The Interagency Autism Coordinating Committee

STRATEGIC PLAN 2012 UPDATE

for Autism Spectrum Disorder Research

IACC
INTERAGENCY AUTISM COORDINATING COMMITTEE

OFFICE OF AUTISM RESEARCH COORDINATION
NATIONAL INSTITUTES OF HEALTH

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December 2012

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ABOUT THE IACC

The Interagency Autism Coordinating Committee (IACC) is a Federal advisory committee charged with coordinating all activities concerning autism spectrum disorder (ASD) within the U.S. Department of Health and Human Services (HHS) and providing advice to the Secretary of HHS on issues related to autism. It was established by Congress under the Children's Health Act of 2000, reconstituted under the Combating Autism Act of 2006, and renewed under the Combating Autism Reauthorization Act of 2011.

Membership of the Committee includes a wide array of Federal agencies involved in ASD research and services, as well as public stakeholders, including self-advocates, parents of children and adults with ASD, advocates, service providers and researchers, who represent a variety of perspectives from within the autism community. This makeup of the IACC membership is designed to ensure that the Committee is equipped to address the wide range of issues and challenges faced by families and individuals affected by autism.

Under the CAA, the IACC is required to (1) develop and annually update a strategic plan for ASD research, (2) develop and annually update a summary of advances in ASD research, and (3) monitor Federal activities related to ASD.

Through these and other activities, the IACC provides guidance to HHS and partners with the broader autism community to accelerate research and enhance services with the goal of profoundly improving the lives of people with ASD and their families.

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For more information about the IACC, see www.iacc.hhs.gov.

INTRODUCTION

The Combating Autism Reauthorization Act (CARA) was signed into law on September 30, 2011. CARA led to the establishment of a new Interagency Autism Coordinating Committee (IACC) by the Secretary of Health and Human Services, Kathleen Sebelius. At their first meeting in July 2012, the new Committee developed a plan and timeline to develop an update on the *IACC Strategic Plan for ASD Research* by the end of 2012. The *IACC Strategic Plan*, first issued in 2009, was also updated in 2010 and in early 2011.[1]

The IACC voted to update the *Strategic Plan* by working with content experts for each of the chapters of the *Plan* to identify recent advances that have added to "What do we know?" as well as new opportunities or gaps that have emerged, which have altered "What do we need?" The Committee decided to postpone consideration of any changes in the specific objectives or other parts of the *Strategic Plan* until 2013. This *2012 IACC Strategic Plan Update* covers advances and new opportunities in the field that have emerged between January 2011 and December 2012, recognizing that the *Plan* could not be updated earlier in 2012 while the IACC was being re-established.

With major findings emerging nearly every week, the speed of progress over the past two years has made composing the current update challenging. For instance, this year substantial changes, from updated prevalence numbers to new diagnostic criteria, were reported. The sheer volume of work that is now being produced in this field is overwhelming. According to the PubMed database of biomedical research literature, more than 1,000 autism papers on genetics or imaging have been published since January 2011, whereas a decade ago there were less than a third of this number of papers published.[2] This intense activity reflects a marked increase in autism research in the scientific community, and the sense of progress was evident in almost every chapter of this update. Autism research has become one of the hottest fields in biomedical science, as demonstrated by Time magazine's recognition of early treatment of autism as one of its "Top 10 Medical Breakthroughs of 2012."

Though the *2012 IACC Strategic Plan Update* will inevitably be unable to capture every important advance and new opportunity that is emerging in the field, the IACC has endeavored to capture in this document the key trends and most groundbreaking new insights from the past two years. This update should be paired with two other publications from the IACC in order to gain a more complete picture of the autism research landscape over the past two years. The *IACC Autism Spectrum Disorder Research Portfolio Analysis Report* [3] describes Federal and non-Federal investments in autism research, including an accounting of how current research aligns with each of the objectives of the *IACC Strategic Plan*. The annual *IACC Summary of Advances in ASD Research* reports in detail specific scientific findings that members of the IACC identify as having significantly advanced the field.[4]

Together, with this *2012 IACC Strategic Plan Update*, we hope these documents provide a useful overview of the state of autism research at the end of 2012.

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Please note: The terms "person with autism," "person with ASD," "autistic person," and "person on the autism spectrum" are used interchangeably throughout this document. Some members of the autism community prefer one term, while others prefer another. The Committee respects the different opinions within the community on the use of this language and does not intend to endorse any particular preference. In addition, the terms "autism" and "autism spectrum disorder (ASD)" are used interchangeably throughout this document unless otherwise noted.

[1] Interagency Autism Coordinating Committee. 2011 IACC Strategic Plan for Autism Spectrum Disorder Research. 2011 Jan. Retrieved from the Department of Health and Human Services Interagency Autism Coordinating Committee website at http://iacc.hhs.gov/strategic-plan/2011/index.shtml.

[2] Office of Autism Research Coordination (OARC), National Institute of Mental Health and Thomson Reuters, Inc. on behalf of the Interagency Autism Coordinating Committee (IACC). IACC/OARC Autism Spectrum Disorder Research Publications Analysis Report: The Global Landscape of Autism Research. July 2012. Retrieved from the Department of Health and Human Services Interagency Autism Coordinating Committee website: http://iacc.hhs.gov/publications-analysis/july2012/index.shtml.

[3] Office of Autism Research Coordination, National Institute of Mental Health, on behalf of the Interagency Autism Coordinating Committee (IACC). 2010 IACC Autism Spectrum Disorder Research Portfolio Analysis Report. July 2012. Retrieved from the U.S. Department of Health and Human Services Interagency Autism Coordinating Committee website: http://iacc.hhs.gov/portfolio-analysis/2010/index.shtml.

[4] Interagency Autism Coordinating Committee. 2011 IACC Summary of Advances in Autism Spectrum Disorder Research. 2012 Apr. Retrieved from the U.S. Department of Health and Human Services Interagency Autism Coordinating Committee website at http://iacc.hhs.gov/summary-advances/2011/index.shtml.

QUESTION 1: WHEN SHOULD I BE CONCERNED?

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

The past two years have seen several developments in the diagnosis of ASD, including changes to the definition in the Diagnostic and Statistical Manual of Mental Disorders (DSM), the standard text used by U.S. mental health professionals for clinical diagnosis, and promising developments in diagnostic instruments and early screening and detection. With the release of new national and international prevalence data, there is ongoing concern surrounding the prevalence of ASD, emphasizing the continued need to improve both monitoring and diagnosis.

Prevalence

Several noteworthy new studies from the U.S., South Korea, and England update the recognized prevalence of autism.

In the U.S., the Autism and Developmental Disabilities Monitoring Network (ADDM), supported by the Centers for Disease Control and Prevention (CDC), released its most recent surveillance data, showing a prevalence of 1 in 88 children or 1.1%—an increase of 78% since the first report in 2002—with larger increases among racial/ethnic minority groups (CDC, 2012). The average age when children were initially diagnosed with ASD, however, remains essentially unchanged, at 4–5 years of age. A second U.S. study found a sharp increase in autism in children (based on parent report) over an 11-year period (Boyle et al., 2011). Importantly, such an increase was not found for other neurodevelopmental disorders other than attention deficit hyperactivity disorder.

Looking internationally, a South Korean study found an ASD prevalence of 1 in 38, or 2.6%, of children when a large population sample of school-aged children was evaluated (Kim et al., 2011). Notably, two-thirds of those identified had not been previously diagnosed with autism or received any services. A British study found a prevalence of 1 in 100 adults, most of whom were not previously diagnosed with ASD (Brugha et al., 2011). The large majority of adults with ASD identified in this study were living independently but at lower levels of socioeconomic success than peers who did not have ASD.

Taken together, these studies suggest that some, but not all, of the increased prevalence observed in children is a result of improved identification and that there may still be a sizable population of children and adults with undiagnosed autism.

Diagnosis

The Diagnostic and Statistical Manual of Mental Disorders (DSM) definition of autism will be revised in 2013 when the new version, DSM-5, is released. The goal is to consolidate all current diagnoses under one category (autism spectrum disorder), while making its criteria more appropriate to the diagnosis of very young children, adults, and girls. While early studies raised concerns that the new criteria would exclude some people from diagnosis, recent findings suggest that this will not happen and that the other goals of the revision will be achieved. Specifically, similar rates of diagnosis were reported in a study based on well-characterized research samples (Huerta et al., 2012) and in preliminary results of the DSM-5 validation studies (Regier et al., 2012). However, there is still a need for prospective studies of the new criteria with larger sample sizes, and no data have yet been collected on adults.

In addition to evaluating the new criteria, recent analyses suggest that the method by which diagnostic information is collected is also critically important. Diagnoses that include information from both clinician observation and parent or caregiver report were found to be more accurate than diagnoses that rely on just one approach or the other (Huerta et al., 2012; McPartland, Reichow & Volkmar, 2012).

Furthermore, because diagnostic criteria are based on behavioral evaluation, clinical diagnoses are inconsistent among practitioners. Variations in diagnostic data from the infant sibling studies (Ozonoff et al., 2011), the CDC ADDM surveillance network sites (CDC, 2012), and the Simons Simplex Collection sites (Lord et al., 2012) suggest that clinical diagnoses still remain more variable than they should. This situation may ultimately be resolved by the development of laboratory tests for autism biomarkers, refined by observation and reporting. Although the criteria for diagnosis are behavioral, the hope is that medical evaluation will identify subtypes and decrease this variability.

Early Screening and Detection

Work on early screening tools has accelerated during the past two years, with two studies using questionnaire-based tools to screen for children at risk for ASD as early as 12 months old in community settings (Pierce et al., 2011a; Turner-Brown et al., 2012). However, researchers continue to have difficulty attaining sufficient sensitivity (the number of children correctly identified as having autism) without excessive rates of "false positives," which are instances when children are identified as being at risk for autism but do not go on to receive an ASD diagnosis. Specificity—correctly identifying the children that do not have ASD by accurately distinguishing ASD from other developmental disabilities or typically developing children—also remains a challenge.

Simplified ASD assessment tools for use across the lifespan are also in development (Allison, Auyeung & Baron-Cohen, 2012), but they have not yet met the need to appropriately identify adolescents and adults of all ages with ASD (Pilling et al., 2012). Additionally, new research continues to highlight disparities in identification of ASD by gender, race, and ethnicity (Valicenti-McDermott et al., 2012; Kočovská et al., 2012), while gaps remain in understanding the

reasons for these disparities and evidence-based ways to close these gaps.

Early Diagnosis

Symptoms of autism may not be visible in the first year of life and currently are not measured reliably until the end of the second year. However, several groups are looking for performance-based measures to bridge that gap. For example, one study in toddlers as young as 14 months showed a strong correlation between a preference for fixating on geometric images and subsequent ASD diagnosis (Pierce et al., 2011b). Similarly, another research group found an association between atypical eye contact at 7–13 months and subsequent diagnosis of ASD (Bedford et al., 2012). A relationship was also identified between differences in vocalization at 6, 9, and 12 months and diagnosis of ASD at 24 months (Paul et al., 2011), and research suggested that a child's temperament in the first two years of life, including characteristics such as increased perceptual sensitivity or reduced interest in cuddling, may predict a future ASD diagnosis (Clifford et al., 2012).

Brain recording and imaging techniques are also showing promise in identifying early biomarkers for autism. Using brain imaging (diffusion tensor imaging, DTI), researchers have identified white matter fiber tract development differences in 6-month-old infants who would later be diagnosed with ASD (Wolff et al., 2012). This suggests that aberrant development of brain pathways may precede the manifestation of autistic behaviors in the first year of life.

Other research has explored electroencephalography (EEG) data as a potential biomarker and quantifier of risk in the first year (Bosl et al., 2012; Elsabbagh et al., 2012). It is thought that EEG signals may contain information about the architecture of the neural networks in the brain and that early detection of abnormalities in EEG signals could be used as a biomarker for ASD and other developmental cognitive disorders. Using this type of signal processing approach—specifically multiscale entropy—to determine if a neural "signature" of autism risk could be observed, researchers were able to classify high risk versus low risk with over 80% accuracy at nine months of age (Bosl et al., 2012). However, it is uncertain whether this is predictive of which infants develop ASD. Another research group found that atypical event related potential (ERP) responses to eye gaze in high-risk infants predicts which infants developed ASD (Elsabbagh et al., 2012). It is too early to tell if this work translates to the general infant population, but it may point the way to very early identification of ASD in children from known at-risk groups. Finally, other studies have made progress toward detecting biomarkers for autism through blood screening, by analyzing gene pathways (Skafidas et al., 2012) or patterns of gene expression (Glatt et al., 2012).

WHAT GAPS HAVE EMERGED IN THE PAST TWO YEARS?

The age at which autism is diagnosed in most children has not changed, even though diagnosis is now possible significantly earlier. Better diagnostic tools and skills have been developed, but their existence has not yet translated to earlier detection in the general population.

Data systems—using the existing ADDM infrastructure or other data collection sites—to understand how the upcoming DSM-5 changes impact diagnosed prevalence and age at identification are recommended. Autism Speaks has funded a study to prospectively examine the impact of DSM-5 criteria on diagnosis at one ADDM site, but more studies are needed with both younger and older individuals.

Prevalence estimates from CDC's ADDM program are now available every two years based on large U.S. populations; however, these data are based on retrospective cohorts of children at eight years of age. Population-based data on younger children are needed, and new data collection is underway for children that are four years of age. However, the goal of obtaining rapidly available population-based estimates on large community samples continues to be a challenge.

The American Psychiatric Association (APA) has proposed a new disorder—Social Communication Disorder (SCD)—to describe people with communication disabilities that are not severe enough to warrant an ASD diagnosis. The community is very concerned that there are no therapies or services currently associated with SCD and that this diagnosis will be interpreted as mild ASD without the need for supports. Further research on SCD and its relationship to ASD is needed, and it will be important to follow this new diagnosis group with longitudinal studies.

The British study identifying the prevalence of ASD in the adult population in the United Kingdom (U.K.) (Brugha et al., 2011) suggests that a significant portion of the adult ASD population remains undiagnosed, despite the existence of screening tools and increasingly widespread public awareness of autism. Unrecognized adults with autism have emerged as an overlooked and underserved population. Some studies show that adults with autism continue to be socially disadvantaged and have significantly lower academic and career attainments as compared to adults in similar settings who do not have ASD (Brugha et al., 2011; Henninger & Taylor, 2012). Autism is a lifelong disability, yet research efforts to date have primarily focused on childhood and adolescent detection and intervention. More emphasis must be placed on individuals of all ages.

As the field increasingly shifts toward pre-symptomatic diagnosis, a series of new, complex bioethical issues are emerging, since diagnosis and treatment could be indicated for an infant without behavioral symptoms. Many in the autism community have expressed concern that research into early detection will lead to prenatal tests for ASD and that the existence of such tests may have family planning implications. On the other hand, very early detection in infants may be one of the keys to providing the best outcomes for people who will grow up with ASD in the future. Prenatal testing could also have significant quality of life implications if it facilitates effective early intervention. Work leading to prenatal tests for ASD potential should be informed by a full discussion of the bioethical issues surrounding the use of these technologies, including those cited above.

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QUESTION 2: HOW CAN I UNDERSTAND WHAT IS HAPPENING?

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

In 2011 and 2012, significant progress was made in understanding the underlying biology of ASD. This includes new observations about differences in neural connectivity in the brains of those with ASD, the discovery of molecular mechanisms that might cause ASD symptoms, and insights from some of the conditions and disorders that co-occur with ASD.

Brain Imaging

In the past two years there have been more than 225 research publications that have used neuroimaging of brain structure or connectivity to look for differences in autism. In response to the urgent need for sensitive and specific biomarkers for the diagnosis of ASD, many research groups have been studying patterns of brain development, including prospective longitudinal studies of infant siblings of children with ASD. Some traction has been gained by using diffusion weighted imaging (DWI, an imaging technique in which the diffusion of water molecules is mapped in order to reveal the underlying structure of the brain) to study white matter pathways. Research using this technique found atypical development of white matter pathways in high-risk infants (infants who had an older sibling with ASD) who later developed symptoms of autism (Weinstein et al., 2011). Abnormal white matter architecture was also found in three-year-old children with autism (Wolff et al., 2012).

Another recent trend is to use structural magnetic resonance imaging (structural MRI) to define neural phenotypes of autism. Several studies (e.g., Hoeft et al., 2011) have demonstrated that young boys with fragile X syndrome have different patterns of brain abnormalities than young boys with idiopathic autism. Other studies have shown that the accelerated brain growth associated with autism is observed mainly in young boys with regressive autism (Nordahl et al., 2011) and does not occur in girls with autism. Interestingly, enlarged brain size may be related to ethnicity, since macrocephaly (abnormally enlarged head) is not a common feature of autism in Israel (Davidovitch et al., 2011).

Over the past two years, an array of studies using functional magnetic resonance imaging (fMRI) and DWI has advanced understanding of the neural circuitry that is affected in ASD. These studies have most often highlighted differences in functional activation within specific brain regions known to be specialized for processing social information (e.g., social

orienting, Greene et al., 2011; affective aspects of social processing, Gotts et al., 2012; gaze on emotional faces, Kliemann et al., 2012; attention, Redcay et al., 2012). DWI studies found disrupted pathways connecting language areas in children with autism (Lewis et al., 2012).

Neurophysiology

Investigating neural circuits in the brain may reveal distinctions that cannot be observed by behavioral approaches alone. For example, brain activity has potential as an early predictor of subsequent ASD diagnosis. Electroencephalography (EEG) is a technique in which electrical activity along the scalp is used to measure current flow in the brain. EEG responses to dynamic eye gaze shifts (viewing faces with eye gaze directed toward versus away from the infant) during the first year of life were predictive of different clinical outcomes at 36 months (Elsabbagh et al., 2012). This difference in brain activity was apparent despite similar patterns of gaze as measured by eye tracking. Atypical audiovisual speech integration in infants at risk for autism has also been shown (Guiraud et al., 2012). As the field strives to develop methods of detecting early developmental indicators of autism, these findings, together with the neuroimaging findings described above, offer hope for the possibility of non-invasive, brain-based screening methods that could detect differences prior to the emergence of ASD behavioral symptoms.

Molecular Basis and Phenotyping

Genetic studies continue to implicate dysfunction at the synapse—the junctions through which neurons transmit signals to each other—as part of the underlying biology of ASD. Of particular interest are the insights into the effects of gene mutations in animal models of syndromic autism, including FMRP (Fragile X Mental Retardation protein) in fragile X syndrome, MecP2 (methyl CpG binding protein 2) in Rett syndrome, and TSC1/2 (Tuberous Sclerosis 1 and 2) in tuberous sclerosis. Remarkably, these mouse studies support the hypothesis that many aspects of the ASD phenotype are reversible in both adults and infants; drugs influencing the mGluR5 (metabotropic glutamate receptor 5) receptor and the mTOR (mammalian target of rapamycin) inhibitor, rapamycin, were found to be particularly effective (Tsai et al., 2012; Silverman et al., 2012; Auerbach, Osterweil & Bear, 2011). Rare mutations in genes that encode proteins forming large complexes at the synapse (Shank/ProSAP (proline-rich synapse-associated proteins)) are now known to be associated with autism. Deletions of these genes in mice were found to cause autism-like behaviors and alterations of synaptic function and glutamate neurotransmission (Schmeisser et al., 2012). Additionally, genetic deletions or duplications—called copy number variants (CNVs)—in other genes may interact with mutations in Shank to cause autism (Leblond et al., 2012).

As risk genes for ASD are identified at an increasing pace (see Question 3), the next step for brain imaging research is to determine how these risk genes impact the development of brain structure and function and contribute to the heterogeneity (diverse array of potential causes and presentation of symptoms) observed in people with ASD. For example, one fMRI study demonstrated

that a common, functional ASD risk variant in the MET (Met Receptor Tyrosine Kinase) gene is an important regulator of key social brain circuitry in children and adolescents with and without ASD and that MET risk genotypes are associated with atypical fMRI activation to emotional faces (Rudie et al., 2012). If validated, these findings highlight how different patterns in genetic variation may lead to an understanding of phenotypic heterogeneity in ASD and help to elucidate the key changes in neural circuitry.

A recent study examining gene expression in postmortem brains of individuals with autism showed a remarkable decrease in the typical variation seen between cortical regions in normal brains, a finding that suggests a simplification of cortical patterning in autism (Voineagu et al., 2012). This study also uncovered patterns of neuronal gene expression in autism that paralleled and confirmed the role of genes known to be associated with autism risk. Surprisingly, the researchers also found a pattern of immune and glial cell gene expression in the autism brain that had not been identified in previous genetic studies, an observation that supports the view that brain immune system responses in autism are likely related to environmental events as well as genetic influences.

Immune System

Recent findings in experimental animals are critical for understanding the role of glial cells (non-neuronal cells that maintain homeostasis, form myelin, and provide support and protection for neurons in the brain and nervous system) and immune pathways in the development of autism and its underlying biology. Models of microglia (glial cells that form part of the immune system) and immune pathway function during brain development and neuroplasticity in experimental animals, which have suggested involvement of microglia in normal neurodevelopmental activities such as the "pruning" of synapses, are the strongest demonstration of a potential role for the immune system in ASD pathogenesis (Schafer et al., 2012; Stephan, Barres & Stevens, 2012).

The potential role of adaptive immunity, environmental factors (such as maternal infections), and autoimmunity in the pathogenesis of ASD has also been identified using animal models. In some recent studies, for example, maternal immune activation resulted in long-term adaptive immune system abnormalities in the offspring of mice exposed to immune challenges during pregnancy (Hsiao et al., 2012; Braunschweig et al., 2012). Interestingly, behavioral abnormalities observed in this model were reduced by reversing cellular immune deficits by performing bone marrow transplants with immunologically normal bone marrow (Hsiao & Patterson, 2012), which has implications for the development of new interventions for ASD.

Although human studies of immune function in ASD have been limited, some observations support a potential link between immune dysfunction and autism. One study that evaluated cytokines and chemokine expression in neonatal blood spot samples in the Danish Newborn Screening Bank suggested that an underactive immune system was present in infants that developed autism (Abdallah et al., 2012).

Co-occurring Conditions

Over the past two years there has been increasing recognition of the substantial overlap between ASD and epilepsy. Past studies indicated that 10-20% of individuals with ASD have concurrent epilepsy. Within the past year, progress has been made on discovering the common roots of ASD and epilepsy, including identification of mutations in a gene coding for a metabolic enzyme (Novarino et al., 2012) and X-chromosome-linked mutations in a gene that produces proteins usually involved in cell adhesion (Marini et al., 2012).

Recent work has also reinforced the overlap between ASD and gastrointestinal disturbances. For instance, 24% of children with ASD enrolled in Autism Speaks' Autism Treatment Network (ATN) were shown to have one or more chronic gastrointestinal problems, and these problems were associated with higher rates of both anxiety and sensory over-responsivity (Mazurek et al., 2012).

Sleep dysfunction is also associated with ASD and often correlates with its severity. Children with ASD who sleep fewer hours per night demonstrate lower overall IQ, verbal skills, overall adaptive functioning, daily living skills, socialization skills, and motor development. Furthermore, children who wake during the night, in addition to sleeping fewer hours, exhibit more communication problems (Taylor, Schreck & Mulick, 2012). Children with autism spend reduced time in the rapid eye movement (REM) phase of sleep, which has been hypothesized to play a role in neuroplasticity—the brain's ability to reorganize itself by forming new neural connections—and brain development (Buckley et al., 2010). Naturally occurring levels of a major metabolite of melatonin, a hormone that regulates sleep and wake cycles, have been documented to be low in adolescents and young adults with autism compared to age- and gender-matched controls (Tordjman et al., 2012). These findings provide the groundwork for treatment trials of melatonin in ASD (see Question 4).

WHAT GAPS HAVE EMERGED IN THE PAST TWO YEARS?

Over the past two years, several landmark efforts in biology have provided new tools and insights that may transform understanding of ASD. While none of these efforts were focused on ASD, they provide unprecedented opportunities for future ASD research. The ENCODE project, for example, has demonstrated that the human genome is loaded with important biological signals beyond genes that code for proteins. While protein-coding genes make up only 2% of the genome, new research has revealed that about 80% of the genome is translated, resulting in some 20,000 non-coding RNA elements (Encode Consortium, 2012). Scientists working on ASD genetics have barely begun to explore these newly discovered elements of the genome.

The Human Microbiome Project, which has mapped the microbial world of 18 different sites in the human body (Human Microbiome Consortium, 2012), has also provided important insights into the role that microbes, including bacteria and fungi that are associated with healthy and

diseased human tissue, may be playing in many human conditions, including ASD. The results have altered thinking about what it means to be human, and the body is beginning to be viewed as more of a complex ecosystem in which microbes compose the bulk, while human cells represent a paltry 10% of the total cell population. However, beyond the sheer numbers, research on the microbiome brings new knowledge about the profound diversity of this ecosystem and striking differences between individuals. How these differences in the composition of the microbial world of each individual influence the development of brain, behavior, and neuroimmune function will be one of the great frontiers of clinical neuroscience in the next decade. In addition, the Human Connectome Project is providing the first detailed diagram of the wiring of the human brain and developing tools for mapping the connections across distant regions of the cortex (Wedeen et al., 2012).

Turning to the basic issue of defining brain differences that contribute to autism, there continues to be a paucity of studies related to the cellular neuropathology of autism. The limited supply of postmortem tissue has slowed research in every area addressed under this question. While this has been a challenge for many years, the loss of frozen samples from more than 50 brains after a freezer malfunction at a tissue bank in June 2012 has been an enormous setback. The loss represented about one-third of the largest autism brain repository and will take years to replace (see Question 7).

In order to study the cellular and molecular underpinnings of autism, researchers also need appropriate cell culture models of neurons. In a landmark paper, investigators generated cortical neurons from induced pluripotent stem cells (iPSCs) derived from skin cells of two individuals with Timothy syndrome, a monogenic (or single gene) cause of autism (Pasca et al., 2011). Interestingly, these neurons showed abnormalities in differentiation and neurotransmitter production that could be reversed by blocking the calcium channel known to be mutated in this disorder. iPSCs are promising both as a biological tool to uncover the pathophysiology of disease by creating relevant cell models and as a source of stem cells for cell-based therapeutic applications and drug discovery. It is noteworthy that, for the first time, the derivation of iPSC lines from the whole blood of children with ASD was recently described (DeRoşa et al., 2012).

The lack of longitudinal studies in autism remains a striking gap in studies of brain function. While cross-sectional studies have provided important findings, there is a lack of essential information about both the time course of brain development from early infancy to adulthood and the aging brain in ASD. The power of longitudinal studies was recently reinforced by the results of a longitudinal structural MRI study that identified an increased rate of amygdala growth in very young children with ASD (Nordahl et al., 2012).

Although a network has been launched to study ASD in females, there remains a pressing need to conduct research aimed at understanding all aspects of ASD (genes, brain, and behavior) in females with ASD. ASD disproportionately affects males, and this skewed sex ratio has resulted in a bias of

published research towards studies focused on males. Interestingly, girls are much less likely to be diagnosed with ASD than are boys unless they also have intellectual or behavioral problems (Dworzynski et al., 2012), which might reflect either a gender bias in diagnosis or genuinely better adaptation/ compensation in girls.

As more insight into the biological mechanisms underlying ASD is gained, one area that has been identified as a new gap is the role of the immune system and microglia in autism, which have recently been found to contribute to brain development and plasticity (Stephan, Barres & Stevens, 2012). Another is to understand the generalizability and pathophysiological significance of the findings of increased oxidative stress markers in the blood plasma of children with autism (Melnyk et al., 2011). Further investigation into these and other gap areas will help explain the underlying biology of ASD, aiding in the identification of biomarkers for diagnosis and informing potential treatments and interventions in the future.

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QUESTION 3: WHAT CAUSED THIS TO HAPPEN AND CAN IT BE PREVENTED?

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

Over the past two years, progress has been made in identifying genetic and environmental risk factors associated with ASD. Furthermore, there is a greater understanding of the mechanisms by which these factors may be acting to increase susceptibility for autism.

Genetic Risk Factors

The past two years have seen an explosion of research on genomic factors associated with autism, with more than 900 papers on "autism and genetics" listed in the National Library of Medicine's (NLM) PubMed database in 2011 and 2012. Progress in genomics has been enabled by the advent of rapid, inexpensive, precise sequencing tools and the availability of large repositories of DNA samples. At the time of the publication of the initial *IACC Strategic Plan for ASD Research* in 2009, most ASD-related genomic research was focused on finding common variants in the genome, which are believed to act in an additive fashion to increase risk for ASD. While these common variants are still of interest, recent research has mapped out three new areas for understanding ASD risk.

First, there are as many as 1,000 rare changes in DNA structure or sequence that contribute to ASD risk (Coe, Girirajan & Eichler, 2012; Neale et al., 2012; O'Roak et al., 2012b; Sanders et al., 2012). Sometimes these changes involve duplications or deletions of more than a million nucleotide bases (the building blocks of DNA), while at other times only a few bases are altered; however, the result in either case can be increased risk for ASD.

Second, these changes are frequently spontaneous, or *de novo*, arising in sperm or eggs prior to or just after conception (Iossifov et al., 2012). That is, if tested, neither parent would show these mutations in body cells such as their blood cells, but the mutations could be found in reproductive cells, such as the father's sperm cells, which divide throughout life.

Third, most of the genetic loci, or regions in the DNA, that are implicated in ASD are not specific to ASD. These include neurodevelopmental loci that also confer risk for other brain disorders such as schizophrenia, epilepsy, and attention deficit hyperactivity disorder (ADHD), as well as loci for intellectual deficit syndromes (Malhotra & Sebat, 2012). While rare and not specific to ASD, the same genomic changes are found repeatedly (O'Roak et al., 2012a).

Risk Factors Converge on Biological Pathways

This complex picture of multiple, nonspecific, spontaneously-arising genetic factors is beginning to converge on a few biological pathways, particularly signaling pathways that stabilize activity at synapses (junctions between neurons) in the brain (Devlin & Scherer, 2012; Malhotra & Sebat, 2012; Veltman & Brunner, 2012; Zoghbi & Bear, 2012). However, synaptic genes are not the entire story. In 2012, two genes associated with metabolic disorders were identified as potential contributors to autism risk. These genes code for enzymes involved in producing and maintaining normal levels of two types of amino acids, carnitine and branch chain amino acids, which are necessary for normal metabolism (Celestino-Soper et al., 2012; Novarino et al., 2012).

While genomic factors were estimated to account for up to 10% of autism cases in 2009, the most recent studies, based on whole exome sequencing, find currently identifiable genomic variants and mutations in 25% of cases (Devlin & Scherer, 2012; Sanders et al., 2012).

These complex results present major challenges, not only in understanding causes of autism, but also in identifying treatments that will be effective for a large fraction of cases. "Autism" is likely several etiologically distinct disorders (disorders with different sets of causal factors) that converge to create a common set of behavioral deficits. Moreover, there is already considerable evidence that the multiple autism genetic risk genes converge on a smaller number of biological mechanisms, suggesting that it may be possible to treat many types of autism by targeting common underlying biological pathways, as opposed to requiring a specific treatment for each different mutation.

Environmental Risk Factors

The complexity of autism risk necessitates research on the interface between genomics and environmental exposures, including research on how biotic (e.g., dietary factors) and xenobiotic (e.g., exposures to drugs and environmental toxicants) factors may interact with genetic susceptibility. New research has emphasized the role of non-genomic risk factors. The largest U.S. twin study compared the concordance rates (the likelihood that both twins share an ASD diagnosis) in identical (monozygotic) twins, who share 100% of their DNA, and fraternal (dizygotic) twins, who share 50% of their DNA. In contrast to earlier, higher estimates, the ASD concordance rate for male identical twins was 77% (58% for strict autism, a smaller subset of ASD) and for male fraternal twins was 31% (21% for strict autism) (Hallmayer et al., 2011). The lower concordance rate for identical twins in this study compared to the rates identified in previous studies suggested that genomic factors (including spontaneous mutations) might be less important than previously claimed from twin studies. In addition, since the concordance rate in fraternal twins was considerably higher than the traditional figure of 3% to 10% estimated for siblings, the study appeared to support the importance of the prenatal environment, which is shared by fraternal twins but not by non-twin siblings.

A recent report from the Baby Siblings Research Consortium, however, challenged

the previously mentioned traditional figure of a 3% to 10% recurrence rate in siblings. The study, using a larger sample size and updated methodology, suggests that the non-twin male sibling rate of developing ASD is 26.2%, which is in the range of concordance for male fraternal twins (Ozonoff et al., 2011). Thus, the rate of autism in fraternal twin siblings and in non-twin siblings may be more similar than previously thought.

A list of candidate environmental exposures identified for future study was developed in a 2010 workshop of experts supported by the National Institute of Environmental Health Sciences (NIEHS) and Autism Speaks. The list, published in 2012, included: lead, methylmercury, polychlorinated biphenyls (PCBs), organophosphate, pyrethroid, organochlorine insecticides, endocrine disruptors, automotive exhaust, polycyclic aromatic hydrocarbons, brominated flame retardants, and perfluorinated compounds (Landrigan, Lambertini & Birnbaum, 2012). These compounds are widely distributed within the environment and have known neurodevelopmental effects that may be relevant to autism. For example, insecticides are known to target neurotransmitter systems known to be impaired in autistic children (Roberts et al., 2007; Shelton, Hertz-Picciotto & Pessah, 2012). Within the past year, developmental exposure to specific types of PCBs (compounds used in many industrial applications as insulators, coolants, and plasticizers) in rodents was reported to alter activity-dependent growth of neuron dendrites by mechanisms implicated in autism (Pessah, Cherednichenko & Lein, 2010; Wayman et al., 2012a; Wayman et al., 2012b), and these chemicals were detected in higher levels in brains of individuals with a syndromic form of autism (Mitchell et al., 2012). In addition, a study of exposure to traffic pollution, which involved examination of residential history of individuals and regional measurement of nitrogen dioxide and particulate matter, found an increased risk for autism among children exposed to the highest levels of pollution, even after controlling for ethnicity, parental education, smoking during pregnancy, or living in a densely populated region (Volk et al., 2012).

Recent studies of immigrant populations and autism risk have shown an elevated risk of having children with autism in these populations, suggesting that environmental factors associated with the migration, such as exposures and lifestyle, may play a role. A population-based study in the Netherlands suggested that immigrants have a higher risk of having a child with severely disabling autism (van der Ven et al., 2012), and another population-based study in Sweden suggested more specifically that immigrating to another country during pregnancy may increase the risk of having a child with autism (Magnusson et al., 2012).

Gene-Environment Interactions

One strategy for identifying environmental risk factors for ASD may be to focus on factors that converge on the same cellular signaling pathways as known ASD susceptibility genes (Pessah & Lein, 2008; Stamou et al., 2012). Genetic factors can amplify the effects of environmental exposures by disrupting the same signaling systems during critical periods of development. The task of detecting environmental risks can be facilitated by the use of analytic approaches that incorporate genetic information. This enables

identification of those combinations of exposures and genes that confer the highest risk. The value of this approach in the field of autism was demonstrated this past year when researchers found evidence that vitamin use during the months before and after conception resulted in a protective effect that reduced ASD risk. This effect was found to be associated with maternal and child genes coding for one-carbon metabolism variants, which play a role in the body's ability to metabolize the vitamins (Schmidt et al., 2011). These findings, however, should be viewed as preliminary and must be replicated.

Finally, a 2012 meta-analysis of existing epidemiologic studies found evidence supporting an independent effect of advancing maternal age on ASD risk (Sandin et al., 2012). A similar 2011 analysis showed an association between paternal age and ASD risk (Hultman et al., 2012). Also, a series of studies confirmed the correlation between paternal age and *de novo* mutation rate (Neale et al., 2012; O'Roak et al., 2012b; Sanders et al., 2012) and showed that the majority of *de novo* ASD mutations are from the father's genome (Iossifov et al., 2012; O'Roak, 2012b). While a *de novo* mutation mechanism seems most important in driving associations between paternal age and autism risk, the mechanism behind the maternal age association remains unknown. Furthermore, the role that environmental factors may play as preceding causes or interacting factors in mechanisms mediated by *de novo* mutations, or in other causal mechanisms, is unknown.

WHAT GAPS HAVE EMERGED IN THE PAST TWO YEARS?

Environmental Risk Factors

Although the *2011 IACC Strategic Plan* update reported that environmental research is an understudied area that has been given insufficient attention and requires heightened priority, there continues to be a need for significant attention to this area of research, with new insights about *de novo* mutations suggesting a potential link between environmental and genomic factors. Given the universe of potential environmental factors, one of the challenges is prioritizing candidate exposures and lifestyle factors that could potentially increase risk for autism. Prioritization can be based on: expert consensus (e.g., list of ten priority exposures developed in 2012) (Landrigan, Lambertini & Birnbaum, 2012); research findings pointing to windows of susceptibility, such as the preconception and prenatal periods; screening of exposures that converge on the same signaling pathways as ASD susceptibility genes; and a focus on replicated findings, such as studies explicitly designed to reveal exposures mediating the association between parental age and autism risk.

The challenges to accurately measuring exposures during critical time windows in development, which in some cases may be many years prior to diagnosis, are substantial. The *2012 NIEHS Strategic Plan* includes exposure research as one of six major themes, and there is little doubt that innovations in biomarker-based exposure assessment would be helpful in the autism research field. In addition, reports of higher

rates in specific immigrant communities suggest a new opportunity to study the role that environmental factors associated with migration may potentially play in elevating autism risk in specific populations (Dealberto, 2011; Haglund & Källén, 2011; Magnusson et al., 2012; van der Ven et al., 2012).

Rapid throughput, high-content screening technologies, which would allow researchers to rapidly analyze large numbers of samples for many different parameters at the same time, need to be developed, validated, and implemented for use in research on environmental factors that may play a role in human disorders. These technologies could be used, for example, to help identify the most potent chemical and/or biochemical agents that alter neuronal connectivity, synaptic structure, and plasticity (ability to adapt or change the strength of signals transmitted through the synapse) by interfering with signaling pathways implicated in autism and related disorders.

Model Systems

Integration of physiological, biochemical, and morphological analysis of neuronal and immunological cellular models is needed to better understand the underlying biology of ASD. These models should be based on cells derived using new techniques such as induced pluripotent stem cell (iPSC) technology (in which one type of adult cell, such as a skin cell, is first reprogrammed into a stem cell and then induced into a different type of cell, such as a neuron) or transdifferentiation technology (similar to iPSC technology, except that adult cells are directly reprogrammed into a different type of mature cell without having to go through the intermediate pluripotent stem cell stage). Furthermore, this research must be conducted on samples collected from patients that have been fully genotyped and deeply phenotyped (analyzed for both genetic makeup and observable traits) in order to understand gene-environment interactions and reveal exposure biomarkers.

Genetic Risk Factors

Given the high degree of genetic heterogeneity in ASD, a high priority should be placed on ascertaining family trios (two parents and one affected child) for comprehensive genomic analysis, including whole exome sequencing (sequencing of only the coding regions of DNA), copy number variant (CNV) studies, and sequencing of mutations in non-coding regions of DNA. The understanding of inherited genetic variation in ASD has been hampered by the lower effect size (the strength of the relationship between the genetic variation and the ASD phenotype) that is characteristic of research into rare and common genetic variants associated with ASD, as well as the need for very large patient cohorts. Successful studies of common inherited variation in conditions like schizophrenia point to the need for larger patient cohorts and very large-scale collaborative analyses.

Gene-Environment Interactions

Further, to understand the interplay of genetic susceptibility and environmental exposure, genomics data must be combined with exposure measures, and appropriate statistical methodologies must be developed and applied. Using this approach will require larger samples than those used for studies

focused on detecting either genetic or environmental effects alone, so that small interactive effects will be able to be detected. Novel analytic approaches must also be developed to maximize accuracy in detecting effects when they exist.

Finally, as discussed in Question 2, studies have continued to document metabolic (e.g., oxidative stress, low glutathione levels, redox imbalances, mitochondrial dysfunction) and immune system abnormalities (e.g., anti-brain antibodies and dysregulated cytokine production) in individuals with ASD and, in some cases, in their mothers during gestation. Additional research should investigate when these abnormalities are present (e.g., at birth or acquired within the neonatal period) and whether they are related to risk for autism.

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QUESTION 4: WHICH TREATMENTS AND INTERVENTIONS WILL HELP?

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

While many treatments and interventions for ASD are still in the early stages of development, several new findings on potentially efficacious interventions for children and adults with ASD have arisen during the past two years.

Early Behavioral Interventions

Evidence for the benefits of early behavioral intervention continues to mount, with researchers now focusing on testing interventions for infants and toddlers, identifying the most effective aspects of treatments, and disseminating these interventions in community settings. While gains have been made in this area of research, the effects of these interventions as measured to date are modest. Positive results of implementation of targeted interventions in community settings have recently been reported (Kaale, Smith & Sponheim, 2012; Lawton & Kasari, 2012).

The past two years have seen the first randomized controlled trials (RCTs) of parent-mediated interventions, an important milestone. However, these interventions have not yet been found to be efficacious (e.g., Carter et al., 2011). Progress has been made in developing social interventions. For example, a longitudinal followup of a targeted, joint attention intervention found that joint attention and play are important targets for interventions aimed at enhancing language acquisition and that these functional gains may persist over the long term (Kasari et al., 2012a).

A study of early intensive intervention using the Early Start Denver Model (ESDM) with toddlers, a method that was studied in an earlier RCT described in the *2011 Strategic Plan*, was found to result in changes in electrophysiological brain activity. This biological marker correlated with positive changes in behavior (Dawson et al., 2012).

In a different RCT, children who received a 12-week, parent-delivered ESDM intervention were compared to a control group of children receiving typical community interventions (Rogers et al., 2012). Both groups of children showed developmental gains and reduced core autism symptoms, although there was no clear advantage of one intervention over the other. However, the degree of improvement across both community and ESDM groups was higher in children that received more hours of intervention, and younger children (14 months) made more developmental gains than older children (24 months).

Behavioral and Psychosocial Interventions for School-Age Children and Adults

There is a general paucity of research on interventions for adolescents and adults, as underscored by a recent systematic review (Taylor et al., 2012). This review noted that evidence-based approaches to support transition to adulthood and employment are particularly lacking.

Although the evidence base for behavioral interventions in older children and adults is less well-developed than early interventions, new research points to a number of promising efficacious interventions. An RCT of a brief social skills intervention documented improvements in peer relationships in the classroom that persisted over time (Kasari et al., 2012b). In another pair of studies that built on earlier findings, cognitive behavioral therapy (CBT) and social skills training were useful for decreasing anxiety in some children with mild ASD, and many children who were re-evaluated after six months showed sustained improvements (Antshel et al., 2011; Reaven et al., 2012). Social skills training may also have positive effects on core social symptoms, as suggested by a recent study of a social skills group intervention in children with ASD (DeRosier et al., 2011). Additionally, one RCT that addressed common psychiatric concerns in ASD found that mindfulness-based therapy was efficacious for reducing anxiety, depression, and rumination in adults (Spek, van Ham & Nyklíček, 2012).

Medications

To date, the only medications approved by the Food and Drug Administration (FDA) for the treatment of any aspect of ASD are the antipsychotic drugs aripiprazole and risperidone, both of which are used for the treatment of irritability associated with ASD. A recent meta-analysis (a study that contrasts and combines results from different studies to identify patterns among the results) of these medications for adolescents and children with ASD confirmed that, while these drugs are effective in the treatment of behavioral disturbances, there are frequently adverse side effects including sedation, involuntary muscle spasms, and weight gain (Cohen et al., 2013). In a study combining treatment and intervention, the combined effects of risperidone and parent training were more positive than medication alone for improving adaptive behavior (Scahill et al., 2012b). Another group of researchers reported potential usefulness of N-acetylcysteine, a glutamate modulator, for treating irritability (Hardan et al., 2012).

Clinical trials for selective serotonin reuptake inhibitors (SSRIs) for reducing repetitive behaviors have produced conflicting results for adults and children, indicating that there may be age-associated drug effects or effects intrinsic to this particular class of drugs (Hollander et al., 2012; Scahill et al., 2012a). No uniform guidance has yet emerged from these studies.

At least twelve medication trials have been launched for the core domains of ASD or neurodevelopmental disorders associated with ASD, such as fragile X syndrome. A Phase 2 RCT of Arbaclofen, a selective GABA-B agonist, with children and adults with fragile X showed positive effects for reducing social avoidance (Berry-Kravis et al., 2012). In addition, at least 10 trials of the pro-social

neuropeptide oxytocin are underway or were recently completed in children and adolescents with ASD (ClinicalTrials.gov website).

Treatment of co-occurring medical conditions continues to be an important area of study. A *Pediatrics* supplement (Perrin & Coury, ed., 2012) based on the work of the U.S. Health Resources and Services Administration (HRSA) Autism Intervention Research Network on Physical Health (AIR-P) and the Autism Speaks Autism Treatment Network (ATN) provided empirically-based physician guidelines for the management of gastrointestinal (GI) issues, sleep, and attention deficit hyperactivity disorder (ADHD), as well as descriptive information on the prevalence and nature of a wide range of co-occurring medical conditions. Studies showed that melatonin, a hormone produced by the brain to regulate sleep, is useful for treating insomnia in ASD (Malow et al., 2012) and that controlled-release melatonin with CBT may be useful for treating night awakening (Cortesi et al., 2012). An open label trial of donepezil, a drug that enhances the function of the neurotransmitter acetylcholine in the brain, was found to increase rapid eye movement (REM) sleep and decrease REM latency in children with ASD (Buckley et al., 2011).

Epilepsy—which commonly co-occurs with ASD—and interictal epileptiform discharges (patterns of electrical activity that resemble those during seizures but are present between seizures) are also associated with sleep disruption. Recently, the antiepileptic drug levetiracetam was shown to reduce nocturnal epileptiform activity (which is present in many individuals that lack a clinical diagnosis of epilepsy) during non-REM sleep (Larsson et al., 2012).

In the broader context of biomedical research, a 2011 National Academy of Sciences report on precision medicine is changing the culture of treatment development (National Research Council, 2011). Noting that most common diseases include cases caused by rare syndromes requiring different treatments, precision medicine argues for the development of targeted treatments based on more precise diagnostics, defined by biomarkers. Thus, biomarkers may play an important role not only in the development of diagnostic tools, but also in advancing the autism treatment field.

Other Treatments and Interventions

A number of other treatments and interventions for ASD have been studied during the past two years. For example, a meta-analysis concluded that exercise is beneficial for social skills and motor performance for people with ASD, with individual interventions more effective than group interventions (Sowa & Meulenbroek, 2012). Additionally, an RCT found that a movement-based yoga, dance, and music therapy program was effective for improving behavior (Rosenblatt et al., 2011). Finally, a 12-week RCT of repetitive transcranial magnetic stimulation (rTMS) in mildly affected individuals with ASD resulted in improved error-related negativity (a proxy measure of executive functioning) and improved error monitoring and correction (Sokhadze et al., 2012).

WHAT GAPS HAVE EMERGED IN THE PAST TWO YEARS?

Although some helpful interventions for ASD have been identified, a precision medicine approach is lacking. Specifically, no biomarkers or clinical features have been identified to indicate which interventions are most likely to be helpful for a given individual. Trial designs need to be improved by: including larger, more diverse samples (e.g., greater ethnic diversity and additional individuals with more severe disability challenges, such as individuals with limited or no verbal communication); examining the length and intensity of interventions; developing objective/physiologic measures of autonomic response or physical activity: and testing measures of how well new skills are maintained and generalized in real-world settings. More sensitive outcome measures and biomarkers need to be developed so that clinical trials may identify mediators and moderators of treatment response. Thus, better characterization of biomarkers and endophenotypes (observable characteristics that are thought to be strongly genetic in origin) may aid in the development of customized, targeted interventions.

Investigators are also beginning to actively link genetic makeup with drug effects—both therapeutic as well as side effects, such as weight gain with risperidone (Adkins et al., 2011; Correia et al., 2010). This area of research has been termed "pharmacogenomics," and its goal within the context of ASD is to both define biomarkers of drug responsiveness among people with ASD as well as to identify those who may be most prone to adverse effects.

Understanding the pathophysiology of ASD will be paramount in the quest for new treatments and delineating the mechanisms behind treatment response. The effect of co-occurring conditions on ASD, and vice versa, is unclear and needs to be better defined. Research needs to be conducted to determine if co-occurring conditions such as anxiety, depression, gastrointestinal disturbances, epilepsy, or atypical immune response involve similar mechanisms in individuals with and without ASD. It is possible that anxiety and/or affective disorders in individuals with ASD stem from core aspects of atypical neurodevelopment in ASD; alternatively, these co-occurring conditions may actually represent reactive compensatory mechanisms in those with ASD. It is also important to understand whether treatments for co-occurring conditions have similar effects in individuals with and without ASD.

Alternatives to pharmacological treatments should also continue to be explored. Likewise, as the effects of behavioral interventions become more apparent, better information regarding the most critical components of treatment is needed. The effectiveness and longevity of treatment effects in real-world settings must also be established.

Additionally, outcome measures that can monitor changes in brain connectivity and activity and correlate those changes with behavioral and social therapies should be developed. For example, more research could be conducted using magnetic resonance imaging (MRI) or electroencephalography (EEG) as a tool to measure the physiological effects of a variety of treatments, including

behavioral, pharmacological, and rTMS. These measures could then be compared to concurrent changes in behavior. This approach has already been successfully used to study the effect of behavioral interventions using EEG (see study described above, Dawson et al., 2012) and functional MRI (Voos et al., 2013). Likewise, standardized measures of sensory processing should be established to measure changes in sensory processing in response to interventions, such as occupational therapy-based interventions.

Clinically, determination of which individuals are most likely to be responsive to particular social and behavioral interventions is needed, as well as efforts to better understand the mechanisms behind efficacy in those individuals. In addition, there is a need for further research on the many cognitive, educational, and computer-based programs used to remediate learning deficits in individuals with ASD to determine which are most effective. These should be compared in well-characterized ASD cohorts. Better understanding of which interventions are likely to be effective for different individuals will help individuals to select the interventions that will best help them address their needs and meet their cognitive and learning potential. Effectiveness studies for relatively inexpensive community-based interventions (e.g., exercise, yoga, acupuncture, mindfulness) should also be conducted.

Some interventions are widely used despite a limited evidence base. These include complementary and alternative treatment approaches, among others. There is a need for more research on these interventions so that consumers can make informed choices about their use. The needed research includes studies to identify potential principles and mechanisms of action and to evaluate safety and efficacy. In addition, research that explores the potential treatment implications of novel biological findings, such as differences in immune functioning in individuals with autism, is needed.

While many interventions (pharmacological, behavioral, and otherwise) successfully change targeted behaviors or symptoms, there is a need to measure the global, and not merely the specific, effects of all interventions. These effects may include the unintentional development of alternate problem behaviors, as well as effects on stress levels, unique talents, and overall life satisfaction, including satisfaction with social and peer groups. When possible, studies should include self-report measures from people with autism who serve as study participants. For example, data from self-report measures might help to understand if the benefits of interventions targeting "harmless" autistic behaviors (e.g., "stimming") outweigh the risk of impacts such as provoking anxiety or confusion. A worthy goal for any intervention is to help individuals with ASD understand and utilize their strengths.

All research involving human participants must be conducted in accordance with high ethical standards, minimizing harms and risks and maximizing benefits; respecting human dignity, privacy, and autonomy; taking special precautions with vulnerable populations; and striving to distribute the benefits and burdens of research fairly. The described research will play an important role in distinguishing

effective interventions from ineffective ones and in identifying risks and benefits that should be taken into consideration before using these interventions.

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QUESTION 5: WHERE CAN I TURN FOR SERVICES?

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

New findings and opportunities relating to ASD services over the last two years stem from both research findings that incrementally advanced the understanding of issues affecting the service system and new legislative initiatives that have the potential to dramatically affect the way individuals with ASD access and pay for services.

Access and Payment

The 2011 addendum to Question 5 of the *IACC Strategic Plan for ASD Research* discusses the Affordable Care Act passed by Congress in 2010 and the Mental Health Parity Act implemented in 2010, both of which have the potential to expand service coverage for individuals with ASD. The importance of the Affordable Care Act was recently highlighted in a report estimating that up to 45% of children identified through the U.S. special education system as being on the autism spectrum (206,330 children in 2011) receive Medicaid-reimbursed services (Semansky, Xie & Mandell, 2012). Within the public insurance system, all 50 States offer waivers under Medicaid to provide home and community-based services to Medicaid recipients, and many of those waivers include individuals with ASD. Nine States also have autism-specific Medicaid waivers.

Not mentioned in the addendum in the *2011 IACC Strategic Plan* is the proliferation of private insurance mandates passed by State legislatures. Since 2008, 31 States have passed legislation requiring private insurance plans that are subject to State regulations to cover ASD-related services (National Conference of State Legislatures, 2012). These mandates range greatly in the types of services covered and the maximum dollar amount allowed, but all have at their core the coverage of behavioral treatments for young children with ASD. All of the mandates address service needs for children, with none mandating service coverage for individuals older than 21 years of age.

Two other major healthcare payers made benefits available for individuals with ASD. The Office of Personnel Management (OPM), which administers health benefits for more than 8 million Federal employees and beneficiaries, recently categorized applied behavior analysis (ABA) as medical therapy. Accordingly, insurance plans in the Federal Employee Health Benefits (FEHB) program were able to propose benefit packages that cover ABA for the 2013 plan year (U.S. OPM, 2012). The OPM decision did not, however, require insurance plans to cover ABA; only 67 of the 230 participating health plans elected to offer this coverage in 2013.

Coverage of ABA therapy for military families through the Department of Defense (DoD) TRICARE program, which provides

health care benefits for uniformed service members, retirees, and their families, has also made some recent advances. Prior to 2012, behavioral health treatment was only covered under TRICARE for active duty service members, but not for nonactive members and retirees. In July 2012, however, a Federal court ruling required TRICARE to cover ABA therapy for all military beneficiaries, including nonactive members and retirees, and TRICARE responded with an interim plan for providing coverage.

In addition, in 2012 both the U.S. House of Representatives and the U.S. Senate passed versions of the Federal defense spending bill that contained amendments offering behavioral health treatment coverage to all members of the military, as well as lifting an annual spending cap on ABA benefits. Because the two defense spending bills and amendments were not identical, the Senate and House met in conference committee in December 2012 to create a final compromise bill to send to the President. Cognizant of the ongoing litigation, Congress decided that the final version of the bill would provide a temporary benefit, with further benefits potentially to be provided in future legislation. The bill creates a 1-year pilot program that enables DoD to provide ABA benefits to all TRICARE beneficiaries, not just active duty members, and requires DoD to submit a report to Congress regarding the cost of extending this coverage, as well as any recommendations for additional legislation, within 270 days of enactment. The bill was signed into law on January 2, 2013.

Translating Research Into Practice

The most important goal of services research is translating the results into practice. A recent review of autism screening instruments and practices suggested that current screening instruments do not meet established quality criteria and thus are not suitable for widespread dissemination, and also that the current healthcare and education systems are not prepared for the influx of children that would result from more reliable and valid screening (Al-Qabandi, Gorter & Rosenbaum, 2011). Despite the negative assessment in this review, there is broad support for autism screening in the professional pediatric services community, and some promising findings have suggested more ideal implementation parameters for pediatric practices. However, more research and attention to the development of the service sector are needed before these innovations can be translated to full-scale utilization.

While the *2011 IACC Strategic Plan for ASD Research* mentions the lack of successful implementation in community settings of treatments that demonstrated efficacy in research settings, it cites no specific research studies examining these issues. Recently, a number of reports have emerged that conclude that community-based behavioral and pharmaceutical treatment implementation does not resemble evidence-based practice, and outcomes do not mirror those found in research trials (Eldevik et al., 2012; Frazier et al., 2011; Mandell et al., *in press*; Nahmias, Case & Mandell, 2012). On a more positive note, models for a medical home (a team-based healthcare delivery system that delivers comprehensive and

continuous medical care) for children with autism have now been developed. Preliminary evidence indicates that these medical homes result in greater parent satisfaction, greater shared decision making, and fewer unmet service needs (Golnik et al., 2012). On the other hand, these models have not been widely disseminated (Hyman & Johnson, 2012), although some efforts to study the implementation of evidence-based care have been funded and are underway.

Disparities

Recent research suggests that the lack of quality care is exacerbated among traditionally underserved minority groups. For example, compared with parents of white children with ASD, parents of Latino children with ASD were 1.5 times as likely to report difficulties getting needed referrals, twice as likely not to have a usual source of care, and almost three times more likely to have unmet routine healthcare needs (Parish et al., 2012). In a Canadian study, foreign-born children were diagnosed an average of two years later than Canadian-born children, and children living in rural areas were diagnosed six months later than children living in urban areas (Coo et al., 2012).

Wandering/Elopement

"Wandering" or "elopement"—defined as a dependent person exposing him or herself to potential danger by leaving a supervised, safe space or the care of a responsible person—is a critical safety concern for many families with children with ASD. As a result of the IACC's focus on wandering/elopement, a survey was conducted through the Interactive Autism Network (IAN) to collect data on parents' experiences with the wandering/elopement of their children with ASD. A study assessing the data collected found that forty-nine percent of those surveyed reported that their child had attempted to flee, and a quarter reported that the child had been missing long enough to cause concern (Anderson et al., 2012). Another result of the IACC's emphasis on this issue was that a medical subclassification code to characterize wandering associated with developmental disabilities was proposed to and accepted by the International Classification of Diseases (ICD) Coordination and Maintenance Committee for inclusion in the ICD-9, which is the ninth revision of the ICD coding system. The addition of this ICD-9 code provides the potential to track autistic wandering through healthcare data systems.

Restraint and Seclusion

The use of restraint and seclusion—techniques involving physical or mechanical means to restrict a person's bodily movement for disciplinary or protective purposes—continues to be an issue for parents of children with ASD due to concerns about potential for harm and possible lack of efficacy. In March 2012, the U.S. Department of Education's Office of Civil Rights released data from 2009-2010 on restraint and seclusion in which they reported that 70% of the cases where students were restrained involved students with disabilities (U.S. Department of Education Office of Civil Rights, 2012). This is the first time that restraint and seclusion data have been collected on such a large scale, and these data will serve as the foundation for future research. Additionally, in May 2012 the U.S. Department of Education issued a resource

document on the use of restraint and seclusion in schools (U.S. Department of Education, 2012). The document provides 15 principles that educators, parents, and other stakeholders can consider when developing or refining policies and procedures to support the use of positive behavioral interventions and supports and to help avoid the use of restraint and seclusion.

Mortality

Among the most compelling recent research findings is the observation that mortality is elevated among individuals with ASD relative to the general population (Gillberg et al., 2010; Mouridsen et al., 2008). Studies reported standardized mortality ratios (ratio of observed deaths in the study group to expected deaths in the general population) close to three for the ASD population, which means that persons with ASD are about three times more likely to die than an age-matched individual in the general population. To a large extent this increase in mortality in the ASD population appears to be due to co-occurring conditions (Bilder et al., 2012), such as epilepsy (Woolfenden et al., 2012; Pickett et al., 2011), rather than ASD itself. Researchers hypothesize that health care professionals who are treating individuals with ASD may overlook other co-occurring conditions.

Family Support

New knowledge is emerging about the causes of caregiver burden in families of people with ASD. For example, British researchers found that when young people with ASD had needs that were not met by the education or healthcare service system, it resulted in increased strain and stress for caregivers (Cadman et al., 2012). A 2011 systematic evidence review found that parent training may reduce parental stress and enhance parental confidence, but the quality of the studies reviewed was deemed to be poor (Zwi et al., 2011).

WHAT GAPS HAVE EMERGED IN THE PAST TWO YEARS?

Most gaps that have emerged in the last two years stem directly from the new findings described above. Of particular concern are the effects on service access and delivery, as well as the quality of the autism insurance mandates. It will be important to determine how State mandates will interact with the Affordable Care Act. Given the recent finding regarding the large proportion of children with ASD who are served through Medicaid, it will be similarly important to estimate how the Medicaid expansion under the Affordable Care Act affects autism-related services.

The recent findings regarding the lack of quality and positive outcomes of community-based care suggested an urgent twofold gap. First, autism researchers should borrow models from dissemination and implementation science to test methods to improve implementation of evidence-based treatments. Implementation science can help identify which components of effective care are the most feasible to implement in community settings. Second, quality measures should be developed to help monitor progress in improving care and outcomes for people with ASD. Research that examines the effects of specific treatment components rather than more complex comprehensive intervention

packages, combined with community-based partnership research, will be required to identify which active treatment components can successfully be implemented in community settings.

Another gap relates to the disparities in care that have been extensively documented. This growing body of research now should be paralleled by research on strategies to reduce or eliminate these disparities. Additional research on effective models for supporting families is also sorely needed.

Findings regarding wandering/elopement suggest the urgent need to develop and test specific prevention strategies and interventions to improve safety for individuals with autism. These may include both direct intervention with the individual and indirect intervention through the training of first responders, healthcare professionals, educators, and the broader community.

Although progress has been made in services policy and services research during the past two years, significant gaps remain. Moving forward, greater focus is needed in these areas to improve the lives of those with ASD and their families.

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QUESTION 6: WHAT DOES THE FUTURE HOLD, PARTICULARLY FOR ADULTS?

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

The needs of adults with ASD continue to be understudied. Over the last two years, relatively few peer-reviewed published studies have examined the needs of adults with ASD or service interventions to improve their functioning and quality of life. Few presented experimental or quasi-experimental evidence, a conclusion supported by the United Kingdom's (U.K.) National Institute for Health and Clinical Excellence (NICE) guidelines for the diagnosis, referral, and treatment of adults with ASD (National Collaborating Centre for Mental Health, 2011; Pilling et al., 2012). Because the NICE guidelines were unable to identify high-quality evidence, many of the adult autism guidelines in the U.K. are based on the guideline developer group's experience.

Diagnosis of ASD in Adults

Several studies have validated strategies to diagnose adults with ASD (Andersen et al., 2011; Bastiaansen et al., 2011; Joshi et al., 2011; Ritvo et al., 2011). However, only one diagnostic instrument was tested in an unselected community sample, which represents a truer test of the instrument's validity (Brugha et al., 2012). This instrument performed only moderately well in the community sample, suggesting the need for more research to identify the best direct observation measures for diagnosis.

Epidemiology of ASD in Adults

Recent research has shown that the prevalence of ASD in the adult population is much higher than previously believed. A new study of adults 16 years and older living in the community in England, using rigorous survey methodology, found the prevalence of ASD in adults to be 0.98%, with no differences by respondent age. This is similar to the prevalence in children, suggesting that a large portion of the observed increase in prevalence in the U.K. observed over the last two decades may be due to improved detection (Brugha et al., 2011). This study also found that adults with ASD were much more likely to be receiving public assistance and have a lower income than their unaffected peers. Interestingly, in the U.S. a similar prevalence of ASD was found among university students (White, Ollendick & Bray, 2011). Finally, new research indicates that in the U.S. as many as 10% of patients in residential psychiatric facilities may have undiagnosed ASD (Mandell et al., 2012).

Quality of Life/ Functional Outcomes

Free time among adolescents with ASD is frequently spent alone or with their mothers (Orsmond & Kuo, 2011). Furthermore, several new findings suggest that functional skills and quality of life for those with ASD plateau or even diminish during adulthood. For example, research in the U.S. showed that daily living skills improved during adolescence and into the early 20s but remained static during the late 20s (Smith, Maenner & Seltzer 2012). This plateau may be caused by adolescents leaving the more supportive high school environment, a notion supported by the recent finding of very low rates of employment and educational activities in young adults immediately following high school (Taylor & Seltzer 2011; Shattuck et al., 2012). In fact, more than 50% of youth with ASD who had left high school in the past two years had no participation in employment or education, a greater percentage than that of any other disability group (Shattuck et al., 2012). A study in Taiwan showed that while self-care and adaptive behaviors indicated the potential for a high level of independence among a sample of Taiwanese adults with ASD, only 14% were employed, and most of these worked only part-time (Lin, Yu & Yu, 2012).

Approaches to improve outcomes for young adults with ASD have had mixed results. For example, there is evidence that sheltered workshops—commonly used as an approach to increase the probability of employment among adults with ASD—do not, in fact, increase the probability of employment, despite being considerably more expensive than other vocational strategies (Cimera et al., 2012). However, social skills intervention has resulted in improvements across a variety of domains for young adults with ASD. Notably, in a randomized controlled trial studying the effectiveness of an evidence-based, caregiver-assisted social skills intervention, young adults with ASD reported decreased loneliness and improved social skills knowledge, while caregivers reported improvements in young adults' empathy, social skills, and frequency of participation in group social interactions (Gantman et al., 2012).

Service Use

Based on data from a nationally representative survey in the U.S., it has been shown that 60% of young adults on the autism spectrum ages 19–23 continue to use mental health and medical services and to receive speech and occupational therapies past high school (Shattuck et al., 2011). Rates of service disengagement are very high after students leave high school; African American adolescents with ASD were more than three times as likely as white adolescents to completely disengage from service use, and adolescents in families with incomes less than $25,000/year were almost six times more likely to completely disengage from service use compared with families with incomes greater than $75,000/year. This highlights the critical importance of Medicaid entitlements, as privately insured adolescents with ASD were more than twice as likely as adolescents with public healthcare insurance to disengage from service use (Shattuck et al., 2011).

WHAT GAPS HAVE EMERGED IN THE PAST TWO YEARS?

New gaps may not have emerged in the last two years as much as they were systematically quantified and highlighted. A systematic review of vocational interventions for adolescents and young adults with ASD, who ranged from 13 to 30 years old, found only five studies, all of poor quality and relatively narrowly focused, indicating the urgent need for rigorous development and testing of these types of interventions (Taylor et al., 2012). A review of social skills interventions for people on the autism spectrum found only two rigorous studies that included young adults, with both studies including only individuals with average or above average intelligence (Reichow, Steiner & Volkmar, 2012). Again, this review points to the critical lack of tested interventions for adolescents and young adults either to address the core symptoms of ASD (social impairments, communication, and repetitive behaviors) or to improve adaptive behaviors that increase the potential for independence. These reviews emphasize the importance of continuing research efforts to develop and test interventions that address the needs of individuals with ASD across the spectrum.

A review of the intersection of ASD and the criminal justice system also highlights a gap in knowledge of the extent to which individuals with ASD exhibit criminal behavior and may enter the criminal justice system (Lerner et al., 2012). The review points out that while most studies find no link between ASD and criminal behavior, some individuals with ASD do end up in the criminal justice system and may require special treatment. In addition, no research has been conducted on the extent to which individuals with ASD are victims of crimes.

Two published reviews also highlight the lack of understanding of what happens to individuals with ASD as they become older adults (Piven & Rabins, 2011; Happé & Charlton, 2012). In this vein, additional research is needed to identify direct observation measures that can be used in adult diagnosis and to validate diagnostic instruments for adults.

Finally, new findings about disparities in service delivery to and outcomes for adults with ASD point to the urgent need for research to understand the reasons for these disparities and to ameliorate them.

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QUESTION 7: WHAT OTHER INFRASTRUCTURE AND SURVEILLANCE NEEDS MUST BE MET?

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

Several advances have been made in developing infrastructure for autism research over the past two years, including increased data sharing and availability of DNA samples for study. Surveillance efforts have continued and are expanding in scope, and investments in the autism research workforce have been made to ensure continued development in the field.

Data Sharing

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

Biobanking

The loss in June 2012 of frozen samples from 55 brains that were part of the ATP collection after a freezer malfunction at the Harvard Brain Tissue Resource Center was a tragic blow to the slowly developing ASD biobank effort, as nearly one-third of the largest autism brain repository was destroyed or compromised in this accident. Quality investigations following the accident showed that while the affected tissue will no longer be able to be used for general research

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

purposes, the tissue integrity and genetic material are adequate for some specialized research uses. The loss will lead to delays in research due to extremely limited availability of samples for some time to come.

Progress is being made in other aspects of brain banking efforts. The ATP has developed a donor registry in which 5,976 individuals have registered to donate brain tissue and carry a card designating their wishes. In the last two years, the program has received 15 brains and 278 individuals have been added to the registry. Brains that are donated to the ATP are analyzed and the data are made available through the ATP informatics portal, which now has 297 neuropathology reports on donor brains (Autism Tissue Program Informatics Portal website). These data are central to the ATP Brain Atlas Project, which began 13 years ago to create a three-dimensional map of the autistic brain that integrates anatomic and gene expression data throughout the adult human brain. Brain repositories contributed 40 brain hemispheres to the original project, and an additional 53 hemispheres have now been processed. During the past two years, the final 10 brain hemispheres were analyzed.

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

In parallel, the NIH has also been addressing the need for more coordination and networking in biobanking by creating the NIH Neurobiobank, a federation linking NIH-supported brain banks via a centralized data management system. The project was launched in October 2012. The accompanying NIH Neurobiobank Information Technology (IT) Portal will provide information about brain and tissue donation for research to the public, disease advocates, and researchers, including links to brain banks and their consent policies and other information.

Genetics

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

Study (IBIS) high-risk infant cohort. These cohorts are expected to accrue an estimated 456,775 and 1,360 DNA samples, respectively (by 2014 for the Biorepository and 2015 for the others). Additionally, Autism Speaks and the Simons Foundation jointly fund the Baby Siblings Research Consortium, with an estimated 1,780 DNA samples expected by 2015.

Furthermore, AGRE expanded its Multiplex Family Collection by more than 28% by making DNA available for an additional 383 families (including 653 probands, or individuals with ASD). The total DNA available from AGRE includes 1,736 families with a documented pedigree, or ancestry. The total number of probands in the collection is 3,348, while the number of fraternal twins is 204 and the number of identical twins is 118. The National Institute of Mental Health (NIMH)-funded Center for Collaborative Genomics Studies on Mental Disorders (CCGSMD) at Rutgers University, a resource center that provides biological samples, data, and data access tools to researchers, has recently increased the number of autism-related samples available to researchers. This makes it possible to conduct studies with increased statistical power, allowing the detection of rarer genetic causes of autism. The CCGSMD currently distributes samples for autism-related research from almost 11,500 children with autism and their families.

Induced Pluripotent Stem Cells (iPSCs)

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

Clinical Trials

Two new networks have been established for clinical trials. First, the Network for Excellence in Neuroscience Clinical Trials (NeuroNEXT) was created to conduct treatment studies (Phase 2 or biomarker studies) through partnerships with academia, private foundations, and industry. The network is designed to expand the National Institute of Neurological Disorders and Stroke's (NINDS) capability to test therapies, increase the efficiency of clinical trials before embarking on larger studies, and respond quickly as opportunities arise to test treatments. Second, the NIMH launched the Fast Fail Trials in Autism Spectrum Disorder (FAST-AS), a contract-based initiative that uses an experimental medicine paradigm to quickly test pharmacologic treatments and rule out ineffective ones, enabling more rapid identification of promising therapeutic approaches.

Autism Speaks convened two workgroups composed of academic and industry leaders, as well as representatives from Autism Speaks and the Simons Foundation, to evaluate existing outcome measures and support the development of medicines to improve social communication, repetitive behaviors, and anxiety associated with autism. The workgroups met with the Food and Drug Administration (FDA) to help develop consensus around appropriate outcome

measures for autism clinical trials, and papers summarizing the outcome are in preparation.

In 2012, the Innovative Medicines Initiative (IMI) launched a major new effort in Europe called the European Autism Interventions - A Multicentre Study for Developing New Medications (EU-AIMS), investing $55 million over five years to accelerate the discovery and development of medicines for ASD.

Surveillance

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

The CDC's ADDM Network infrastructure has now been expanded to include six sites evaluating prevalence among younger children. One ADDM site, funded by Autism Speaks, will include direct population-based screening and evaluation to compare to records-based surveillance. Additionally, CDC, Autism Speaks, and NIH are co-funding a project that is underway to determine the prevalence of ASD among Somali children in Minneapolis, Minnesota. Other surveillance programs also have made progress over the last two years, yielding results that have informed further autism initiatives. For example, findings from CDC and HRSA's National Survey of Children's Health (NSCH) led to the development of the Pathways to Diagnosis and Services Survey, a population-based study of the diagnostic and service experiences of children with autism (CDC, 2012).

Communication and Dissemination

Direct studies of family involvement in autism research shows participation still lags behind that for other diseases. Results from a 2005 national online survey of the general population (not specific to autism) reported that only 15% of adults have had the opportunity to participate in a clinical research study (Gullo, 2005). Similar results were found in a 2007 market research survey on autism research attitudes and behavior, where only 14% of respondents reported having participated in an autism-related research study, though 90% reported that they would like to participate (Patchwork Consulting LLC, 2004). Unfortunately, 2012 data from IAN continues to corroborate that finding, reporting that only 16% of respondents say they have participated in autism research (IAN Data Explorer website).

Research Workforce Development and Support

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

The American Recovery and Reinvestment Act (ARRA), enacted by Congress in February 2009, included funds that were awarded to autism research grantees during a 2-year period from 2009 to 2010. During that time period, ARRA provided $123,916,638, or 22%, of federal funds for autism research. Now that ARRA funding has ended, even with an unchanged NIH budget appropriation, autism research funding will experience a real decline.

WHAT GAPS HAVE EMERGED IN THE PAST TWO YEARS?

Data Sharing and Databases

The NDAR program has identified several critical data sharing issues that must be addressed as the field continues to move forward:

- Timeliness – Researchers are currently expected to share data updates every six months and full results at the time of publication. However, this process is frequently delayed, which is an issue that must be remedied.

- Data Quality – While provisions have been made to include the cost to share data within a project's budget, further support is needed to ensure data are professionally maintained and shared throughout the life of a project.

- Culture – Offering funding opportunities for secondary use of existing data is needed to demonstrate and improve the utility of the investment made in data sharing infrastructure.

- Data Storage and Computational Approaches – Costs associated with the storage and processing of data may overwhelm the existing infrastructure. Establishing the mechanisms for efficient data storage and use of available emerging computational pipelines is recommended.

In this era of "big data," there are emerging opportunities for large datasets that can

be used for secondary analyses. The first manuscript from the NIH-funded Autism Health Outcomes Study, with claims data from one large commercial insurance company on 33,000 individuals with ASD, nearly 100,000 of their family members, and over 100,000 controls, is expected to be published in 2013. The Mental Health Research Network, a consortium of public-domain research centers based in large not-for-profit healthcare systems with 11 million patients, including nearly 24,000 children with an ASD diagnosis, could also be a useful resource. Additionally, claims data from Medicaid, the single largest healthcare insurer of children in the United States and the largest insurer of individuals with disabilities, could provide data on more than 75,000 individuals with ASD each year for secondary data analyses. Linking these large datasets to environmental data would provide another untapped resource for future research.

Biobanking

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

Genetics

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

Infrastructure Support

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

Induced Pluripotent Stem Cells (iPSCs)

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

Clinical Trials

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

Surveillance

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

Communication and Dissemination

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

Research Workforce Development and Support

Continued focus on developing a diverse research workforce through investment in young investigators at levels of predoctoral and postdoctoral training is a high priority. Similarly, there is a need to focus on developing a funding mechanism to support early-career investigators in order to bridge the gap between postdoctoral training and assistant professorship. Retention of investigators in active research and

investment in vital ongoing autism research efforts will be affected by the loss of ARRA funding. These and other potential impacts will need to be monitored. The decline in Federal spending post-ARRA has raised significant concerns about the sustainability of research progress and the possible loss of well-trained, productive autism researchers. Active efforts must be made to maintain and continue enhancing the research workforce needed to address the many research needs and challenges presented by ASD.

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CONCLUSION

The *IACC Strategic Plan for Autism Spectrum Disorder (ASD) Research*, first published in 2009, has now been updated in 2010, 2011, and 2012. The changes in "What do we know?" and "What do we need?" that are described in the *2012 IACC Strategic Plan Update* are intended to recap recent research accomplishments and provide further guidance to researchers, research funders, and other members of the community about the opportunities for progress in each of the seven question areas of the *Plan*. The *2012 IACC Strategic Plan Update* does not address the need for an increased focus on services provision issues, which has been discussed at IACC meetings and is an area of intense interest among several IACC members as well as some of the content experts who participated in the process of developing the *2012 IACC Strategic Plan Update*. In the coming year, the Committee looks forward to an opportunity to delve more deeply into this and other issues that emerged as gaps during the update process.

The IACC wishes to express its appreciation to the many people who assisted in developing the *2012 IACC Strategic Plan Update*. A list of these external experts is provided at the end of this document. In addition to the experts from the advocacy, research, and services communities who generously volunteered their time to work with the IACC on this effort, the Committee also received input from many members of the public who sent in ideas or provided written recommendations for consideration. While the final *2012 IACC Strategic Plan Update* could not reflect every concept or concern that was raised during the updating process, this document was assembled by the IACC with the intent of capturing the current state of the science with respect to autism research, as well as a sense of where the newest opportunities and challenges lie in this effort to meet the evolving needs of people with ASD and their families.

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