play a role in the development of ASD (Lintas et al., 2010), and a study of urinary porphyrin excretion found elevated levels in children with ASD when compared to their typically developing peers, indicating a potentially unusual pattern of metabolism (Woods et al, 2010). In addition, recent progress has been made in the development of mouse models of autism (Silverman et al., 2010, Hamilton et al., 2011). These studies and others highlight the importance of continuing to investigate multiple potential pathways and develop improved model systems to better understand the complexity of ASD.

What gap areas have emerged since last year?

The Committee highlighted the newly emerging area of metabolomics, which in well controlled studies may provide a way to examine genotype-phenotype relationships. The Committee also noted the importance of staying abreast of research from other fields that may be helpful in identifying "endophenotypes" in autism. Endophenotypes are partial/constituent phenotypes that may be more highly linked to specific genetic causes which may not be appreciated in studies which combine all symptom profiles. Endophenotypes may aggregate in families and be amenable to deep sequencing genetic studies to identify genetic underpinnings. They also can be common to multiple neurodevelopmental disorders and offer leverage for understanding similarities and differences between different forms of developmental psychopathology.

Public comment received by the Committee in the last year points to the need for continued study of regressive autism and females with ASD. In addition, new concerns were raised about the relationship between ASD and epilepsy, liver issues, and other diseases. The relationship between inflammation in expectant mothers and ASD, as well as the association of ASD with apraxia of speech were also identified as potential issues for further examination.

Several "implementation" related issues were raised by the Committee. These include the need to add rapidly emerging findings related to cell metabolism, signaling, neuroimaging, genetics, epigenetics, and co-existing medical conditions into existing databases designed to phenotype the "autisms." Finally, the committee emphasized the urgent need to accelerate translation of research findings to clinical practice.

What Progress is Being Made in Fulfilling Objectives?

As exemplified by the progress in the literature and funding as documented by the *2009 IACC ASD Research Portfolio Analysis*, autism research is proceeding at a brisk pace. There are many promising studies of the neural correlates of autism-related symptoms that have yet to be classified.

***ASPIRATIONAL GOAL*: DISCOVER HOW ASD AFFECTS DEVELOPMENT WHICH WILL LEAD TO TARGETED AND PERSONALIZED INTERVENTIONS.**

Research Opportunities

- Multi-disciplinary, longitudinal, biobehavioral studies of children, youths, and adults beginning during infancy that characterize neurodevelopmental and medical developmental trajectories across the multiple axes of ASD phenotype and identify ASD risk factors, subgroups, co-occurring symptoms, and potential biological targets for intervention. Such studies could include:
    - High-risk siblings of children, youths, and adults with ASD, children without a family history of ASD, and typically developing children.
    - Multi-disciplinary assessments of brain imaging, metabolic and immunity markers, microbiomics, metabolomics, electrophysiology, and behavior. *(Revised 2011)*
- Research on females with ASD to better characterize clinical, biological and protective features.
- Human and animal studies that examine immune, infectious and environmental factors in the occurrence of ASD.
- Research on the unique strengths and abilities of people with ASD with evaluation of functional and biological mechanisms behind social, linguistic, and cognitive profiles.
- Research on individuals with ASD who are nonverbal and /or cognitively impaired
- Research targeting the underlying biology of co-occurring syndromes and co-occurring conditions.
- Prospective research on children with autistic regression, including potential underlying genetic and other risk factors including seizures and epilepsy. *(Revised 2011)*

Short-Term Objectives

A. (Revised 2011) Support at least four research projects to identify mechanisms of fever, metabolic and/or immune system interactions with the central nervous system that may influence ASD during prenatal-postnatal life by 2010. *IACC Recommended Budget: $9,800,000 over 4 years. (Fever studies to be started by 2012.)* **(no recommended budget change resulting from revisions to objective) (Provided by NIH)**

B. Launch three studies that specifically focus on the neurodevelopment of females with ASD, spanning basic to clinical research on sex differences by 2011. *IACC Recommended Budget: $8,900,000 over 5 years.*

C. Identify ways to increase awareness among the autism spectrum community of the potential value of brain and tissue donation to further basic research by 2011. *IACC Recommended Budget: $1,400,000 over 2 years.*

D. (2010) Launch three studies that target improved understanding of the underlying biological pathways of genetic conditions related to autism (e.g. Fragile X, Rett syndrome, tuberous sclerosis complex) and how these conditions inform risk assessment and individualized intervention by 2012. *IACC Recommended Budget: $9,000,000 over 5 years.*

E. (2010 – revised in 2011) Launch three studies that target the underlying biological mechanisms of co-occurring conditions with autism including seizures/epilepsy, sleep disorders, wandering/elopement behavior, and familial autoimmune disorders by 2012. *IACC Recommended Budget: $9,000,000 over 5 years.* **(no recommended budget change resulting from revisions to objective) (Provided by NIH)**

F. (2010) Launch two studies that focus on prospective characterization of children with reported regression, to investigate potential risk factors by 2012. *IACC Recommended Budget: $4,500,000 over 5 years.*

G. (2010) Support five studies that associate specific genotypes with functional or structural phenotypes, including behavioral and medical phenotypes (e.g., nonverbal individuals with ASD and those with cognitive impairments) by 2015. *IACC Recommended Budget: $22,600,000 over 5 years.*

Long-Term Objectives

A. Complete a large-scale, multi-disciplinary, collaborative project that longitudinally and comprehensively examines how the biological, clinical, and developmental profiles of individuals, with a special emphasis on females, youths, and adults with ASD, change over time as compared to typically developing people by 2020. *IACC Recommended Budget: $126,200,000 over 12 years.*

B. (2010) Launch at least three studies which evaluate the applicability of ASD phenotype and/or biological signature findings for performing diagnosis, risk assessment, or clinical intervention by 2015. *IACC Recommended Budget: $7,200,000 over 5 years.*

3. WHAT CAUSED THIS TO HAPPEN AND CAN THIS BE PREVENTED?

- **Is there something in my genetic or family history that poses a risk for ASD?**
- **What environmental exposures pose risks for the development of ASD?**
- **How might genetics and the environment interact to influence the occurrence of ASD?**

What do we know?

As with many complex disorders, causation is generally thought to involve some forms of genetic risk interacting with some forms of non-genetic environmental exposure. The balance of genetic risk and environmental exposure likely varies across the spectrum of ASD. The greatly increased concordance of strictly defined autism in monozygotic (identical) twins (70 - 90%) compared to dizygotic (fraternal) twins (0-10%) argues for the importance of genetic factors (Bailey et al., 1995; Steffenburg et al., 1989). Moreover, there are subpopulations of those diagnosed with ASD that have a known genetic mutation, often associated with a genetic disorder, such as Fragile X syndrome, Rett syndrome, or tuberous sclerosis, understanding of which has led to identification of possible pharmaceutical interventions. In many cases the same genetic variation does not result in an ASD phenotype, suggesting possible genetic or environmental modifiers that could be important intervention targets. Using new technology that reveals gaps and extra copies in DNA sequences, researchers have found that some people with ASD have deletions and duplications of genetic material not found in their parents' DNA (Sebat et al., 2007). Recent genetics research has identified common genetic variations (e.g., Wang et al., 2009; Weiss et al., 2009), changes in chromosomal structure in specific genomic regions, (Marshall et al., 2008; Kumar et al., 2008; Weiss et al., 2008) and rare mutations in genes all associated with synaptic connectivity (Alarçon et al., 2008; Bakkaloglu et al., 2008; Durand et al., 2007; Jamain et al., 2003; Laumonnier et al., 2004.; Strauss et al., 2006). Some of these findings have contributed to new hypotheses about the inheritance of ASD. In families with just one affected member, spontaneous deletions and duplications may be causal factors of ASD. However, what causes these spontaneous deletions and duplications is not clear and could be due to environmental exposures.

Taken together, rare genetic mutations, chromosomal abnormalities and sub-microscopic deletions and duplications of genetic material are involved in at least 10% of ASD cases, yet individually each abnormality is found in no more than about 1-2% of cases (Abrahams & Geschwind, 2008). Since common genetic variations confer only modest increase in risk, this suggests that the genetic factors in ASD may involve many different genes and interactions between genes and environment. Possible models include: many additional rare genetic mutations to be discovered; multiple common genetic variations each conferring a small increased risk; and, many forms of ASD with different genetic contributions, both common and rare in the population. There is growing recognition that the

same genetic contributions can lead to a wide variety of different phenotypes across individuals. As one good example, deletions and duplications in chromosomal region 16p11 have been associated with a broad range of phenotypes, including disorders outside the autism spectrum. The factors responsible for this variability in disease phenotypes remain to be defined.

Researchers are working to better understand the interaction of genetic vulnerability with developmental experiences, such as a specific environmental exposure. While gene-environment interactions have been hypothesized to play a role in many medical disorders, these interactions have been difficult to prove or disprove beyond statistical tests showing that some genetic subgroups have a greater response to some environmental factors. Epigenetics is one mechanism by which it is thought that environmental factors may be influencing gene expression, and now molecular tools are allowing researchers to gain insight into epigenetic phenomena that may be contributing to a variety of disorders, including ASD (Baccarelli and Bollati, 2009; Nagarajan et al., 2008).

While genetics maps the sequence of DNA, epigenetics maps the modifications of the structure of DNA due to proteins or other factors that bind to the DNA helix. DNA is essentially linear text that gets "read" into RNA that in turn codes for proteins. Epigenetic modifications do not change the text but they highlight or redact large sections of text, changing how it is read. Epigenetic modifications consist of biochemical "tags" that attach to the DNA in different places, leading to the "silencing" or "activation" of genes. The pattern of epigenetic silencing or activation of genes can differ between genders, between species or between generations, and can change during specific time windows in development or in response to environmental cues. It is thought that the addition or removal of epigenetic tags from DNA is one mechanism by which developmental experience (i.e., exposure to physical or emotional stimuli) can cause long-term biological and behavioral effects. In the past year, the first maps of the human epigenome have provided the first comprehensive look at where and how nature and nurture may interact (Lister et al., 2009).

Progress in identifying environmental factors which increase autism risk has been made recently (Eskenazi et al., 2007; Palmer et al., 2006; Palmer, Blanchard, & Wood, 2009; Rauh et al., 2006; Roberts et al., 2007; Windham et al., 2006), although this area of research has received less scientific attention and far fewer research dollars than genetic risk factors. Environmental factors may be pertinent not only to brain development but also to chronic systemic features of at least some subgroups of ASD. An Institute of Medicine (IOM) workshop held in 2007 summarized what is known and what is needed in this field (Forum on Neuroscience and Nervous System Disorders, Institute of Medicine, 2008). Numerous epidemiological studies have found no relationship between ASD and vaccines containing the mercury based preservative, thimerosal (Immunization Safety Review Committee, 2004). These data, as well as subsequent research, indicate that the link between autism and vaccines is unsupported by the epidemiological research literature. However, the IOM report acknowledged that the existing population-based studies

were limited in their ability to detect small susceptible subpopulations that could be more genetically vulnerable to environmental exposures.

Of note, the Committee receives many public comments that reflect concerns about vaccines as a potential environmental factor in autism. Some members of the public are convinced that the current data are sufficient to demonstrate that vaccines do not play a causal role in autism and argue against using limited autism research funds to do additional vaccine studies when many other scientific avenues remain to be explored. At the same time, those who believe that prior studies of the possible role of vaccines in ASD have been insufficient argue that investigation of a possible vaccine/ASD link should be a high priority for research (e.g., a large-scale study comparing vaccinated and unvaccinated groups). A third view urges shifting focus away from vaccines and onto much-needed attention toward the development of effective treatments, services and supports for those with ASD.

In addition, a number of other environmental factors are being explored through research because they are known or suspected to influence early development of the brain and nervous system. Recent studies suggest factors such as parental age, exposure to infections, toxins, and other biological agents may confer environmental risk. These findings require further investigation and testing, some of which is ongoing through the CDC's Centers for Autism and Developmental Disabilities Research and Epidemiology (CADDRE) and Studies to Explore Early Development (SEED) programs, as well as through several NIH-funded studies including the Norwegian Autism Birth Cohort (ABC) study, the Childhood Autism Risks from Genetics and the Environment (CHARGE) study, the Early Autism Risk Longitudinal Investigation (EARLI) study, and the Children's Centers for Environmental Health and Disease Prevention, which is supported collaboratively by NIEHS/NIH and the Environmental Protection Agency (EPA).

What do we need?

Although most scientists believe that risk factors for ASD are both genetic and environmental, there is considerable debate about whether potential environmental causes, genetic precursors, or interactions between genes and environmental factors should be the highest priority for research aimed at identifying the causes of ASD. To date, few studies have ruled in or ruled out specific environmental factors. There are reports of associations of ASD with exposure to medications, maternal antibodies, toxicants, and infections prenatally or postnatally; however these observations need to be the subject of additional study. It is still not known whether any specific factor is necessary or sufficient to cause ASD. Similar to other disease areas, advancing research on the potential role of environmental factors requires resources and the attraction of scientific expertise. Bringing this to bear on autism will help define the environmental factors to study, as well as the best approach for staging studies to examine environmental factors, interaction between factors, and between individual susceptibility and various environmental factors.

For example, some researchers believe that it is important to study a large number of exposures, or classes of

exposure, that are known to affect brain development. Others support more tightly focused studies of one exposure or a limited number of exposures, with greatest biologic plausibility for interacting with known or suspected biologic or genetic ASD risk factors. In addition, it is also important to designstudies that assess environmental exposure during the most relevant exposure windows: pregnancy and early development. In doing this research, it will be important for the field to develop sound standards for identifying and claiming that environmental factors contribute to ASD, as it is for genetics.

Research studies on risk factors can be pursued through several means. Smaller, focused studies are needed for hypothesis testing and to provide insight for replication studies. Similar to other health outcomes research for relatively rare conditions, case-control studies can be an effective first line of inquiry. The NIH-supported CHARGE and CDC-supported CADDRE/SEED studies are good examples of this approach where environmental exposures and biological pathways, along with genetics, are being examined. Other existing cohorts could also be identified and used for epigenomic as well as traditional genomic and environmental studies.

To address public concerns regarding a possible vaccine/ASD link, it will be important for the IACC to continue to coordinate with the National Vaccine Advisory Committee (NVAC), a Federal advisory committee chartered to advise and make recommendations regarding the National Vaccine Program.

Epigenomics provides a ready mechanism for understanding how genes and environment may act jointly to affect autism risk. Studies are needed to investigate whether candidate environmental exposures alter epigenetic mechanisms that modify the expression of suspected autism susceptibility genes or genomic regions. Such studies should incorporate examination of time or stage of development as an important factor determining the impact of environmental agents on epigenetic programming. Finally, studies are needed to understand how changes in epigenetic tags in response to environmental stimuli could lead to specific phenotypic characteristics associated with autism.

Another approach for studying risk factors for ASD requires large sample sizes to disentangle the many possible genetic and environmental factors that contribute to and help explain ASD and the frequently co-occurring conditions. For other complex disorders, large DNA collections, i.e. >20,000 samples, have been necessary to detect the full genetic risk architecture. There are no genetic repositories of this size for ASD. Similarly, large birth cohort studies, in which biological samples have been collected throughout pregnancy and early postnatal life may be essential for detecting the interplay of environmental exposures and genetic factors that lead to ASD. As a complement to these large-scale studies, research on critical sub-populations that may be at higher risk could provide leverage in identifying genetic and environmental risk factors.

2011 Addendum to Question 3: What Caused This To Happen And Can It Be Prevented?

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

A variety of discoveries have advanced knowledge of the biological underpinnings of autism. It was found that, among individuals with ASD, copy number variants, submicroscopic deletions and duplications in the genome occur more frequently in areas containing ASD risk genes. Some of these copy variants involved genes previously found to be associated with autism and some involved new rare mutations (Pinto et al, 2010). In addition, it was reported that neurodevelopmental disorders are more common in infants born prematurely and that preterm infants are at increased risk of developing autism (Johnson et al., 2010b). A study of blood mercury levels in 452 children in the NIH –funded Childhood Autism Risk from Genetics and the Environment (CHARGE) study showed that total mercury in blood was neither elevated nor reduced in pre-school children with ASD (Hertz-Picciotto et al., 2010). In a separate study, no link was found between the exposure to thimerosal, a mercury-containing preservative used in vaccines and increased risk for ASD (Price et al., 2010).

New data based on the Autism Speaks supported Autism Treatment Network (ATN) patient registry and studies of high-risk infants indicate that autism is associated with high rates of several medical conditions, including gastrointestinal dysfunction, sleep disturbance, psychiatric conditions, and seizures (Presentation to IACC on the Autism Treatment Network, 2010). These co-occurring conditions are poorly studied, yet investigating them may reveal unexpected clues to environmental risk factors. For example, nonmotor features associated with Parkinson's disease (e.g., GI problems, olfactory deficits, autonomic abnormalities) have yielded information about Parkinson's disease etiology and can serve as harbingers of the condition.

On September 8, 2010, the National Institute of Environmental Health Sciences (NIEHS/NIH) and Autism Speaks co-sponsored a meeting of scientists from both inside and outside the field of autism to identify novel opportunities and mechanisms to accelerate research on environmental factors and autism. Environmental factors considered included all factors affecting health that are external to the individual (such as physical, biological, chemical, dietary, social, and cultural), as well as the non-genetic characteristics of an individual (such as age, nutritional status, physical functioning and medical history). As noted in the meeting report, understanding environmental influences to autism will require both agnostic, discovery-based science as well as hypothesis-driven science in parallel. Strong interdisciplinary teams are needed to move findings back and forth from clinical and epidemiologic settings to mechanistic studies. Research needs and opportunities identified included expansion of epidemiology investigations to capitalize on existing resources, development of a range of model systems that can address the complexity of autism, exploration of bioinformatics and

screening approaches to identify environmental chemicals of interest, increased emphasis on neuropathology, enhancement of capacity for measurement of environmental analytes, harmonization of exposure assessment instruments and mechanisms for expanding the workforce.

Technical advances in the past year increase traction for finding genetic and environmental risk factors. Novel bioinformatics platforms can be used to map genes to specific signaling pathways and to explore what environmental exposures are most likely to influence those pathways. Toxicogenomics data such as that produced by the EPA's National Center for Computational Toxicology could be mined to determine which environmental compounds act on the genes of interest. An important finding this year revealed the extent of "parent of origin" effects – for many genetic variations, risk depends on whether this variation was inherited from the maternal or paternal genome. And recent studies have revealed the importance of epigenetic mechanisms in disease etiology, bringing together genetic and environmental factors for the first time.

Information on the utility of induced pluripotent stem cells and mesenchymal stem cells for exploring the biological basis of ASD is rapidly developing, pointing to the opportunity to use these tools as molecular assays for understanding genetic variation as well as for translational toxicology. Although research this year revealed several differences between these adult-derived stem cells and embryonic stem cells, adult-derived stem cells continue to be one of the most promising new frontiers for understanding risk for ASD.

In a 2009 report by the National Vaccine Advisory Committee (NVAC), it was recommended that, in the context of immunization research, the ASD clinical subset of particular interest is regressive autism (National Vaccine Advisory Committee, 2009). Although the NVAC stressed that the temporal occurrence of this regression and the immunization schedule is not evidence of a causal relationship, regressive autism warrants further research in rigorously defined subsets of ASD. The NVAC noted that studies in this subpopulation might involve comparison of immune cytokine profiles between regressive and non-regressive ASD to screen for differential immune system profiles, or prospective immunization responsive profiling in siblings of children with regressive ASD. In addition, the NVAC recommended that studies assess whether adverse events following immunization (e.g. fever and seizures) correlate with risk of ASD, and that immune response profiles be examined in ASD cases with history of adverse events following immunization.

The *2009 IACC ASD Research Portfolio Analysis* indicated that about one third of autism research studies funded across the federal government and private organizations corresponded to risk factors/ Strategic Plan Question 3, with the majority of this funding directed toward the identification of genetic risk factors and less funding and attention toward environmental research. This analysis suggests that environmental research is an understudied area that has been given insufficient attention and requires a heightened priority.

Based on this, the Committee made several specific recommendations for research objectives and needed resources, which are reflected in the new objectives added to the Plan in 2011.

What gap areas have emerged since last year?

Suitable model systems and those that offer better high-throughput capabilities, for the study of environmental risk factors and their interaction with genetic susceptibility are needed. For example, models such as *Drosophila melanogaster* (fruit flies) and *Danio rerio* (zebra fish) have been extremely useful in identifying environmental contributors to other conditions, such as Parkinson's and Alzheimer's disease. The genetics and biology of synapse formation and function are increasingly well-understood, underscoring the potential utility of vertebrate and invertebrate models for exploring how environmental exposure can affect brain function at the cellular and molecular levels.

Expansion and integration of epidemiological studies using different designs and types of data are needed. Combining data from multiple studies will be necessary to enhance statistical power, requiring standardization of protocols, instrument development, and data harmonization methods. This should also include standardized protocols on biological specimen collection, storage, and analysis. International studies offer unique opportunities to examine populations with different genetic and environmental exposure backgrounds. It would be helpful to create an autism "atlas" to examine differences in autism prevalence as a function of geography. Such analysis has proven useful in both cancer and asthma research.

There is a need for greater collaboration between genetic and environmental science investigators. Studies collecting genetic information should include data on environmental exposures and vice-versa; large data sets are needed allowing mapping of detailed genetic, detailed environment, and detailed phenotypic information, including co-occurring medical conditions, inflammatory markers, pattern of onset and developmental course and family history.

To accelerate our understanding of the role of epigenetics in autism etiology, further development and application of sensitive assays to measure DNA methylation, histone modification, and other epigenetic marks are needed. Studies are also needed to examine how exposures may act on maternal or paternal genomes via epigenetic mechanisms to influence risk for ASD.

The lack of adequate postmortem brain tissue continues to be a major barrier to progress in understanding the neurobiology of ASD, including the potential influence of environmental factors on the functional pathways involved in ASD.

Efforts to increase analytical capacity and core facilities are needed. For example, adding an environmental, immune, or animal models core to an already existing multidisciplinary team that studies autism would be beneficial. Access to these core facilities and services could encourage individual scientists to expand the scope of their studies to address environmental hypotheses.

***ASPIRATIONAL GOAL*: CAUSES OF ASD WILL BE DISCOVERED THAT INFORM PROGNOSIS AND TREATMENTS AND LEAD TO PREVENTION/PREEMPTION OF THE CHALLENGES AND DISABILITIES OF ASD.**

Research Opportunities

- Genetic and epigenetic variations in ASD and the symptom profiles associated with these variations.
- Environmental influences in ASD and the symptom profiles associated with these influences.
- Family studies of the broader autism phenotype that can inform and define the heritability of ASD.
- Studies in simplex families that inform and define de novo genetic differences and focus on what role the environment might play in inducing these differences.
- Standardized methods for collecting and storing biospecimen resources from well-characterized people with ASD as well as a comparison group for use in biologic, environmental and genetic studies of ASD.
- Case-control studies of unique subpopulations of people with ASD that identify novel risk factors.
- Monitor the scientific literature regarding possible associations of vaccines and other environmental factors (e.g., ultrasound, pesticides, pollutants) with ASD to identify emerging opportunities for research and indicated studies.
- Better understanding environmental and biological risk factors during pre- and early post-natal development in "at risk" samples.
- Cross-disciplinary collaborative efforts to identify and analyze biological mechanisms that underlie the interplay of genetic and environmental factors relevant to the risk and development of ASD, including co-occurring conditions.
- Convene ASD researchers on a regular basis to develop strategies and approaches for improving data standards and sharing, understanding gene – environment interactions, improving the speed of replication of findings, and enhancing the translation of research on potential causative factors to prevention and treatment studies.
- Measures of key exposures for use in population and clinic based studies and standards for sample collection, storage, and analysis of biological materials.
- Studies of behavioral, developmental, and medical variations across those with ASD who share common genetic factors.
- Studies of clinically meaningful subgroups to examine common genetic and environmental factors, as well as unique epigenomic signatures.

Short-Term Objectives

A. Coordinate and implement the inclusion of approximately 20,000 subjects for genome-wide association studies, as well as a sample of 1,200 for sequencing studies to examine more than 50 candidate genes by 2011. Studies should investigate factors contributing to phenotypic variation across individuals that share an identified genetic variant and stratify subjects according to behavioral, cognitive, and clinical features. *IACC Recommended Budget: $43,700,000 over 4 years.*

B. Within the highest priority categories of exposures for ASD, identify and standardize at least three measures for identifying markers of environmental exposure in biospecimens by 2011. *IACC Recommended Budget: $3,500,000 over 3 years.*

C. Initiate efforts to expand existing large case-control and other studies to enhance capabilities for targeted gene – environment research by 2011. *IACC Recommended Budget: $27,800,000 over 5 years.*

D. Enhance existing case-control studies to enroll racially and ethnically diverse populations affected by ASD by 2011. *IACC Recommended Budget: $3,300,000 over 5 years.*

E. (2010) Support at least two studies to determine if there are subpopulations that are more susceptible to environmental exposures (e.g., immune challenges related to infections, vaccinations, or underlying autoimmune problems) by 2012. *IACC Recommended Budget: $8,000,000 over 2 years.*

F. (2010) Initiate studies on at least 10 environmental factors identified in the recommendations from the 2007 IOM report "Autism and the Environment: Challenges and Opportunities for Research" as potential causes of ASD by 2012. *Estimated cost $56,000,000 over 2 years.*

G. (2011) Convene a workshop that explores the usefulness of bioinformatic approaches to identify environmental risks for ASD by 2011. **IACC Recommended Budget: $35,000 over 1 year. (Provided by NIH)**

H. (2011) Support at least three studies of special populations or using existing databases to inform our understanding of environmental risk factors for ASD in pregnancy and the early postnatal period by 2012. Such studies could include:

- Comparisons of populations differing in geography, gender, ethnic background, exposure history (e.g. prematurity, maternal infection, nutritional deficiencies, toxins), migration patterns
- As well as comparisons of phenotype (e.g. cytokine profiles), in children with and without a history of autistic regression, adverse events following

immunization (such as fever and seizures), mitochondrial impairment, and siblings of children with regressive ASD.

Emphasis on environmental factors that influence prenatal and early postnatal development is particularly of high priority. Epidemiological studies should pay special attention to include racially and ethnically diverse populations.
IACC Recommended Budget: $12,000,000 over 5 years. (Provided by NIH)

I. (2011) Support at least two studies that examine potential differences in the microbiome of individuals with ASD versus comparison groups by 2012. **IACC Recommended Budget: $1,000,000 over 2 years. (Provided by NIH)**

J. (2011) Support at least three studies that focus on the role of epigenetics in the etiology of ASD, including studies that include assays to measure DNA methylations and histone modifications and those exploring how exposures may act on maternal or paternal genomes via epigenetic mechanisms to alter gene expression, by 2012. **IACC Recommended Budget: $20,000,000 over 5 years. (Provided by NIH)**

K. (2011) Support two studies and a workshop that facilitate the development of vertebrate and invertebrate model systems for the exploration of environmental risks and their interaction with gender and genetic susceptibilities for ASD, by 2012. **IACC Recommended Budget: $1,535,000 over 3 years. (Provided by NIH)**

Long-Term Objectives

A. Conduct a multi-site study of the subsequent pregnancies of 1,000 women with a child with ASD to assess the impact of environmental factors in a period most relevant to the progression of ASD by 2014. *IACC Recommended Budget: $11,100,000 over 5 years.*

B. Identify genetic risk factors in at least 50% of people with ASD by 2014. *IACC Recommended Budget: $33,900,000 over 6 years.*

C. Determine the effect of at least five environmental factors on the risk for subtypes of ASD in the pre- and early postnatal period of development by 2015. *IACC Recommended Budget: $25,100,000 over 7 years.*

D. Support ancillary studies within one or more large-scale, population-based surveillance and epidemiological studies, including U.S. populations, to collect data on environmental factors during preconception, and during prenatal and early postnatal development, as well as genetic data, that could be pooled (as needed), to analyze targets for potential gene/environment interactions by 2015. *IACC Recommended Budget: $44,400,000 over 5 years.*

4. WHICH TREATMENTS AND INTERVENTIONS WILL HELP?

- **When should treatments or interventions be started?**
- **What are the medical issues I need to know about?**
- **How do I know that treatments are both safe and effective?**

What do we know?

Although autism is defined and diagnosed by deficits in core behaviors, accumulating evidence suggests that the breadth of this disorder extends well beyond the behavioral diagnosis. There is increasing recognition that the multiple systemic issues in children with ASD may influence vulnerability, onset, and severity of symptoms and behaviors. The systemic component of autism supports the possibility that both the core behaviors and medical issues have a convergent mechanistic basis that if identified, could provide new insights into treatment targets, candidate genes, and strategies for prevention.

A wide range of treatment and intervention options are available for children and adults with ASD that can target core symptoms, ameliorate associated symptoms, and prevent further disability. For example, interventions such as speech therapy facilitate language development, pragmatic communication and social interaction. Occupational therapy can improve functioning in everyday activities (e.g., eating, bathing, and learning) as well as sensory integration. Both types of therapy can promote the development of life skills, which help people with ASD to gain more independence. People with ASD can benefit from adaptive technologies, such as the use of keyboards and computers that promote expressive communication skills, and visual representation tools such as the Picture Exchange Communication System (PECS) that assist those with little or no language to communicate more effectively. For pre-school and school age children, public school systems and private schools can provide essential interventions including curricula that are individualized to the child, testing for cognitive and academic strengths and weaknesses, and special education services with lower teacher to student ratios, to name a few. For all of these interventions, there is a range of improvement, with some people making profound gains and others showing little response. We do not know how to predict which people will benefit from any of the available treatments.

Of the numerous behavioral interventions currently in use, little scientific evidence from randomized controlled trials (RCT) supports their efficacy. Behavioral therapies, such as Applied Behavior Analysis (ABA) based therapies, which use the principles of reinforcement and repetition, have been used since the 1960s and have been studied most extensively. Controlled trials have shown ABA to be effective for improving social skills and language when provided for at least 25-40 hours per week for 2 years (Lord & McGee, 2001). Efficacy is greatest when behavioral interventions are used early, but improved skills have been reported with adolescents and adults (McClannahan, MacDuff, & Krantz, 2002; Weiss & Harris, 2001).

Medications to improve some of the symptoms associated with autism have been studied. However, thus far, no medication has been shown in controlled trials to enhance social behavior or communication. In 2006, risperidone became the first Food and Drug Administration (FDA)-approved pharmacologic therapy for certain symptoms of autism. First introduced in 1993 as medication used to treat symptoms of schizophrenia, risperidone has now been shown to be effective as a treatment of irritability and aggression seen in some children with ASD. Selective serotonin reuptake inhibitors have had mixed results in decreasing certain repetitive and stereotyped behaviors (Kolevzon, Mathewson, & Hollander, 2006; King et al., 2009). Other biological and pharmacological treatments that have been investigated in small studies and may warrant fuller attention include omega-3 fatty acids, memantine, oxytocin, and pioglitazone (Ammiger et al., 2007; Chez et al., 2007; Hollander et al., 2007; Boris et al., 2007).

There are other treatments in wide use that have not been studied in randomized controlled trials. These include nutritional supplements and diets (e.g., probiotics, mitochondrial cocktails, CoQ10, carnitine, and gluten-casein free diets), and chelation. One such treatment, the neuropeptide secretin, that had been reported to improve symptoms of ASD, was studied in a placebo-controlled trial and found to be ineffective (Esch & Carr, 2004). Some parents and therapists suggest that these treatments are effective, that recovery is possible, and that further studies are needed. Others are concerned that these treatments involve more than minimal risks and urge caution before recommending large-scale studies.

What do we need?

Safe and effective interventions are needed across the lifespan, from early development shortly after the detection of risk or diagnosis, through childhood, school age, adolescent, adult, and senior phases of life. Going forward, research needs to be balanced between two poles. On the one hand, there is a need for novel, targeted interventions based on an understanding of the molecular mechanisms of ASD. These interventions, analogous to ongoing efforts in cancer and cardiovascular research, will require a successful commitment to earlier elements of this Strategic Plan. On the other hand, there is a need for rigorous studies to develop and safely test the efficacy of current interventions, identifying which elements are most effective in reducing or ameliorating symptoms for which persons. Intervention research should collect information about the mode of delivery, intensity, duration, and dose as well as unique characteristics of the people with ASD (e.g., behavioral, biological, genetic) in an effort to develop more personalized interventions, treatments, services and supports, and help inform basic research about additional targets for study. This research will require large-scale multidisciplinary randomized controlled trials.

The identification of biomarkers, for instance, in plasma, saliva, cerebrospinal fluid (CSF), or tissue is necessary to provide insights into targeted treatment strategies designed to improve or reverse autistic symptoms as well as insights into preventive measures. Further, if

biomarkers present in children with ASD are found to be present in infants and toddlers at high risk of developing autism, targeted intervention strategies to normalize these biomarkers could be tested for potential to arrest or reverse the symptoms and progression of autism.

Decision makers (people with ASD, families, clinicians, and payors) frequently lack critical information about which treatment is best for an individual person. While there are many interventions in wide use, the field lacks comparative studies of their value or how these various interventions should be staged or combined. Comparative effectiveness research yields information from head to head comparisons of interventions or policies that, when combined with a personalized approach, can inform decision makers about health care choices. This approach, already helpful for cardiovascular and cancer research, needs to be developed to inform ASD interventions.

Special attention is needed on treatment of co-occurring medical conditions, developing pharmacological treatments, and testing interventions that are in wide use, (e.g., nutritional supplements) but for which little rigorous efficacy data exist (Levy & Hyman, 2003). Co-occurring conditions, such as gastrointestinal symptoms and sleep disorders, may influence the effectiveness of interventions designed to affect the core symptoms of ASD. Similarly, interventions that focus on co-occurring conditions may also affect or reduce core symptoms. Animal models and/or cell lines relevant to autism are needed to develop new or test existing pharmacological agents for ASD, understand the mechanisms of action, and serve as a first-step in testing drug safety. Such model systems research may be crucial in leveraging the pharmaceutical industry to develop medications that target the core symptoms of ASD.

While some people with ASD have been reported to show marked improvement, little is known about the characteristics of these people or the types of interventions they have received that may help to explain these changes. Studies of these people may provide an opportunity for discovering important clues with regard to risk factors and intervention strategies for specific ASD subgroups.

2011 Addendum to Question 4: Which Treatments and Interventions Will Help?

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

Several notable studies and reviews on the efficacy of specific interventions for improving outcomes of individuals with ASD were published in 2010. These include a 2010 study showing that medications such as risperidone are most effective for reducing irritability and aggression when they are combined with intensive behavioral intervention (Frazier et al., 2010). A study of psychotropic medication use over time in youth and adults with ASD showed an increasingly high likelihood of staying medicated across the life course (Esbensen et al., 2009).

Recent research also supports the benefits of social skills training for people with ASD. A 2010 study showed improved levels of social interaction and peer relationships (Frankel et al., 2010), while a randomized controlled trial (RCT)

evaluating a social skills group intervention found improvements in social behavior for children with ASD who had high cognitive ability (Derosier et al., 2010).

In other notable work conducted in 2010, a systematic review concluded that modified cognitive behavioral interventions are efficacious for reducing anxiety in individuals with Asperger syndrome (Lang et al., 2010). In addition, a RCT of a caregiver mediated joint engagement intervention for toddlers showed positive results; it represents the first controlled data to suggest that short-term parent-mediated intervention can be efficacious for improving joint attention and functional play acts with maintenance of skills one year post-intervention (Kasari et al., 2010).

An environmental scan study, supported by the Centers for Medicare & Medicaid Services (CMS), examined interventions for children, youth, and adults with ASD (Young et al., 2010). The scan included services addressing the core impairments associated with ASD as well as other support services such as behavioral interventions, peer training, and supported employment. For children, 15 interventions met the "evidence-based" criteria established, while the other 16 interventions studied met only the criteria for emerging or unestablished interventions. Far less evidence was available on services and supports for transitioning youth and adults, underscoring the need for more research in this area.

In the area of early behavioral interventions, a randomized controlled trial demonstrated the efficacy of a comprehensive early intensive behavioral intervention, based on the Early Start Denver Model, which integrates developmental approaches with principles of applied behavioral analysis (ABA) for improving IQ, language, and adaptive behavior, and reducing severity of autism diagnosis in toddlers with ASD (Dawson et al., 2010b). In addition, three reviews of the effectiveness of early intensive behavioral intervention based on ABA were published. The Institute of Education Sciences reviewed findings specific to the Lovaas model of ABA, concluding that this model has been shown to have potentially positive effects on cognitive development but had no discernable effect on communication/ language competencies, social-emotional development and behavior, and functional abilities (Institute of Education Sciences, 2010). In the *Annual Review of Clinical Psychology*, Vismara and Rogers (2010) concluded that both comprehensive and targeted early intervention programs based on ABA are effective for improving communication, social skills, and management of behavioral challenges.

Finally, results of a meta-analysis showed that long-term, comprehensive ABA interventions for children with ASD lead to medium to large positive effects in intellectual functioning, language development, acquisition of daily living skills and social functioning (Virues-Ortega, 2010). Effects for language-related outcomes (IQ, receptive and expressive language, communication) were more robust than non-verbal IQ, social functioning, and daily living skills.

What gap areas have emerged since last year?

Recent data indicate that several rare and highly-penetrant gene variants and copy number variations (e.g. NLGN3, NLGN4, NRXN1, SHANK 2 and 3, PTCHD1, maternally-inherited 15q11-q13, among others) are involved in ASD (Pinto et al., 2010). There is a need for translational research that can take advantage of these new genetic findings to (1) identify subgroups of individuals with ASD who respond well to specific medications and intervention approaches, (2) inform which molecular signaling pathways are affected in ASD, (3) develop animal models to explore the downstream effects of these genetic variants on brain function, and (4) discover targets for development of therapeutics. In order to develop effective medical and behavioral interventions, there is a continuing need for autism intervention networks which can provide platforms for conducting clinical trials and comparative effectiveness research using genetic and other biomarkers for specific subtypes, other individual characteristics, and their relationship to response to specific treatments for people with ASD.

In a 2010 presentation to the IACC, data were presented from the autism Speaks supported Autism Treatment Network (ATN), a system of 14 academic health centers throughout the US and Canada that provide care to over 5,000 individuals with ASD, which showed that 65% of individuals with ASD experience sleep disturbances and 14% of those with sleep problems also have seizures (Presentation to the IACC on the Autism Treament Network, 2010). Gastrointestinal (GI) problems were also reported in 50%, and those with gastrointestinal problems were more likely to have sleep disturbances, behavioral problems, and a lower health related quality of life. Other health issued identified include seizures, food sensitivities, anxiety and depression. It is not known whether these medical conditions are a primary aspect of some forms of autism or whether they are secondary features. Recent consensus statements and expert reviews indicate that assessment and treatment of such conditions can lead to improvement in behavior and quality of life (Buie et al., 2010a,b; Coury, 2010), and represent a critical unmet need and great opportunity for improving overall health and quality of life for people with ASD. The existence of co-occurring medical conditions in ASD underscores the importance of identifying subgroups of individuals with specific medical conditions who might respond favorably to a particular targeted treatment. In addition, it will be necessary to develop and test multifaceted treatment approaches (e.g., combined behavioral and medical) that address co-occurring medical conditions.

In April 2010, an NIH-sponsored workshop identified the urgent need for more research on children with ASD who have not developed functional verbal language by five years of age (Summary of NIH Workshop on Nonverbal School-Aged Children with Autism, 2010). Among the topics discussed was the development of new intervention approaches that directly teach spoken communication skills and Augmentative and Alternative Communication (AAC). More research is needed on the efficacy of novel service-provision, education, and treatment approaches that facilitate communication skills in people with ASD who are nonverbal and in individuals with

challenges in verbal ability, including the need for evidence on the utility of AAC for specific subpopulations of persons with ASD. Potential areas of investigation include oral-motor skills, auditory/speech processing, social attention mechanisms, and impairments in intentional communication. In addition, research is needed on ways to improve access to AAC and the most appropriate means of AAC to utilize with specific subpopulations of individuals on the autism spectrum, including both individuals who are nonspeaking and individuals with speech which is partially or periodically limited. Comprehensive studies focusing on both adults and children on the autism spectrum should address the components of the most effective AAC approaches and factors which enhance or moderate improvements in communication, behavior and quality of life as a result of AAC usage.

Additional focus is needed to identify and address health disparities for people with ASD. While attention has been given to closing disparities in access to health care and health outcomes on the basis of race and income, little has been done to close this gap for people with developmental and intellectual disabilities, including autism (Presentation to IACC on NICHD Workshop "Disparities in the Identification of Children with ASD," 2010). Recent legislative initiatives, including the Children's Health Insurance Program Reauthorization Act (CHIPRA) and the Affordable Care Act support this research, as well as the refinement of quality of life measures for children, and the development of quality of life measures for adults. Data generated from the National Core Indicators (NCI) Project, sponsored by the National Association of State Directors of Developmental Disabilities Services (NASDDS), has revealed some data regarding quality of life specifically for people with ASD enrolled in state programs (National Core Indicators Project Web site).

***ASPIRATIONAL GOAL*: INTERVENTIONS WILL BE DEVELOPED THAT ARE EFFECTIVE FOR REDUCING BOTH CORE AND ASSOCIATED SYMPTOMS, FOR BUILDING ADAPTIVE SKILLS, AND FOR MAXIMIZING QUALITY OF LIFE AND HEALTH FOR PEOPLE WITH ASD.**

Research Opportunities

- Large scale studies that directly compare interventions and combinations of interventions (e.g., pharmaceutical, educational, and behavioral interventions) to identify what works best for which people and how much it will cost.
    - Best practice models that are being used in community-based ASD intervention programs.
    - Clinical trials that assess the safety and efficacy of widely used interventions that have not been rigorously studied for use in ASD populations.
    - Studies in diverse populations.
- Interventions that improve functioning and quality of life for people with ASD across the lifespan, including older children, adolescents, and adults with ASD.
- Early interventions that aim to prevent the development of ASD in

very young "at risk" children and reduce family burden.

- Innovative treatments that specifically target core symptom clusters unique to ASD.
- Development of emerging technologies, such as assisted communication, that provide opportunities for people with ASD to become more engaged in the community.
- Animal models and/or cellular lines that can be used to test efficacy and/or safety of ASD interventions and treatments.
- Strategies that facilitate rapid translation of promising basic scientific discoveries and community practices into clinical research and trials.
- Methods of treating co-existing medical or psychiatric conditions and assess how such treatments affect ASD symptoms and severity.
- Interventions that may enhance neural plasticity and adaptive brain reorganization in children, adolescents, and adults with ASD thereby promoting significant improvement of ASD.
- Outcome studies of the effectiveness of behavioral, developmental, and cognitive therapies and approaches.
- Methods for measuring changes in core symptoms of ASD from treatment.
- Dissemination research (coordinated with subsequent objectives) to ensure that evidence-based interventions are implemented in diverse communities with fidelity and efficiency.
- Investigation of the use of medications to control challenging behaviors in people with ASD, particularly adults.

Short-Term Objectives

A. Support at least three randomized controlled trials that address co-occurring medical conditions associated with ASD by 2010. *IACC Recommended Budget: $13,400,000 over 3 years.*

B. Standardize and validate at least 20 model systems (e.g. cellular and/or animal) that replicate features of ASD and will allow identification of specific molecular targets or neural circuits amenable to existing or new interventions by 2012. *IACC Recommended Budget: $75,000,000 over 5 years.*

C. Test safety and efficacy of at least five widely used interventions (e.g., nutrition, medications, assisted technologies, sensory integration, medical procedures) that have not been rigorously studied for use in ASD by 2012. *IACC Recommended Budget: $27,800,000 over 5 years.*

D. Complete two multi-site randomized controlled trials of comprehensive early intervention that address core symptoms, family functioning and community involvement by 2013. *IACC Recommended Budget: $16,700,000 over 5 years.*

E. (2010) Convene a workshop to advance the understanding of clinical subtypes and treatment personalization (i.e. what are the core symptoms to target for treatment studies) by 2011. *IACC Recommended Budget: $50,000.*

F. (2010) Launch five randomized controlled trials of interventions including biological signatures and other measures to predict response, and monitor quality of life and functional outcomes, in each of the following groups:

- Five trials in infants and toddlers by 2013*. IACC Recommended Budget: $30,000,000 over 5 years.*
- Three randomized controlled trials of interventions for school-aged children and/or adolescents by 2013. *IACC Recommended Budget: $18,000,000 over 5 years.*
- Three trials for adults by 2014. *IACC Recommended Budget: $18,000,000 over 5 years.*

L. (2011) Support at least five studies on interventions for nonverbal individuals with ASD by 2012. Such studies may include:

- Projects examining service-provision models that enhance access to Augmentative and Alternative Communication (AAC) supports in both classroom and adult service-provision settings, such as residential service-provision and the impact of such access on quality of life, communication and behavior

- Studies of novel treatment approaches that facilitate communication skills in individuals who are nonverbal, including the components of effective AAC approaches for specific subpopulations of persons with ASD
- Studies assessing access and use of AAC for children and adults with ASD who have limited or partially limited speech and the impact on functional outcomes and quality of life.

IACC Recommended Budget: $3,000,000 over 2 years. (Provided by NIH)

M. (2011) Support at least two studies that focus on research on health promotion and prevention of secondary conditions in people with ASD, by 2012. Secondary conditions of interest include overweight and obesity, injury, and co-occurring psychiatric and medical conditions. **IACC Recommended Budget: $5,000,000 over 3 years. (Provided by CDC)**

Long-Term Objectives

A. Complete at least three randomized controlled trials on medications targeting core symptoms in people with ASD of all ages by 2014. *IACC Recommended Budget: $22,200,000 over 5 years.*

B. Develop interventions for siblings of people with ASD with the goal of reducing the risk of recurrence by at least 30% by 2014. *IACC Recommended Budget: $6,700,000 over 5 years.*

C. (2010) Conduct at least one study to evaluate the safety and effectiveness of medications commonly used in the treatment of co-occurring conditions or specific behavioral issues in people with ASD by 2015. *IACC Recommended Budget: $10,000,000 over 5 years*.

D. (2011) Support at least five community-based studies that assess the effectiveness of interventions and services in broader community settings by 2015. Such studies may include comparative effectiveness research studies that assess the relative effectiveness of:

- Different and/or combined medical, pharmacological, nutritional, behavioral, service-provision, and parent or caregiver-implemented treatments
- Scalable early intervention programs for implementation in underserved, low resource, and low literacy populations
- Studies of widely used community intervention models for which extensive published data are not available.

Outcome measures should include assessment of potential harm as a result of autism treatments, as well as positive outcomes. **IACC Recommended Budget: $37,500,000 over 5 years. (Provided by NIH)**

5. WHERE CAN I TURN FOR SERVICES?

- **What types of services and supports should I seek and where can I find them?**
- **What is my state or local government doing to provide services for ASD?**
- **What is the cost of services and how will it be paid?**

What do we know?

To fulfill the mission to "profoundly improve the health and well being of every person on the autism spectrum across the lifespan," scientific discoveries must be implemented in communities and supported by public policy. The gap between knowledge and action can only be overcome by an aggressive focus on engaging families, people with ASD, and the services community in the research process, disseminating research findings into the community, eliminating barriers to services and helping people with ASD and their families identify which services are needed.

The communities in which children are diagnosed vary tremendously in their ability to meet the needs of people with ASD (Shattuck & Grosse, 2007). Local school districts vary in their ability to identify and provide appropriate educational and related programs for children with ASD (Mandell & Palmer, 2005; Palmer et al., 2005). States vary in the policies they have developed to organize, finance and deliver care. The professional infrastructure or capacity is often inadequate to provide timely diagnosis, appropriate care, services and supports, and assure health and safety.

While remarkable improvements have been made during the last three decades in understanding the best ways to identify, assess, educate and support people with autism and their families, these improvements rarely enter community practice. In fact, some have suggested that the lag between research and practice is close to 20 years. When services with proven efficacy are implemented in community settings, they often do not result in the same positive outcomes (i.e., they are efficacious in research settings, but not effective in community practice). The reasons for this lag and ways to improve services only recently have become an area of research in autism.

Another important issue for service delivery is that community needs far outpace the state of research. Most autism services research has focused on behavioral interventions for young children. Behavioral interventions for youth and adults, as well as community supports that address quality of life (as opposed to core symptoms) for people with autism and their families have almost no traditional evidence base to support them. Yet these types of services are some of the most requested and most needed. Providers and policy makers must therefore make decisions in the absence of evidence. Local resources, advocacy, and creativity about existing funding streams all may affect what services get funded, by whom, and for whom.

These differences in policies, resources and organization result in marked differences in the prevalence of ASD across geographic areas, the types of services and support that are received, availability of appropriate lifespan

transition opportunities, and the associated costs (Fujiura, Roccoforte, & Braddock, 1994; Ganz, 2007; Järbrink, Fombonne, & Knapp, 2003; Mandell et al., 2008; Ruble et al, 2005; Stahmer & Mandell, 2007). In general, children with ASD have a much more difficult time accessing appropriate services than children with other special healthcare needs (Krauss et al., 2003). Data are still lacking on how these differences in policy and infrastructure relate to the differences in services used, and in turn how these differences affect outcomes for children and families, and adults with ASD.

What do we need?

People with ASD and their families need assistance navigating complex service systems to find the most appropriate services and supports. Providers and people with ASD and their families need help choosing and implementing evidence-based services that are effective and sustainable. Policy makers and payers for services, including private insurers and school districts, need assistance creating organizational structures and financial incentives so that high-quality interventions are institutionalized. Equally important, services researchers and community organizations must collaborate to quickly and efficiently develop much-needed services and supports for underserved groups among people with ASD, and to test widely-used, safe, and promising services that may not have much evidence to support them.

Strategies to educate people with ASD and their families about the best ways to obtain appropriate services and supports should be developed and tested. Methods for simplifying the process by which people access services also are needed, with a focus on improving collaboration across the many agencies that provide services to people with ASD. This is especially important for traditionally underserved groups whose members often are diagnosed late (or not at all), and who are even more likely than other people with ASD to receive inappropriate or inadequate services.

An initial part of this process is the assessment of needs and costs. Services for developmental disorders are financed largely by federal, state and local agencies in both the healthcare and education sectors. Because there are significant regional differences in ASD resources, describing this varied landscape across states and localities in the U.S. will provide important baseline data for those with ASD and policymakers so they can appropriately seek and plan for services respectively. Research can also define the cost-effectiveness of evidence-based practices and thereby provide the data needed by various payers and policymakers.

Observational studies of current practice can play an important role in understanding how best to address questions surrounding services and supports. They can identify malleable barriers and appropriate points of intervention, and provide a baseline against which to measure future progress. Because service systems vary greatly from place to place, these types of studies also can take advantage of the natural experiments that occur as systems struggle to respond to the needs of people with ASD.

Experimental studies are more difficult to design and conduct in this area of science than they are for traditional intervention trials, and yet are key to understanding the best ways to improve community services. Designs such as those used in comparative effectiveness research, where both groups receive intervention (rather than having a "treatment as usual" control), will be critically important to satisfy ethical and practical concerns. Because the unit of analysis for many of these studies is the provider or system, rather than the person with ASD, large-scale network studies and quasi-experimental designs will also yield information.

Families, people with ASD, and communities can be empowered to become partners in research that can in turn inform policy. Research must include services that are built upon principles of self-direction and self-determination, and emphasize quality of life across the ASD spectrum. All people with ASD, their families, and support systems should have the services and supports they need and desire throughout the lifespan to lead productive lives in the community, and to reach their fullest potential.

2011 Addendum to Question 5: Where can I Turn For Services

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

Recent legislative initiatives, including the Affordable Care Act, passed by the Congress in 2010, support research and state and Federal programs that will positively impact health and quality of life for people with ASD. These include expanded opportunities in 2014 for individuals at 133% of the Federal poverty line to access health care; increased attention to health and medical home care coordination; expanded Health Information Technology; a national quality improvement strategy that will develop and refine quality measures; the expansion of Medicaid options to provide home and community-based services (HCBS) through several new venues, including "targeting" to people who do not meet traditional institutional level of care program requirements, and Community First Choice services; the extension of the Centers for Medicare & Medicaid Services' (CMS) Money Follows the Person Rebalancing Demonstration Program; the CLASS Act; increased opportunities surrounding the removal of barriers to providing HCBS; incentives to offer HCBS as an alternative to nursing homes; a new focus on improved coordination for individuals eligible for both the Medicare and Medicaid programs through the Federal Coordinated Health Care Office; and establishment of the Center for Medicare and Medicaid Innovation (Innovation Center Web site).

The Mental Health Parity and Addiction Equity Act of 2008 (MHPAEA), went into effect in 2010. Details of how parity will be implemented are still being resolved, but the concept of comparable coverage for mental health and substance use disorder benefits and physical health services has broad implications for children and adults with ASD. An interim final rule was published in February 2010 by the Departments of Labor and Treasury and HHS (Federal Register, 2010).

Several recent articles focused on oral health issues, highlighting a need to further investigate the impact of dental

treatment on people with ASD throughout the life course. Oral disease is a major health challenge for people with developmental disabilities including ASD (Altun et al., 2010a,b; Loo, Graham, & Hughes, 2009). In 2010 and 2011, many State Medicaid programs that support adults with ASD have or will substantially reduce optional adult dental care services (Smith, Gifford, & Ellis, 2010).

A 2010 Swedish study examining risk factors and causes of death in a cohort of 120 people with ASD found that co-occurring disorders (including Sudden Unexplained Death in Epilepsy), accidents, and deaths occurred at a rate 5.6 times higher than that of the general population (Gillberg et al., 2010). In addition, information was presented in 2010 to the IACC regarding wandering incidents, some that resulted in death (Presentation to the IACC on Wandering and ASD, 2010). In response, the IACC formed a Safety Subcommittee to gather information and take appropriate actions to address wandering and other important safety issues that impact the autism community.

What gap areas have emerged since last year?

Access to quality and affordable oral health care services continue to be a challenge for children, youth, and adults with ASD (Government Accountability Office, 2010). In addition, access to psychiatric expertise specific to intellectual and developmental disabilities (ID/DD) and ASD in state mental health systems is poor, overall capacity is lacking, and issues of seclusion and restraint persist (Barry, Huskamp, & Goldman, 2010; Munir, 2009; Prouty et al., 2008). There is greater need during a time when disabled family members are remaining at home longer to coordinate community resources, including mental health services.

***ASPIRATIONAL GOAL*: COMMUNITIES WILL ACCESS AND IMPLEMENT NECESSARY HIGH QUALITY, EVIDENCE-BASED SERVICES AND SUPPORTS THAT MAXIMIZE QUALITY OF LIFE AND HEALTH ACROSS THE LIFESPAN FOR *ALL* PEOPLE WITH ASD.**

Research Opportunities

- Development and effective dissemination of evidence-based community practices for people with ASD across the spectrum and lifespan.
- Comparative effectiveness studies of services and supports for people with ASD across the spectrum and lifespan.
- Studies that characterize current ASD diagnostic and service utilization patterns in community settings, examine the relationship between the likelihood of a diagnosis and services availability for ASD, and evaluate services and intervention outcomes across the spectrum and lifespan.
- Development of a coordinated, integrated, and comprehensive community-based service delivery system for people with ASD.

Short-Term Objectives

A. Support two studies that assess how variations in and access to services affect family functioning in diverse populations, including underserved populations, by 2012. *IACC Recommended Budget: $1,000,000 over 3 years.*

B. (2010) Conduct one study to examine how self-directed community-based services and supports impact children, youth, and adults with ASD across the spectrum by 2014. *IACC Recommended Budget: $6,000,000 over 3 years.*

C. (2010 – revised in 2011) Implement and evaluate five models of policy and practice-level coordination among state and local agencies to provide integrated and comprehensive community-based supports and services that enhance access to services and supports, self-determination, economic self-sufficiency, and quality of life for people with ASD across the spectrum and their families, (which may include access to Augmentative and Alternative Communication (AAC) technology), with at least one project aimed at the needs of transitioning youth and at least one study to evaluate a model of policy and practice-level coordination among state and local mental health agencies serving people with ASD, by 2015. **IACC Recommended Budget: $25,000,000 over 5 years. (Provided by NIH)**

D. (2011) Support two studies to examine health, safety, and mortality issues for people with ASD by 2012. **IACC Recommended Budget: $4,500,000 over 3 years. (Provided by CDC)**

Long-Term Objectives

A. Test four methods to improve dissemination, implementation, and sustainability of evidence-based interventions, services, and supports in diverse community settings by 2013. *IACC Recommended Budget: $7,000,000 over 5 years.*

B. Test the efficacy and cost-effectiveness of at least four evidence-based services and supports for people with ASD across the spectrum and of all ages living in community settings by 2015. *IACC Recommended Budget: $16,700,000 over 5 years.*

C. (2010) Evaluate new and existing pre-service and in-service training to increase skill levels in service providers, including direct support workers, parents and legal guardians, education staff, and public service workers to benefit the spectrum of people with ASD and promote interdisciplinary practice by 2015. *IACC Recommended Budget: $8,000,000 over 5 years.*

D. (2011) Evaluate at least two strategies or programs to increase the health and safety of people with ASD that simultaneously consider principles of self-determination and personal autonomy, by 2015. **Budget to be determined.**

NOTE: HRSA was unable to provide a budget estimate because they are not currently conducting any activities related to safety/wandering behaviors. They recommended consulting CMS or ADD.

E. (2011) Support three studies of dental health issues for people with ASD by 2015. This should include:

- At least one study on the cost-benefit of providing comprehensive dental services, including routine, non-emergency medical and surgical dental services, denture coverage, and sedation dentistry to ~~adults~~ youth with ASD as compared to emergency and/or no treatment. **IACC Recommended Budget: $900,000 over 3 years. (Provided by HRSA)**

- At least one study focusing on the provision of accessible, person-centered, equitable, effective, safe, and efficient dental services to people, including children and youth, with ASD. **IACC Recommended Budget: $900,000 over 3 years (or $100,000 over 1 year if conducted as secondary data analysis). (Provided by HRSA)**

- Evaluating at least one new and existing pre-service and in-service training program to increase skill levels in oral health professionals to benefit people with ASD and promote interdisciplinary practice. **IACC Recommended Budget: $900,000 over 3 years. (Provided by HRSA)**

NOTE: HRSA's authority under the Combating Autism Act is limited to the child and young adult population so they have edited two portions of the objective above to focus on children and youth with ASD. If adults are the intended population for some of these studies, consultation with another agency will be required to obtain budget estimates.

6. WHAT DOES THE FUTURE HOLD, PARTICULARLY FOR ADULTS?

- **What will my family member be like when he/she gets older?**
- **What is known about adults with ASD and how can I plan for the future?**
- **How does American society support people with ASD?**

What do we know?

An overarching goal of ASD research is to enable people with ASD to lead fulfilling and productive lives in the community. We are in critical need of information about the current landscape of long-term outcomes for all people with ASD across the spectrum. The lack of knowledge about adults with ASD and their lifetime support needs has repeatedly arisen as a critical issue when stakeholders are queried about their most fundamental concerns. Longitudinal studies designed to capture the range of possible outcomes for people with ASD are best suited to inform public policy decision-making, service and support delivery, and funding strategies. It is also important to improve public understanding of ASD in adults, including older adults, so that they may receive support from the communities where they live. Efforts to improve public awareness and community supports help foster acceptance, inclusion, and appreciation of people with ASD.

ASD poses economic and social costs for people with ASD, their families, and society at large. Although ASD symptoms vary greatly in character and severity, autism occurs in all ethnic and socioeconomic groups and affects every age group. Some scientists and economists have estimated that the combined direct and indirect costs to provide lifelong supports for all Americans with ASD exceeds $35 billion, and that each person accrues approximately $3 million in costs over his or her lifetime (Ganz, 2007). Families often report incurring large debts related to medical and educational services not covered through public programs or medical and dental insurance. Many families find the transition from the education system, where services are mostly obligatory, to the developmental disabilities and vocational systems, where services are optional, difficult to understand and manage. This fragmentation of service systems impedes access to services, especially for youth transitioning to adulthood, as well as during other periods of transition. In addition to financial challenges, ASD can lead to emotional hardships for people with ASD and their families throughout life.

What do we need?

Although considerable research has focused on the earliest phase of ASD, through early screening, improved diagnostics and early intervention, far less effort has addressed the adolescent, adult, and older adult phases of life. Minimal guidance exists for people with ASD across the spectrum and their families about the trajectories of ASD across the lifespan. Although the general assumption is that children who possess expressive and receptive language skills and coping strategies and who do not demonstrate significant challenging behaviors can sometimes excel as adults, while children who do not currently

possess typical expressive language skills and who engage in significant challenging behavior will grow up to need long-term, 24/7 supports and services, the evidence base for these ideas is lacking. Scientists have not yet identified key prognostic factors or detailed information about how adults across the spectrum with ASD function, where they are, and how they are best supported.

More research is needed to tailor treatments, interventions, and services and supports to the evolving needs of adolescents transitioning to adulthood, and adults across the spectrum with ASD, with an emphasis on principles of self-determination. There is a need to address co-occurring conditions and developmental changes that coincide with transitions such as adolescence to adulthood, to better assess functional outcomes, and to integrate standardized quality of life measures for adults across the spectrum with ASD living in community settings. Factors that contribute to improved quality of life and health outcomes in adulthood are virtually unknown.

A number of other areas raise serious concerns. There is little information about the number of adults with ASD within the criminal justice system. Some adults with ASD may not be diagnosed, or may have been misdiagnosed. Although issues surrounding the direct support workforce are well documented, we do not know if they differ respective to adults with ASD. Community integration and access to individualized, quality adult supports and services are problematic across the United States, and long waiting lists for subsidized community-based services persist. Many services are available only to people who meet institutional level of care requirements. Additionally, there is scant research on the use and safety of psychopharmaceutical medications in adults with ASD.

2011 Addendum to Question 6: What Does The Future Hold, Particularly For Adults?

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

The continuing lack of research on youth and adults diagnosed with ASD (as well as those that go undiagnosed), public comment received by the IACC in 2010, and the *2008 and 2009 IACC ASD Research Portfolio Analysis* reports continue to highlight the urgent need for additional scientific research specific to this group. In 2010, several national advocacy organizations devoted private resources to initiatives on adult services that have been brought to the IACC's attention.

In September 2010, Health and Human Services (HHS) announced a joint grant program administered by the Centers for Medicare & Medicaid Services (CMS) and the Administration on Aging, in part to expand the Aging and Disability Research Centers to better assist people with disabilities, older adults, and their caregivers (HHS Press Release, 2010). As greater numbers of adults with disabilities including ASD access the strengthened infrastructure, more research is needed regarding their support needs. To help define a national research agenda on autism and aging, a privately –funded conference, "Autism and Aging," was held in March 2010 that brought experts in the field together to discuss what is currently known on the subject and what future research is

needed. Participants identified several priority areas including the development of diagnostic criteria and instruments for diagnosing and assessing the needs of older adults with ASD. They also cited the need for descriptive studies that examine the symptoms and behaviors, neuropsychiatric features, and related medical conditions in the population, as well as the progression of these characteristics over time (Piven et al., 2010).

Several articles related to transitioning from entitlement-based education services to the adult services system and higher education were published in 2010 (Chappel et al., 2010; McDonough et al., 2010; Schall et al., 2010, Wehmeyer et al., 2010). These indicated that early collaboration between services system partners greatly increased access to adult services and employment. A small survey of Japanese adults with ASD who did not have intellectual disability suggested that higher levels of education increased the likelihood of obtaining employment, but that education did not improve the likelihood that the job would be retained. (Yokotani, 2010). A study from the United States indicated that the transition from high school may actually have the most negative impact on individuals with higher cognitive levels, who are more likely to lose services (Taylor et al., 2010a,b).

In July 2010, President Obama indicated the Administration's commitment to expand disability employment in the Federal workforce, emphasizing the need for additional research in the area of ASD employment across the spectrum.

In other new research, recent studies examining the role of behaviors and co-occurring conditions in adults with ASD indicated that many people with ASD, especially those with intellectual and developmental disabilities (ID/DD), have ongoing deficits related to independence and quality of life (Chowdhury et al., 2010; Cohen et al, 2010; Esbensen et al., 2010a; Hodge et al., 2010; Smith et al., 2010a)

A 2010 article on the prevalence of ASD in Iceland also indicated that ASD may be about 50% underdiagnosed in adults, especially in people who have ID as their primary diagnosis (Saemundsen et al., 2010). This finding is consistent with recent state data specific to ASD from the National Core Indicators Project, sponsored by the National Association of State Directors of Developmental Disabilities Services (NASDDS) (National Core Indicators Project Web site, 2010).

Finally, an environmental scan of interventions for people with ASD, sponsored by the Centers for Medicare & Medicaid Services, examined interventions for adults with ASD and found effectiveness for only nine interventions for adults (Young et al.). Only a third of the interventions evaluated rated as "evidence-based." The report also highlighted the need for further research on effective community-based services for adults. For example, adults with ASD commonly attend "day programs," but no formal research exists on the practice.

What gap areas have emerged since last year?

Although some minimal improvement is predicted for state budgets in 2011, state and local governments are anticipated to face continuing fiscal constraints

(National Governors Association & National Association of State Budget Officers). Budget cuts, somewhat mitigated by ongoing Federal financial assistance, have resulted in fewer optional services in programs including Medicaid, that provide many poor adults who have ASD with acute care, home and community-based services, and other supports (Johnson, Oliff, & Williams, 2010).

There is little research specific to older adults with autism and their caregivers, although some research from the University Centers of Excellence in Developmental Disabilities (UCEDD) program, supported by the Administration on Developmental Disabilities (ADD)/Administration for Children and Families (ACF), is directed at cross-disability aging issues (Association of University Centers on Disabilities, 2010). Although some research is focused on adults on the ASD spectrum and their families, more is needed, including greater utilization of the Participatory Action Research (PAR) and Community-Based Participatory Research (CBPR) models (Viswanathan et al., 2004). The Administration on Developmental Disabilities (ADD) supported development of a PAR Toolkit, which could serve as a potential resource (Oregon Health & Science University - PAR Toolkit).

***ASPIRATIONAL GOAL*: ALL PEOPLE WITH ASD WILL HAVE THE OPPORTUNITY TO LEAD SELF-DETERMINED LIVES IN THE COMMUNITY OF THEIR CHOICE THROUGH SCHOOL, WORK, COMMUNITY PARTICIPATION, MEANINGFUL RELATIONSHIPS, AND ACCESS TO NECESSARY AND INDIVIDUALIZED SERVICES AND SUPPORTS.**

Research Opportunities

- Studies of the scope and impact of the spectrum of ASD in adults, including diagnosis of ASD in adulthood, needs during critical life transitions, and quality of life.
- Longitudinal studies that follow carefully characterized cohorts of the broad spectrum of adults with ASD and their families into adulthood in order to better understand their needs during critical life transitions, and to identify and track risk and protective factors that account for improved quality of life and health outcomes.
- Projects that increase coordination across State and local delivery systems to improve access to services and supports, particularly those that focus on transitioning youth and adults with ASD.
- Improved understanding of the challenges associated with accessing community housing for people with ASD.
- It is important to include people with ASD and their families in the

scientific research process. The use of models such as Participatory Action Research (PAR) and Community-Based Participatory Research (CBPR) will facilitate full participation by people with disabilities and their family members in the planning, implementation, and evaluation of research. (*Added 2011*)

Short-Term Objectives

A. (2010) Launch at least two studies to assess and characterize variation in the quality of life for adults on the ASD spectrum as it relates to characteristics of the service delivery system (e.g., safety, integrated employment, post-secondary educational opportunities, community inclusion, self-determination, relationships, and access to health services and community-based services) and determine best practices by 2012. *IACC Recommended Budget: $5,000,000 over 3 years.*

B. (2010) Evaluate at least one model, at the state and local level, in which existing programs to assist people with disabilities (e.g., Social Security Administration, Rehabilitation Services Administration) meet the needs of transitioning youth and adults with ASD by 2013. *IACC Recommended Budget: $5,000,000 over 3 years.*

C. (2010) Develop one method to identify adults across the ASD spectrum who may not be diagnosed, or are misdiagnosed, to support service linkage, better understand prevalence, track outcomes, with consideration of ethical issues (insurance, employment, stigma) by 2015. *IACC Recommended Budget: $8,400,000 over 5 years.*

D. (2010) Conduct at least one study to measure and improve the quality of life-long supports being delivered in community settings to adults across the spectrum with ASD through provision of specialized training for direct care staff, parents, and legal guardians, including assessment and development of ASD-specific training, if necessary, by 2015. *IACC Recommended Budget: $7,500,000 over 5 years.*

Long-Term Objectives

A. (2010) Develop at least two individualized community-based interventions that improve quality of life or health outcomes for the spectrum of adults with ASD by 2015. *IACC Recommended Budget: $12,900,000 over 5 year*

B. (2010) Conduct one study that builds on carefully characterized cohorts of children and youth with ASD to determine how interventions, services, and supports delivered during childhood impact adult health and quality of life outcomes by 2015. *IACC Recommended Budget: $5,000,000 over 5 years.*

C. (2010 – revised in 2011) Conduct comparative effectiveness research that includes a cost-effectiveness component to examine community-based interventions, services and supports to improve health outcomes and quality of life for adults on the ASD spectrum over age 21 by 2018. Topics should include:

- Community housing for people with ASD
- Successful life transitions for people with ASD, including from post-secondary education to adult services, employment, sibling relationships, and day programs

- Meeting the service and support needs of older adults with ASD.

IACC Recommended Budget: $6,000,000 over 5 years. **Budget to be determined.**

NOTE: HRSA was unable to provide a budget estimate for this objective and noted that because their authority is limited to children and youth with ASD, any studies on adults would have to be carried out in partnership with an appropriate agency.

D. (2010) Conduct implementation research to test the results from comparative effectiveness research in real-world settings including a cost-effectiveness component to improve health outcomes and quality of life for adults on the ASD spectrum over age 21 by 2023. IACC Recommended Budget: $4,000,000 over 5 years.

7. WHAT OTHER INFRASTRUCTURE AND SURVEILLANCE NEEDS MUST BE MET?

- **What infrastructure systems need to be supported, strengthened, or built to support this plan?**
- **How can we ensure that resources and data are shared to support the scientific research process?**
- **How can we ensure that findings are communicated to the public in a responsible and timely manner?**
- **How can we improve autism surveillance efforts?**

What do we know and what do we need?

Current infrastructure may be insufficient to adequately support the research programs outlined in this plan. Additional investment in infrastructure is necessary to collect and share data among researchers, to encourage and enable individuals with ASD and their families to participate in research, and to improve the speed with which findings are disseminated and the extent to which findings are translated into practice and policy.

Data Sharing:

In 2006, the National Institutes of Health (NIH) launched the National Database for Autism Research (NDAR) to improve sample sizes and enable researchers to share data for increased analyses. The NIH-supported national Autism Centers of Excellence (ACE), as well as the grants funded under the "Research to Address the Heterogeneity in Autism Spectrum Disorders" Request for Applications as part of the American Recovery and Reinvestment Act (ARRA), receive funding contingent upon acceptable plans and means for data sharing. Incentives are needed, however, to encourage data submission by other researchers. It will also be necessary to link other significant ASD databases with NDAR. In addition, databases that collect information and coordinate recruitment of people with ASD and their families to participate in research studies need to be enhanced and expanded. Programs to support contribution of data for recruitment, healthcare, education, social services and administrative databases, like the Interactive Autism Network (IAN), collaboratively supported at the Kennedy Krieger Institute by Autism Speaks, the Simons Foundation and NIH, should be encouraged. Collecting information about people with ASD will facilitate the study of whether early diagnosis, entry to services and type of intervention affects the course of ASD over time. Multiple data sources from existing research or service systems (e.g., education, Medicaid, etc.) currently operate in isolation. Compiling and sharing data from existing data sources need to address data standardization as well as important privacy and ethical issues. Methods for merging such databases and linking investigator-recruited samples to these merged databases have been used in other populations and in specific locales with success and need to be further developed.

Biobanking:

Many in the field have highlighted the need to establish nationally coordinated

strategies for the collection and preservation of post-mortem tissue from both people with and without ASD. The existing brain and tissue bank resources must be expanded to meet the high and continuously increasing demand for post-mortem tissue by scientific investigators. More well-preserved brains are needed from people at various stages of development and particularly from those with few co-occurring disorders. Additional matched controls are needed, as well, to supplement the limited supply in existing repositories.

In addition, it will be necessary to develop methods, standards and protocols for collecting and storing other biological specimens such as blood and urine which might be used to study biological differences or signatures, and skin fibroblasts for creation of pluripotent stem cells.

Surveillance:

Autism surveillance provides important estimates on the numbers of children affected with ASD and helps describe the characteristics of the people with autism spectrum disorders in the general population. Surveillance must be sustained over a period of many years in order to track trends in prevalence estimates over time, and is an essential building block for population-based research — providing clues about potential risk factors that warrant further study. Surveillance provides important data regarding early identification of children with autism, and informs education and health systems regarding areas in which programs can be modified in order to improve early identification and intervention. Surveillance data also provide critically important information for communities to use when planning for services.

In 2007, CDC's Autism and Developmental Disabilities Monitoring (ADDM) Network published the first and most comprehensive summary of autism prevalence estimates in the United States (CDC, 2007). These data showed that between 1 in 100 to 1 in 300 (with an average of 1 in 150 children) were identified with ASD. In October 2009, investigators from HRSA and CDC reported that ASD occurs in an estimated 1.1% of children 3 to 17 years, based on parent-report during the National Survey of Children's Health (NSCH), sponsored by HRSA (Kogan et al., 2009). Updated estimates from CDC's ADDM Network, published in December 2009, confirmed that approximately 1% of children were identified with an ASD (between 1 in 80 to 1 in 240 children with an average of 1 in 110) (CDC, 2009). There was an increase of 57% in identified ASD prevalence from 2002 to 2006 in multiple areas of the US. While these data provide important information for service planning, and begin to help us understand that the increases are not fully accounted for by improved identification, many questions related to the multiple causes of ASD increases remain.

There are a number of areas in which prevalence studies could be improved, including the continued estimation and evaluation of prevalence in the same population over time; assessment of ASD prevalence in the context of other neurodevelopmental disorders; further analyses of existing datasets to examine the multiple identification and potential risk factors as they vary by prevalence; collection of data beyond core ASD symptoms, including genetic data and co-

occurring medical, dental, and behavioral conditions; and expansion of studies across ages. Supporting international autism surveillance activities, prevalence estimates, and epidemiologic research will also be important, in order to compare prevalence estimates and epidemiologic characteristics across countries.

Communication and Dissemination:

Research data regarding autism is now being published at a rapid rate. It is critical that new findings are communicated promptly and appropriately to the public so that research findings can be better translated into practice as appropriate. Effective translation is important so that new findings can be utilized to improve risk assessment and implementation of individualized interventions to reduce the disabling symptoms and promote a positive developmental trajectory as early as possible. Additional attention needs to be paid to improving the communication channels between scientists, practitioners, people with ASD and their families.

There is also need to build a system for rapid replication of studies concerning key findings. In addition, there is still not agreement about meaningful subtypes or about how to individualize treatment. As more professionals become involved in autism research, there is a need for organized input from established scientists to provide guidance and expertise.

In addition, it will be necessary to identify and address the wide range of ethical and clinical issues related to the diagnosis, assessment, and communication of genetic, environmental, and clinical risk for autism.

Research Workforce Development:

In order to accomplish the necessary research in the field of autism, it will also be important to develop an adequate scientific workforce. While much autism research is already underway, there are several areas of research that are new and growing, including interdisciplinary research, where additional researchers will be needed in the coming years. The continued expansion and development of this research workforce will be essential to fulfilling the goals laid out in the IACC Strategic Plan.

2011 Addendum to Question 7: 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), collaboratively supported by NIH, Autism Speaks and the Simons Foundation, was launched 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: the Autism Genetic Resource Exchange (AGRE), supported by Autism Speaks; the Interactive Autism Network (IAN) at the Kennedy Krieger Institute supported by NIH, Autism Speaks and the Simons Foundation; the Simons Foundation; Prometheus Research, supported by the Simons Foundation Autism Research Initiative (SFARI); and the National Database for Autism Research (NDAR), supported by NIH. The AIC held its first workshop on August 26-27, 2010 at the National Institute of Mental Health (NIMH)/NIH 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 NDAR. 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 allows 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.

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)

The Autism Genome Project (AGP), a collaborative effort between Autism Speaks and several other international partners including, the Health Research Board of Ireland, Genome Canada, the United Kingdom's Medical Research Council (MRC) and the Hillibrand Foundation, 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 (individuals who are the first member within their family identified as having an ASD).

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/NIH 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 about 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 CDC's ADDM Network (CDC, 2009) and a report from the HRSA-sponsored 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 & Delwiche, 2009; Saemundsen, 2010; King & 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 (Young et al., 2010; Lang et al., 2010) and several states have formed task forces or councils for ASD and other developmental disability (DD) services and have compiled service plans based on the current state of knowledge (Summary of the Massachusetts Act Early State Team Autism Summit).

In October of 2010 the Administration on Developmental Disabilities (ADD)/Administration for Children and Families (ACF) awarded The Arc of the United States $1.87 million for fiscal year 2010 to establish a National Resource and Information Center on Autism Spectrum Disorder (ASD) and other developmental disabilities. The AutismNOW Project is collaborating with several partners, including the Autistic Self Advocacy Network (ASAN), the Autism Society and several ADD Network entities to engage and leverage a national network of disability, aging, and family organizations. The Center will provide high-quality resources and information related to community-based services that support independent living and self-

determination, treatment protocols that promote community-based experiences (e.g. education, employment, recreation, transportation, early intervention and child care), and evidence-based interventions. The intended audience for the Center includes people with ASD, family members, service providers, researchers, and the general public. The Center will also host a parent-to-parent call-in center for families addressing issues relating to autism and other developmental disabilities. More information about the Center can be found at http://www.autismNOW.org.

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 (ARRA). Private research organizations such as Autism Speaks and the Autism Science Foundation also supported several research training awards in 2009 and 2010.

What gap areas have emerged since last year?

Data sharing

The Autism Informatics Consortium (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 globally unique identifier (GUID) usage, procedures for maintaining phenotype resources with associated biospecimens (i.e., imaging and genetics), 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 for high-throughput screening tools to quickly evaluate gene-environment interactions relevant to ASD (e.g., induced pluripotent stem cells). 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 CDC's 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 (i.e., Governor's councils, task forces and the Department of Education) 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.

Focusing more on the issue of translating research into practice, the IACC Services 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, including efforts to include people with disabilities and in particular individuals with ASD. Funds from the American Recovery and Reinvestment Act (ARRA) increased investments in ASD research, which contributed to recent expansion of the research workforce (particularly the numbers of graduate students and post-doctoral students working in the field). With ARRA funding ending in 2011 and the potentially constrained fiscal climate anticipated for FY 2011 and FY2012, there is growing concern about the ability for both federal and private entities to support recent gains in the research workforce.

ASPIRATIONAL GOAL: DEVELOP AND SUPPORT INFRASTRUCTURE AND SURVEILLANCE SYSTEMS THAT ADVANCE THE SPEED, EFFICACY AND DISSEMINATION OF AUTISM RESEARCH.

Short-Term and Long-Term Objectives

A. Conduct a needs assessment to determine how to merge or link administrative and/or surveillance databases that allow for tracking the involvement of people living with ASD in healthcare, education and social services by 2009*. IACC Recommended Budget: $520,000 over 1 year.*

B. (revised in 2011) 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.*

C. Develop and have available to the research community means by which to merge or link databases that allow for tracking the involvement of people in ASD research by 2010. *IACC Recommended Budget: $1,300,000 over 2 years.*

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. *(Revised 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: $82,700,000 over 5 years. (Formerly $32,700,000) **(Provided by NIH)**

Note from NIH Program staff: To accomplish the three bullets, including the new task of developing a web-based digital brain atlas, would require an additional $10 M per year for 5 years or $50 M Total Costs. This would be for about 50 subjects, which is minimal for a population as heterogeneous as ASD.

E. (2010) Begin development of a web-based toolbox to assist researchers in effectively and responsibly disseminating their finding to the community, including people with ASD, their families, and health practitioners by 2011. *IACC Recommended Budget: $400,000 over 2 years.*

F. (2010) Create funding mechanisms that encourage rapid replication studies of novel or critical findings by 2011.

G. (2010) Develop a web-based tool which provides population estimates of ASD prevalence for states based on the most recent prevalence range and average identified by the ADDM Network by 2012. *IACC Budget Recommendations: $200,000 over 2 years.*

H. (2010) Create mechanisms to specifically support the contribution of data from 90% of newly initiated projects to the National Database for Autism Research (NDAR) and link NDAR with other existing data resources by 2012. *IACC Recommended Budget: $6,800,000 over 2 years.*

I. (2010) Supplement existing ADDM Network sites to use population-based surveillance data to conduct at least 5 hypothesis-driven analyses evaluating factors that may contribute to changes in ASD prevalence by 2012. *IACC Recommended Budget: $660,000 over 2 years.*

J. (2010) Develop the personnel and technical infrastructure to assist states, territories, and other countries who request assistance describing and investigating potential changes in the prevalence of ASD and other developmental disabilities by 2013. *IACC Recommended Budget: $1,650,000 over 3 years.*

K. (2010) Encourage 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.*

L. (2010 – revised 2011) Expand the number of ADDM sites in order to conduct ASD surveillance in children and adults; conduct complementary direct screening to inform completeness of ongoing surveillance; and expand efforts to include autism subtypes by 2015. *IACC Recommended Budget: $16,200,000 over 5 years.*

M. (2010) Support 10 "Promising Practices" papers that describe innovative and successful services and supports being implemented in communities that benefit the full spectrum of people with ASD, which can be replicated in other communities by 2015. *IACC Recommended Budget: $75,000 over 5 years.*

N. (2011) Enhance networks 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. **IACC Recommended Budget: $1,850,000 over 1 year. (Provided by Autism Speaks)**

O. (2011) 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, by 2013.

- 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.

IACC Recommended Budget: $2,000,000 over 2 years. (Provided by NIH)

P. (2011) 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. **IACC Recommended Budget: $1,100,000 over 2 years. (Provided by NIH)**

Research Resources

Below is a list of currently available resources for conducting ASD research. It includes government and non-government resources spanning topics such as genetics, bioinformatics, brain and tissue samples, and animal resources, as well as resources related to surveillance, prevalence, and services.

Government Resources

Autism and Developmental Disabilities Monitoring (ADDM) Network

www.cdc.gov/ncbddd/autism/addm.html

A surveillance network that provides data about ASD prevalence and describes the population of children with ASD. Supported by CDC.

Autism Now: The National Autism Resource and Information Center

www.autismNOW.org

A center that provides access to resources and information on community-based services and interventions for people with ASD and their families, through a national dissemination network, regional events, training and technical assistance, and the web. Supported by the Administration on Developmental Disabilities/Administration for Children and Families.

Centers for Autism and Developmental Disabilities Research and Epidemiology (CADDRE)

www.cdc.gov/ncbddd/autism/caddre.html

Regional centers of excellence for ASD and other developmental disabilities which are currently conducting the largest U.S. study of ASD risk factors. Supported by CDC.

National Children's Study

www.nationalchildrensstudy.gov

A population-based study of environmental influences on child health and development that could be used to investigate the relationship between genetic and environmental risk markers and ASD diagnosis. Supported by NIH.

NDAR (National Database for Autism Research)

ndar.nih.gov

A secure bioinformatics platform for scientific collaboration and data-sharing between ASD investigators. Supported by NIH.

NDAR Data Definition

http://ndar.nih.gov/ndarpublicweb/standards.go

Provides data definitions of ASD research terminology. Supported by NIH.

NICHD Brain and Tissue Bank

http://medschool.umaryland.edu/BTBank

A brain tissue repository to support and enhance the acquisition and distribution of tissue samples from deceased individuals diagnosed with intellectual and developmental disabilities for use in research studies. Supported by NIH.

NIF (Neuroscience Information Framework)

http://nif.nih.gov

NeuroLex is a dynamic lexicon to improve communication among neuroscientists about their data. Supported by NIH.

NIH Pediatric MRI Data Repository

http://nih-pediatricmri.org

A multi-site longitudinal study used technologies (anatomical MRI, diffusion tensor imaging [DTI], and MR spectroscopy [MRS]) to map pediatric brain development. Supported by NIH.

NIMH Center for Collaborative Genetic Studies of Mental Disorders

http://nimhgenetics.org

A repository of biospecimens from individuals with mental illnesses such as schizophrenia, bipolar disorder, autism spectrum disorders, depression, and obsessive compulsive disorders. Supported by NIH.

NIMH Transcriptional Atlas of Human Brain Development

www.developinghumanbrain.org

A foundational resource created using funds from the American Recovery and Reinvestment Act (ARRA) for studying transcriptional mechanisms involved in human brain development. Supported by NIH.

NITRC (Neuroimaging Informatics Tools and Resources Clearinghouse)

www.nitrc.org

A neuroimaging tools repository, NITRC facilitates finding and comparing neuroimaging resources for functional and structural neuroimaging analyses. Supported by NIH.

Non-Human Primate Atlas of Gene Expression through Development

www.blueprintnhpatlas.org/nhp

An atlas mapping the expression of particular genes to specific neuroanatomical locations across several timepoints in development in the rhesus monkey. Supported by NIH.

Non-Government Resources

AGRE (Autism Genetic Resource Exchange)

www.agre.org

A repository for biomaterials and associated phenotype and genotype information from over 1,000 individuals with an ASD diagnosis and their families. Supported by Autism Speaks.

Autism Genome Project

www.autismspeaks.org/science/research/initiatives/autism_genome_project.php

A study to find the genes associated with inherited risk for autism. Supported by Autism Speaks and other partners, including the Health Research Board of Ireland, Genome Canada, the United Kingdom's Medical Research Council (MRC) and the Hillibrand Foundation.

Autism Tissue Program

www.brainbank.org

An ASD brain tissue repository. Supported by Autism Speaks.

Autism Treatment Network

www.autismspeaks.org/science/programs/atn

A network of hospitals and physicians dedicated to developing a model of comprehensive medical care for children and adolescents with autism. A program of Autism Speaks funded in part through grants from HRSA and NIH.

Baby Siblings Research Consortium

www.autismspeaks.org/science/research/initiatives/babysibs.php

A consortium studying the infant siblings of children with ASD in order to identify early behavioral and biomedical markers of the disorder. Supported by Autism Speaks and NIH.

IAN (Interactive Autism Network)

www.ianproject.org

An online registry of over 35,000 people who have or are related to those with ASD. Collaboratively supported at the Kennedy Krieger Institute by Autism Speaks, the Simons Foundation and NIH.

ISAAC (Internet System for Assessing Autistic Children)

www.autismtools.org/index.cfm

A web-based application for administering and managing health research projects/studies and the associated data. Supported by Autism Speaks.

REDCap(Research Electronic Data Capture)

http://project-redcap.org

Two secure, web-based applications (REDCap and REDCap Survey) designed to support data capture for research studies. Maintained by the REDCap Consortium, comprised of 194 active institutional partners.

Simons Simplex Collection

https://sfari.org/simons-simplex-collection

A repository of genetic samples and phenotypic data from families where parents without ASD give birth to a child with the disorder. Supported by the Simons Foundation Autism Research Initiative (SFARI).

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