THE
INTERAGENCY AUTISM COORDINATING COMMITTEE

STRATEGIC PLAN

FOR AUTISM SPECTRUM DISORDER RESEARCH

2013 UPDATE

IACC
INTERAGENCY AUTISM COORDINATING COMMITTEE

OFFICE OF AUTISM RESEARCH COORDINATION
NATIONAL INSTITUTES OF HEALTH

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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 (CAA) of 2006, and renewed under the Combating Autism Reauthorization Act (CARA) 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 biomedical 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 Act (CAA; Public Law 109-416) and the subsequent Combating Autism Reauthorization Act (CARA; Public Law 112-32) established an Interagency Autism Coordinating Committee (IACC) to advise the Secretary of Health and Human Services on issues related to Autism Spectrum Disorder (ASD). One responsibility of the IACC is the development of a strategic plan for ASD research, to be updated yearly. The *IACC Strategic Plan*, first issued in 2009, was produced by the IACC, composed of federal officials and public stakeholders, with extensive input from researchers, adults on the autism spectrum, parents, advocates, and the general public that was gathered through a series of meetings and public comment opportunities. This inclusive process ensured that the *IACC Strategic Plan* reflected diverse perspectives from across the autism community.

The *IACC Strategic Plan* is organized around seven general topic areas that are represented in the plan as consumer-focused Questions (e.g., Question 1, "When should I be concerned?" which covers the topic of screening and diagnosis). Each Question is assigned a chapter that provides a description of the state of the science in that area. Each chapter also contains a section describing the research and community needs for its relevant Question; the aspirational goal, or long term vision, for each area; and a list of specific long- and short-term objectives. The objectives were created by the Committee to address critical gaps and opportunities they perceived in the research landscape in 2009. Each objective also includes a recommended budget that serves as an estimate of how much the Committee projects it might cost to conduct the research-related activities described. The *IACC Strategic Plan* was updated in 2010 and 2011, adding several new objectives over these years. In 2012, following the reauthorization of the Committee, the plan was updated with advances and new research opportunities.

For the 2013 update of the *IACC Strategic Plan*, the Committee voted to focus on accountability without adding new objectives or re-writing the previous version. With access to an extensive portfolio analysis conducted by the National Institutes of Health (NIH) Office for Autism Research Coordination (OARC) linked to every objective, as well as the annual *IACC Summary of Advances* documents from past years, the IACC reviewed what has been invested in ASD research in the United States since 2008. Using data from both public and private funders, the IACC determined the level of progress for each of the 78 objectives in terms of the number of projects funded and dollars committed to each objective since 2008. To assess the return on this investment, the IACC also invited a group of external experts to evaluate how research has supported progress toward the aspirational goals in each of the seven chapters of the *IACC Strategic Plan*.

This update summarizes both investment and scientific progress across all seven Questions of the *IACC Strategic Plan*. Most areas have received extensive investment ($1.5 billion expended from 2008-2012 by federal and private funders) and significant progress has been made since the original *Plan* was published in January, 2009. According to the PubMed database of biomedical research literature, over 11,000 journal articles on autism have been published since January, 2009, more than double the number published in the preceding 5 years. The world of ASD research has changed profoundly during this period, with increases in United States ASD prevalence estimates, changes in ASD diagnostic criteria, greater

understanding of co-occurring conditions and services needs, and new insights from genetics, environmental studies, and neuroimaging into the biology and etiology of ASD. In addition to this review of the investment and progress, the Committee and external experts identified current research gaps, needs and barriers, as well as new opportunities created by advances in the field, which can provide direction for future investment.

In preparing the *2013 Strategic Plan Update*, the IACC also recognized some cross-cutting issues that have emerged with greater urgency since January, 2009. While much of the research literature has been focused on infants and children, the IACC encouraged more attention to the needs of adults with ASD. Additionally, because ASD research has frequently been limited to individuals with less severe levels of disability or those who live in communities with greater resources and access to healthcare, the IACC felt that more focus on the most disabled individuals and underserved populations would be essential. Finally, in both public comments received by the IACC as well as discussions within the Committee meetings, the need for interventions for co-occurring or associated conditions was emphasized, as for many individuals and families these issues are equally or more challenging than the core symptoms of ASD. Throughout the seven Question areas in the *IACC Strategic Plan*, the Committee underscored the need for research to focus on developing efficacious, efficient, scalable, and cost-effective interventions, tools, and practices that can be translated into affordable and practical healthcare and service options for the autism community. The Committee also highlighted the urgent need to accelerate translation of scientific discoveries into interventions that can improve quality of life for individuals with autism and their families.

Though this *2013 IACC Strategic Plan Update* will inevitably be unable to capture all the changes in the ASD field since 2008, the IACC has endeavored to deliver through this document an accounting of the investments made and how research has evolved since the January, 2009 publication of the original *IACC Strategic Plan*. This update should be read with two other IACC publications to gain a more complete picture of the autism research landscape. The ***IACC Autism Spectrum Disorder Research Portfolio Analysis Report*** describes Federal and non-Federal investments in autism research. 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. Together, with this *2013 IACC Strategic Plan Update*, the Committee hopes that these documents will provide a useful overview of the state of autism research at the end of 2013.

QUESTION 1

WHEN SHOULD I BE CONCERNED?

INTRODUCTION

Aspirational Goal: Children at risk for ASD will be identified through reliable methods before ASD behavioral characteristics fully manifest.

When originally framed, Question 1 was directed toward identifying at-risk children by the age of 24 months to facilitate the greatest chance of successful early intervention. Scientific advances since then have shown that, in infants at high genetic risk for ASD due to having an older sibling with autism, symptoms of autism begin to emerge as young as 6 months of age in those who later develop ASD. These new findings suggest that it may someday be possible to screen for children at risk for ASD before the emergence of the full symptoms of autism and early enough to facilitate even more effective intervention. While recent findings have demonstrated this early screening potential in high-risk infant siblings, future challenges include determining whether the same potential for very early identification can be extended to other high risk populations (e.g., very low birth-weight infants) and/or to the general population.

Many of the advances in the screening and diagnosis area have been in development and refinement of screening tests. Moving forward, more attention needs to focus on innovations in diagnostic tools. There also remains a great need for the development of efficient and cost effective screeners for use in children below 18 months of age, as well as more efficient methods of deploying developmental and ASD screening in community settings, including evaluation of effective parent-professional communication strategies for coping with concerns, referrals, follow-up

evaluations for services and diagnosis, and linkage to appropriate services and supports. In addition, the development of culturally sensitive diagnostic tools that can be more easily used in both clinical and research settings is urgently needed. Finally, there has been a growing awareness of the need for better tools to diagnose adolescents and adults on the autism spectrum and to provide meaningful assessments of functioning--an issue that is captured in an objective in Question 6 of the *IACC Strategic Plan*, but may involve adaptation of tools that are currently used to diagnose children.

PROGRESS TOWARD THE STRATEGIC PLAN OBJECTIVES

The *2011-2012 IACC ASD Research Portfolio Analysis* reviewed projects funded by both government agencies and private foundations from 2008-2012. From 2008-2012, the total funding devoted to projects that address Question 1 was $187 million, and if just the years since the publication of the first *IACC Strategic Plan* in 2009 are considered, the funding for Question 1 related projects was $158 million. On average for each year from 2009-2012, the funding levels for this Question were 35 percent higher than the 2008 level ($29 million) that preceded publication of the *IACC Strategic Plan*. Also in years 2009-2012, 11 percent of the funding for this Question supported core/other research projects outside of the research gaps covered by the nine objectives in Question 1.

Of the nine specific objectives under Question 1, four objectives addressing development of screening and diagnostic tools, identification of risk biomarkers, and a workshop on ethical issues, met or exceeded the recommended budget and fulfilled the recommended number of projects. Three objectives, concerning determining the utility of genetic tests and developing measures of heterogeneity and symptom severity, partially met the recommended budget and had a number of projects underway. One objective, on understanding the reasons for disparities in screening and diagnosis, was far below the recommended budget and number of projects. The remaining objective, on studies to understand if early diagnosis leads to early intervention and better outcomes, did not have any dedicated funding or projects, though some aspects of this research topic are covered in projects that are categorized elsewhere, such as a project in Question 4 on early intervention (that was preceded by early diagnosis) that also partially addresses the issue of outcomes.

PROGRESS IN THE FIELD

Over the past 5 years, progress has been made toward developing tools and practices for more effective screening and diagnosis. New research suggests that existing screening tools, such as the Modified Checklist for Autism in Toddlers (in particular, the new M-CHAT-revised with follow-up interview (M-CHAT-R/F), which is not yet in widespread use)[1,2] and the Infant-Toddler Checklist,[3] can be effectively used by pediatricians and other community providers. The M-CHAT-R/F shows promise as a screen for communication and developmental delays and as an ASD screen with the follow-up interview between 18 – 36 months of age. The Infant-Toddler Checklist shows promise as a broadband screen for communication impairments that can identify children with autism between 12 and 24 months and has practical value as the basis of a 5-minute screen during the 1-year well-baby check-up.[4] New research suggests that with repeated screening at the ages of 6, 12, and 18 months, it might be possible to identify as many as 95 percent of children with ASD by the age of 24

months. While this represents a remarkable scientific advance, validation and translation of this potential into reality in the general population and in community settings remains an enormous gap.

The clinical reality is that currently only about 20 percent of children with ASD are being identified early (by 3 years of age).[5] Barriers to the broader deployment of advanced screening and diagnostic tools include cost and the expertise required to administer the tests. Also, repeat screenings at 6 month intervals beginning at 6 months of age are not being done in practice, despite demonstrated efficacy of such screenings in at-risk infants.[6] In addition, it appears that children who are identified in early screens are not always being referred for diagnosis and early intervention, even though there is now strong evidence to suggest the benefit of early intervention.[7-9] Thus, we need to better understand the barriers that are preventing caregivers from seeking a diagnostic evaluation after a child fails an autism screen and to identify strategies that will help caregivers navigate the pathway from screening to diagnosis to entry into early intervention. Until this gap between screening and intervention is closed, the potential impact of ASD screening on improving outcomes for individuals with ASD will not be realized.

More needs to be done to raise awareness in the practitioner community of the current capabilities and benefits of early, repeated screenings, early diagnosis, and early intervention. Although not within the scope of a research plan, the severe lack of capacity of professionals to conduct screening and diagnosis and to provide services and supports remains a major stumbling block. Currently, in the United States, over 1 percent of children are estimated to have an ASD and about 15 percent of children are identified with developmental disorders throughout childhood. Although not all developmental disorders are identifiable in the first 3 years of life, research indicates that only an estimated 2.8 percent of infants and toddlers receive early intervention services, suggesting that many children who need early intervention services are not receiving them.[10] More complete data are needed to estimate the population and characteristics of children with ASD and other developmental delays that are likely to need early intervention services so that early identification leads to timely evaluation and access to services and supports.

Some progress has been made in understanding the prevalence of ASD in diverse communities, with recent results now suggesting that what initially appeared to be lower prevalence of ASD in some minority populations may instead be a reflection of less effective diagnosis of ASD in those communities.[11,12] There is still a gap, however, in understanding the reasons for disparities in access to screening, diagnosis, referral, and early intervention services. While this issue was targeted by the IACC in the *2009 IACC Strategic Plan*, much more work is needed to address this gap, and it should remain the subject of intense focus.

An area of groundbreaking research for Question 1 has been the detection of ASD risk in high risk infants (infant siblings) as young as 6 months of age. Among infant siblings, differences in the development of white-matter tracts have been observed in 6-month-olds who are later diagnosed with ASD.[13] A similar population of high risk infants has also been shown to have significant delays in postural development, including slower emergence and mastery of advanced postures such as sitting and, later, standing.[14] Additionally, differences in the developmental trajectories of visual attention to social stimuli were identified as a marker of those infant siblings who later developed ASD. Eye tracking technology that gives children a choice between looking at moving geometric patterns or human faces was found to reliably distinguish children with ASD, who prefer to look at the geometric images, as young as 14 months of age.[15] A decline in a child's visual attention to the eyes of others during social interactions when he/she is 2 to 6 months of age is another biomarker of infants who are later diagnosed with ASD.[16] These exciting results suggest new potential screening tools based on eye tracking technology,

which, like other existing tools, must now be validated in other high risk populations and in the general population. If proven efficacious, these tools must be modified for broader use in order to be beneficial to the wider community.

At the molecular level, there has been significant progress in identifying genetic differences in ASD. Mutations associated with genetic risk for ASD can now be identified in about 30 percent of individuals diagnosed with ASD.[17-23] This increase in the capability to link cases of ASD with specific genetic markers has risen substantially over the past 5 years, and further progress is anticipated. In order for these genetic markers to be useful from a screening perspective, they too will need to be validated in general populations. Such an advance could also help address the issue of adult diagnosis. It is noteworthy that the overwhelming majority of screening and diagnostic tools currently under development are designed for and are being tested in infants and children, but there is a scarcity of tools that can be used effectively in adults. More effort needs to be focused on developing, adapting, and validating screening and diagnostic tools for use across the lifespan.

Advances in capabilities to detect ASD early create a variety of legal, ethical, and social concerns, and the *IACC Strategic Plan* update of 2011 recommended that a workshop be held to address these issues. The NIH, the Autistic Self Advocacy Network, and Autism Speaks all held workshops that either directly or partially addressed this topic, fulfilling the original *IACC Strategic Plan* objective. Still, continued attention to this topic is warranted as the legal, ethical, and social implications of ASD screening will continue to evolve in response to changing technologies.

In 2013, the ***Diagnostic and Statistical Manual of Mental Disorders (DSM)*** was revised for the release of its fifth edition, consolidating previous ASD diagnoses together into a single "autism spectrum disorder" category.[24,25] The ***new criteria*** in DSM-5 raised potential concerns in parts of the autism community that some people who would have previously met the criteria for diagnosis (and potentially benefitted from ASD-specific services) may no longer be diagnosed under the new criteria. Some studies have been conducted to better understand the potential implications of the change in diagnostic criteria,[26-28] but more research will be needed to further assess the reliability and validity of *DSM*-5 ASD criteria, and to understand the impact of these new criteria on diagnosis, prevalence estimates, and access to services. In addition, diagnostic instruments must be adapted to accommodate the new criteria.

PROGRESS TOWARD THE ASPIRATIONAL GOAL

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

Within the past 5 years, tools and technologies have emerged that have the potential capability to detect children at risk for ASD before the full manifestation of behavioral symptoms, which is the aspirational goal of this Question. The challenges that remain are to develop practical, cost effective tools that will be broadly accessible; validate and adapt these tools for use in a variety of diverse populations; support the development of the needed provider workforce; and deploy these tools so that this capability becomes a clinical reality across communities. Additionally, the link between screening and referral to intervention remains weak, but must be strengthened for the realization of the aspirational goal.

Even when early screening takes place and at-risk children are identified in clinical and community settings, almost half the children are not progressing through the system to diagnosis and early intervention and face major roadblocks in the ultimate goal of accessing needed services and supports as early as possible. Future work should focus on identifying and removing the cultural and logistical impediments that may be preventing families and providers from following up on screening results that have identified a child with increased risk for ASD.

In the area of continued screening tool development, there is a need for increased investigation of risk factors in the 0-12 month age group. Currently there is no combination of genetic and behavioral markers in this age group that are reliable indicators of ASD risk. Also, the focus of the search for biomarkers has been on behavior and genetics, but this focus needs to be broadened to include a number of physiologic markers as well (e.g., sleep, autonomic measures, and neurological, metabolic/microbiome, immune, and gastrointestinal (GI) function measures). In addition, in the period prior to the development of language skills, biomarkers such as early motor tone, posture, symmetry, visual attention, and joint attention should be explored further. To improve accuracy of identification, emphasis should be placed on both direct observation and parent report.

In order to increase community usefulness of established tools, more investment is needed for community-based studies with larger sample sizes that will increase knowledge of disparities among various groups in access to screening and in applicability of screening tools. New technologies such as portable device applications (apps), electronic health records (EHRs), and video tasks will also be important for the development of innovative screening methods and screeners that could be used for diagnosis in children and adults. Finally, rigorous validation of existing tools is necessary so the community will know which ones are reliable in which populations.

True realization of the aspirational goal is dependent on progress on the other Questions of the *IACC Strategic Plan*. While all the Questions are interrelated, the success of screening and diagnosis in terms of its benefit for those identified will depend most heavily on the development and deployment of effective interventions (Question 4) and services (Question 5) that address the needs of the whole spectrum, including those with mild or moderate levels of disability. In addition, while the aspirational goal of Question 1 focuses on early diagnosis in children, there is also a need to greatly strengthen efforts to develop and adapt diagnostic tools for use in adult populations, addressed in Question 6 of the *IACC Strategic Plan*, in order to enhance the potential to reduce disability and improve quality of life across the lifespan.

Question 1 Cumulative Funding Table

IACC Strategic Plan Objectives	Funding					
Year	2008	2009	2010	2011	2012	Total
Develop, with existing tools, at least one efficient diagnostic instrument (i.e., briefer, less time intensive) that is valid in diverse populations for use in large-scale studies by 2011. *IACC Recommended Budget: $5,300,000 over 2 years*	1.1 $75,000 2 projects	1.S.A $4,728,120 15 projects	1.S.A $4,963,192 15 projects	1.S.A $2,387,955 8 projects	1.S.A $2,214,544 8 projects	$14,368,811
	1.S.A. Funding: The recommended budget was met. Significantly more than the recommended minimum budget was allocated to projects specific to this objective **Progress:** Though several projects are underway to develop efficient screeners and diagnostic tools, the overarching aim of this objective has not yet been achieved. **Remaining Gaps, Needs, and Opportunities:** In addition to efficiency, emphasis should be placed on developing cost-effective, performance-based tools, and on validating these across diverse populations. Recent RFAs issued by NIMH and Autism Speaks that focus on parental engagement and early access to care could result in projects that address this objective. Currently, many screening tools exist, and these tools in many cases can be adapted for broader uses, but improved diagnostic tools remain an outstanding need.					
Validate and improve the sensitivity and specificity of new or existing screening and diagnostic tools, including comparative studies of general developmental screening versus autism-specific screening tools, in both high-risk and population-based samples, including those from resource-poor international settings and those that are diverse in terms of age, socio-economic status, race, ethnicity, gender, characteristics of ASD, and general level of functioning by 2012. *IACC Recommended Budget: $5,400,000 over 3 years*	1.2 $1,246,922 8 projects	1.S.B $3,973,711 11 projects	1.S.B $2,443,557 11 projects	1.S.B $970,284 9 projects	1.S.B $2,126,824 12 projects	$10,761,298
	1.S.B. Funding: The recommended budget was met. Significantly more than the recommended minimum budget was allocated to projects specific to this objective **Progress:** Efforts to validate screening tools in diverse populations have begun, including ACF and CDC-funded work with a general developmental screener in Native American populations. More efforts are needed, however, to cover other diverse populations. **Remaining Gaps, Needs, and Opportunities:** There is a need for more comparative studies between general developmental screeners and autism-specific tools. Remaining needs in this area are promotion of family engagement and follow-through, training of intervention and primary care providers and family members, and development of free and validated diagnostic tools for international communities.					
Conduct at least three studies to identify reasons for the health disparities in accessing early screening and diagnosis services, including identification of barriers to implementation of and access to screening, diagnosis, referral, and early intervention services among diverse populations, as defined by socioeconomic status, race, ethnicity, and gender of the child, by 2012. *IACC Recommended Budget: $2,000,000 over 2 years*	N/A	1.S.C $139,072 1 project	1.S.C $0 0 projects	1.S.C $28,000 1 projects	1.S.C $629,521 3 projects	$796,593
	1.S.C. Funding: The recommended budget was partially met. **Progress:** The projects supported are only a beginning and more needs to be done to address this objective. **Remaining Gaps, Needs, and Opportunities:** The studies coded to this objective do not focus on identifying reasons for early screening and diagnosis disparities; instead, they are aimed at developing tools to address these disparities. The progress in this area is poor for autism relative to other disease fields, and the more sophisticated approaches employed in fields such as AIDS prevention should be applied to autism. More work should be done to identify the reasons for disparities and to validate the tools that are being developed. A barrier to progress is the need for qualitative studies and the difficulty in securing funding for such studies.					

Table 1: Question 1 Cumulative Funding Table, see appendix for a color-coding key and further details.

Question 1 Cumulative Funding Table

IACC Strategic Plan Objectives	Funding					
Year	2008	2009	2010	2011	2012	Total
Conduct at least two studies to understand the impact of early diagnosis on choice of intervention and outcomes by 2015. *IACC Recommended Budget: $6,000,000 over 5 years*	N/A	1.S.D $0 0 projects	1.S.D $0 0 projects	1.S.D $0 0 projects	1.S.D $0 0 projects	$0
	1.S.D. Funding: There has been no specific funding for this objective. **Progress:** No projects that are specifically targeted to this area have been initiated, though there are some projects coded to Question 4 that represent progress on this objective (e.g., Early Start Denver Model studies that study children who were diagnosed early and some of their outcomes following treatment, and studies coded to 4.S.F. that investigate early interventions for toddlers with ASD). **Remaining Gaps, Needs, and Opportunities:** The Planning Group felt that the wording of this objective is confusing. Based on transcripts from when this objective originated, it appears that the committee wanted to better understand if early diagnosis led to early intervention, and if so, if that led to better outcomes. Some of the questions that could be asked are whether or not early diagnosis leads to early intervention, and whether or not early diagnosis is always associated with better outcomes when compared to late diagnosis, or if the outcomes depend on the type of early intervention used. In future revisions of the ***Strategic Plan***, the committee may want to refocus this objective.					
Conduct at least one study to determine the positive predictive value and clinical utility (e.g., prediction of co-occurring conditions, family planning) of chromosomal microarray genetic testing for detecting genetic diagnoses for ASD in a clinical setting by 2012. *IACC Recommended Budget: $9,600,000 over 5 years*	N/A	N/A	1.S.E $2,180,042 3 projects	1.S.E $690,019 1 project	1.S.E $1,273,122 4 projects	**$4,143,183**
	1.S.E. Funding: The recommended budget for this objective was partially met. **Progress:** Microarray testing is now recommended in AAP guidelines. The utility of this testing is more clear in cases where there is already a concern than for diagnostic use in the general population. **Remaining Gaps, Needs, and Opportunities:** There is a need to better understand the relationship of genotype to phenotype, implications of genotype for treatment or medical management options, and to understand the potential impact of microarray testing on providers and families.					
Convene a workshop to examine the ethical, legal, and social implications of ASD research by 2011. The workshop should define possible approaches for conducting future studies of ethical, legal, and social implications of ASD research, taking into consideration how these types of issues have been approached in related medical conditions. *IACC Recommended Budget: $35,000 over 1 year* **This objective was fulfilled in 2011*	N/A	N/A	1.S.F $0 0 projects	1.S.F* $71,489 1 project	1.S.F* $0 0 projects	$71,489
	1.S.F. Funding: The recommended budget for this objective was met. **Progress:** The objective was accomplished as the committee intended. NIH held a workshop, "The Ethical, Legal and Social Implications of Autism Spectrum Disorder Research," ASAN held a symposium of the same title on this topic, and Autism Speaks held a related conference, "Ethics of Communicating Scientific Findings of Autism Risk." **Remaining Gaps, Needs, and Opportunities:** Although the workshop called for was completed, this area remains of interest due to the ethical concerns that will continue to arise as screening tools progress. Responsible communication of risk and examination of barriers to care and services for positively screened patients are among these concerns. This topic should be revisited continually to address issues that may arise as the field advances. Additional workshops would be one way to continue to work on these issues.					

Table 1: Question 1 Cumulative Funding Table, see appendix for a color-coding key and further details.

Question 1 Cumulative Funding Table

IACC Strategic Plan Objectives	Funding					
Year	2008	2009	2010	2011	2012	Total
Identify behavioral and biological markers that separately, or in combination, accurately identify, before age 2, one or more subtypes of children at risk for developing ASD, and evaluate whether these risk markers or profiles can improve early identification through heightened developmental monitoring and screening by 2014. *IACC Recommended Budget: $33,300,000 over 5 years*	1.3 $2,885,940 14 projects	1.L.A $16,465,034 43 projects	1.L.A $13,270,045 45 projects	1.L.A $12,416,466 43 projects	1.L.A $12,894,621 40 projects	$57,932,106
	1.L.A. Funding: The recommended budget was met. Significantly more than the recommended minimum budget was allocated to projects specific to this objective. **Progress:** More than 40 projects have been supported in this area, but most projects are still in the discovery phase. Identifying reliable early biomarkers has been challenging, but some progress has been made. More work is needed to achieve the full intent of the objective. **Remaining Gaps, Needs, and Opportunities:** Remaining research needs include continued discovery of biomarkers, linking biomarkers to treatment response, validation of biomarkers discovered in high risk populations for applicability in the general population, and evaluation of whether these biomarkers translate to improvement in screening and diagnosis real-world settings. There is also a need for biomarkers that are cost-effective.					
Develop at least five measures of behavioral and/or biological heterogeneity in children or adults with ASD, beyond variation in intellectual disability, that clearly relate to etiology and risk, treatment response and/or outcome by 2015. *IACC Recommended Budget: $71,100,000 over 5 years*	1.4 $5,773,203 18 projects	1.L.B $8,760,010 34 projects	1.L.B $15,228,060 52 projects	1.L.B $9,376,400 42 projects	1.L.B $12,813,396 39 projects	$51,951,069
	1.L.B. Funding: The recommended budget was partially met. **Progress:** Over 50 projects were supported in this area. While behavioral and/or biological heterogeneity are well covered by existing projects, gaps still exist in relating these measures to etiology and risk, treatment response, and/or outcomes. **Remaining Gaps, Needs, and Opportunities:** There was a discussion of whether this objective should be expanded to be compatible with the Research Domain Criteria (RDoC) now being used by NIMH, which focus on functional domains rather than disorder-specific characteristics.					
Identify and develop measures to assess at least three "continuous dimensions" (i.e., social reciprocity, communication disorders, and repetitive/restrictive behaviors) of ASD symptoms and severity that can be used by practitioners and/or families to assess response to intervention for people with ASD across the lifespan by 2016. *IACC Recommended Budget: $18,500,000 over 5 years*	1.5 $912,159 2 projects	1.L.C $861,069 6 projects	1.L.C $3,893,622 22 projects	1.L.C $2,353,440 15 projects	1.L.C $2,600,028 15 projects	$10,620,318
	1.L.C. Funding: The recommended budget was partially met. **Progress:** Basic science and clinical aspects of the research are underway, but more work is needed for the studies to be applied for use by practitioners and/or families. **Remaining Gaps, Needs, and Opportunities:** There is a need for finer ways to quantify social behavior and detect change in response to successful treatment. There is a need to move toward performance-based measures and away from the checklist approach.					

Table 1: Question 1 Cumulative Funding Table, see appendix for a color-coding key and further details.

Question 1 Cumulative Funding Table

IACC Strategic Plan Objectives	Funding					
Year	2008	2009	2010	2011	2012	Total
Not specific to any objective (Core/Other Activities)	**1. Core/ Other Activities** $18,229,985 63 projects	**1. Core/ Other Activities** $9,766,926 37 projects	**1. Core/ Other Activities** $3,643,562 18 projects	**1. Core/ Other Activities** $2,310,877 16 projects	**1. Core/ Other Activities** $2,175,749 13 projects	**$36,127,099**
Total funding for Question 1	**$29,123,209** 107 projects	**$44,693,942** 147 projects	**$45,622,080** 166 projects	**$30,604,930** 136 projects	**$36,727,805** 134 projects	**$186,771,966**

Table 1: Question 1 Cumulative Funding Table, see appendix for a color-coding key and further details.

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QUESTION 2

HOW CAN I UNDERSTAND WHAT IS HAPPENING?

INTRODUCTION

Aspirational Goal: Discover how ASD affects development, which will lead to targeted and personalized interventions.

Over the course of the last several years, a great deal has been learned about altered neurodevelopment in ASD and a few interventions are in the early phases of testing. The knowledge base, however, is still not sufficient to support the long-term goal of personalized interventions. Objectives within Question 2 have also evolved as the science has provided more insight into the complexity of ASD. Specifically, through recent groundbreaking brain mapping and brain imaging research, much has been learned about how the brain develops and how autism unfolds in early development. Insights from syndromic forms of ASD (ASD that is caused by known genetic syndromes) have provided clues about the general mechanisms and genetic pathways that are affected in ASD. Recent studies have also begun to elucidate the role of the immune system in brain development and potentially in autism, and progress has been made in understanding and developing guidelines to address co-occurring conditions such as gastrointestinal (GI) symptoms, sleep disorders, and epilepsy that can greatly impact quality of life for people with ASD. Finally, the biological mechanisms by which specific gene mutations cause syndromic autism are now better understood.

PROGRESS TOWARD THE STRATEGIC PLAN OBJECTIVES

The *2009 IACC Strategic Plan*, which was revised in 2010 and 2011, included nine objectives under the heading of Question 2, encompassing seven short-term objectives and two long-term objectives designed to address gaps in current research on the biological basis of autism. IACC Portfolio Analysis data from 2008-2012 indicated that the cumulative investment in research categorized under Question 2 during this period was $362 million. Approximately half of the investments that align with Question 2 were made in gap areas identified in the *IACC Strategic Plan* objectives, while the other half were invested in core/other research activities on the underlying biology of autism. The substantial activity in core/other research areas indicates long-standing investment in research toward understanding the biology of autism that has been augmented by growth in emerging areas of scientific research.

Of the nine objectives in Question 2, four objectives (addressing fever and immune system interactions with the central nervous system (CNS), biological pathways of genetic conditions related to autism, biological mechanisms of co-occurring conditions, and specific genotypes that underlie ASD phenotypes) met or exceeded the recommended budget and fulfilled the recommended number of projects. The remaining five objectives (studies on females with ASD, raising awareness of brain and tissue donation, characterization of regression, application of biosignatures to diagnosis, and large scale longitudinal studies of diverse populations with ASD) were below the recommended budget and number of projects. However, some progress has been made on all objectives.

Of note, in 2009, NIH received funds from the American Recovery and Reinvestment Act (ARRA) that were used to support a series of initiatives totaling $122 million over 2 years on key scientific areas. The heterogeneity of ASD was one such area, encompassing research on topics that were responsive to the newly released *IACC Strategic Plan for ASD Research* such as basic biology of ASD, biomarkers, risk factors, and treatments. This infusion of new funds helped jumpstart efforts to address *IACC Strategic Plan* objectives and is reflected in the portfolio across all Questions of the *IACC Strategic Plan*.

PROGRESS IN LONGITUDINAL AND COMPREHENSIVE EXAMINATION

OF THE BIOLOGICAL, CLINICAL, AND DEVELOPMENTAL PROFILES OF INDIVIDUALS WITH ASD

Autism is considered a neurodevelopmental disorder that begins in early life, and longitudinal studies are necessary to understand how brain function is altered throughout the lifespan. Indeed, much science points to the prenatal period and the first years of life as the critical window for onset and development of ASD. Recent gene expression studies demonstrated that key ASD-related genes and genetic pathways are activated during specific times in fetal development.[1,2] Furthermore, epidemiological studies have found that prenatal conditions and environmental exposures, such as air pollution and certain medication use, are associated with increased risk, while prenatal vitamin use appears to reduce risk.[3–8] A recent small, longitudinal study of infants demonstrated normal eye tracking behavior that then declined over 2-6 months after birth predicted later development of autism.[9] Another study found that white matter tracts in infants who develop ASD are detectably different from those of neurotypical children at 6-24 months of age.[10] Additionally, a number of imaging studies have demonstrated greater brain volume in ASD, but only during a specific early developmental stage.[11] Other functional and structural imaging studies are beginning to uncover correlates of ASD differences in processing of visual[12] and language[13] inputs. New sophisticated techniques to look at brain structure and function such as resting state magnetic resonance imaging (MRI), resting state electroencephalography (EEG), magnetoencephalography (MEG), and magnetic resonance spectroscopy (MRS) are being used to noninvasively examine neural circuits in ASD. Repeated over time, these measures can help chart neurodevelopment. Such techniques hold the potential to be useful for early diagnosis as well as measure efficacy of therapies that harness neuroplasticity to improve functional deficits.

PROGRESS IN THE FIELDS OF FEVER, METABOLISM, AND IMMUNITY

Research on the potential relationship between the immune system and ASD has grown considerably over the past 2 years, resulting in several major breakthroughs. In the realm of basic developmental research, immune cells and immune signaling molecules have been identified as essential for establishing stable connections between neurons during early brain development.[14,15] Brain tissue studies of the expression patterns of genes have indicated differences in immune pathways in those with autism compared to that of typically developed individuals.[16,17] Of note, the role of immune genes was not detected in population genetic studies, suggesting a non-genetic basis for the immune differences.[1,2] Specific autoantibodies targeting fetal brain proteins have been found in a subgroup of mothers of children with ASD and in some children with ASD.[18] These maternal autoantibodies appear to alter neurodevelopment in non-human primates.[19] Further, children born to mothers with these autoantibodies were found to have an abnormal brain enlargement in MRI studies compared to that of typically developing controls and persons with ASD without the antibodies.[20] Preliminary research

findings suggest that metabolic and immune factors may play a role in ASD in some individuals.[21–26] Reports of improved behavior in persons with ASD during periods of fever still remain unexplained, warranting further efforts in this area.[27]

In addition, there have been intriguing new findings with regard to the role of metabolism in autism. For example, a rare hereditary form of autism that presents with epilepsy and intellectual disability is caused by mutation of a gene that codes for the enzyme BCKDK (Branched chain ketoacid dehydrogenase kinase), which prevents the body from breaking down the essential branched-chain amino acids leucine, isoleucine, and valine after eating food.[25] When BCKDK is inactivated, individuals cannot maintain adequate levels of the above mentioned amino acids and they experience a deficiency. The problem can be addressed through amino acid supplementation, but research is needed to determine whether supplementation can reverse the autism symptoms associated with this disorder in humans. In a separate study, preliminary findings have linked a rare form of autism with a gene defect that interferes with the body's ability to manufacture carnitine, an amino acid that helps convert fat into energy, suggesting that another form of autism also may be potentially amenable to treatment through nutritional supplements.[26] Further work in this emerging field may yield new insights into the mechanisms of ASD and potential for novel treatments.

PROGRESS IN UNDERSTANDING NEURODEVELOPMENT IN FEMALES

While ASD affects more males than females, there is a growing awareness that ASD in females may be underdiagnosed, potentially due to differences in the manifestations of ASD in females, such as less disruptive behavioral disorders and stronger ability to recognize emotions in facial expressions, which mask symptoms.[28,29] Multiple familial and genetic studies suggest that female gender may protect against autistic behavior and that more genetic disruptions are required to cause autism in females.[30,31] The abnormal brain growth patterns that have been observed in people with ASD are also more pronounced in females than in males.[11,32,33] One of the newly funded NIH Autism Centers of Excellence (ACE) networks, including Yale University, the University of California Los Angeles, Harvard, and the University of Washington, is now devoted to understanding this potential "female protective factor".[34]

PROGRESS IN THE FIELD OF BRAIN AND TISSUE DONATION

The research community is in extreme need of brain and other types of tissue to enable important studies. One example of the value of brain tissue is the recent study using modern stereological techniques. In these studies, researchers observed that young children with autism have 67 percent more neurons in the prefrontal cortex – the region of the brain centrally involved in higher-order social and communication behaviors.[35] Since prefrontal neurons are generated in the second trimester, this neuron excess indicates that abnormal brain development in autism begins before birth. These types of studies can only be performed if appropriate brain tissue is available. The Autism BrainNet initiative, a multi-site, private

effort supported by the Autism Science Foundation, the Simons Foundation, Autism Speaks, and the Nancy Lurie Marks Family Foundation, will target autism specifically and will include an autism-specific brain donation outreach campaign to address this need. In the public sector, NIH recently launched the NIH Neurobiobank which includes samples for research on autism as well as other brain disorders and has an associated online publication "Why Brain Donation? A Legacy of Hope" to increase awareness about brain donation. As efforts to collect brain tissue progress, the collection of other biological samples from very young children at risk for ASD is another potential opportunity to facilitate multidisciplinary efforts to establish biomarkers of ASD risk.

PROGRESS IN UNDERSTANDING GENETIC CONDITIONS RELATED TO AUTISM AND SYNAPTIC FUNCTION

The largest area of scientific progress related to Question 2 has come from studies of the biological processes regulated by genes that either cause syndromic forms of autism (Fragile X syndrome, Rett syndrome, Tuberous Sclerosis) or are associated with increased risk of non-syndromic autism. Overlap has been uncovered in the biological mechanisms that give rise to ASD, especially at the level of synaptic function. For instance, deletion or mutation of the SHANK3 gene is known to cause one type of syndromic autism,[36] and the Shank3 protein encoded by this gene was found to play a critical role in the function of glutamatergic synapses – those synapses that transmit neuronal signals using the excitatory neurotransmitter glutamate.[37] Glutamatergic neurotransmission was also found to be altered in Fragile X and Tuberous Sclerosis, two other syndromes that often include autism.[38,39] A variety of other rare genetic mutations associated with autism have been found to affect synaptic function, raising the question of whether a common synaptic deficit with multiple causes results in autism. After finding these functional deficits at the synapse, investigators have asked whether it is possible to reverse functional synaptic deficits and indeed this has been demonstrated in some animal models.[40] Moreover, early stage clinical trials have been mounted to treat Tuberous Sclerosis with rapamycin, a drug that affects synaptic transmission via effects on mTOR signaling,[41] and non-syndromic autism with specific synaptic glutamate receptor antagonists.[42] Recent studies have shown that oxytocin can alter synaptic function and that the oxytocin receptor gene may be mutated or epigenetically altered in people with ASD.[43–45] Consistent with these findings, exciting new clinical trial data suggest that intranasal oxytocin can improve social function in ASD.[46,47]

The new field of epigenetics, the study of DNA modifications (such as methylation – the addition of methyl chemical groups onto DNA, causing the "silencing" of genes) that change over time and affect gene expression, has also been explored in ASD-related research. Recent publications have found that the methylation of DNA occurs in several brain regions in autism.[48] One report determined that the DNA in typically developing females is less methylated than that of females with ASD. A similar trend is observed in neurotypical males compared to males with ASD.[49] Furthermore, new data suggests that there are various genetic alterations and mutations in neurons that may occur during development.[50] Evidence suggesting that DNA hypermethylation may be involved in the development of cerebellar abnormalities associated with ASD has also emerged, thus reinforcing the value of integrative genomic approaches in better understanding the etiology of ASD.[51]

PROGRESS IN UNDERSTANDING CONDITIONS CO-OCCURRING WITH AUTISM

Much progress has been made in understanding the prevalence and biology of conditions that commonly co-occur with ASD, including epilepsy, sleep disorders, gastrointestinal (GI) disturbances, attention deficit hyperactivity disorder, and other psychiatric comorbidities.[52–57] A recent study found three distinct patterns of specific co-occurring conditions in persons with ASD, which suggests that such groupings of symptoms may represent distinct etiologies with different genetic and environmental contributions.[58] In 2012, an NIH workshop on epilepsy and ASD offered recommendations for next steps and research opportunities to better understand seizure disorders in ASD.[59] The workshop report reviewed several studies that identified genetic mutations, malfunctioning ion channels, interneuron deficits, and other factors that may play a critical role in ASD with co-occurring seizure disorders. In the field of sleep, abnormalities in circadian rhythms have been identified as potential cause of sleep disorders in ASD.[60] Outside the central nervous system, several recent studies have pointed to differences in gut microbiota as playing a potential role in ASD.[61–63] In a recent finding, the common co-occurring issue of gastrointestinal (GI) dysfunction was linked to ASD and treatment with a probiotic ameliorated the bacterial, GI, and behavioral changes in a mouse model,[62] suggesting the possibility of probiotic treatments to help a subset of individuals whose ASD is accompanied by GI symptoms. Another common issue reported by families with a member on the autism spectrum in a recent research study is the propensity for children with ASD to wander away from safe environments.[64] Currently, though wandering/elopement presents an important safety issue for families with children on the spectrum, there is very limited knowledge regarding the biological basis of this behavior and further research is needed in this area.

PROGRESS TOWARD THE ASPIRATIONAL GOAL

The challenges to understanding the underlying mechanisms of ASD are substantial. One opportunity for expanding the research horizon in ASD is to understand the gender-associated protective factors in females, as this might lead to therapeutic breakthroughs. The roles of the immune system in sculpting neural circuits and in neuroinflammation's response to stress also need further elucidation. It is especially important to be able to gauge the effects of maternal immune processes on the developing fetal brain. Careful longitudinal studies of important neurodevelopmental processes are needed as studies examining single time points are likely to miss important occurrences in this dynamic period of brain development. There is still very little known about why certain children with autism are noted to deteriorate over relatively short periods of time. Ongoing longitudinal studies of high risk children may lead to a better understanding of regression and whether it is a distinct syndrome or part of the continuum of neurodevelopmental abnormalities in ASD. The underlying basis for various disabilities (e.g., verbal vs. non-verbal ASD), specific behaviors, heterogeneity in severity, sleep

disorders, and gastrointestinal disturbances remain poorly understood and lack effective treatments. A systems biology approach is thus necessary to understand the multifaceted disturbances that occur in ASD.

Many new tools to further reveal the biological basis of ASD are emerging. Launched in 2013, the President's **Brain Research through Advancing Innovative Neurotechnologies (BRAIN) initiative**, which aims to map the interactions of individual brain cells and complex neural circuits, is focused on neurotechnology development. It will advance the ability to characterize the cellular differences in ASD compared to typically developing individuals. It also promises to substantially improve the ability to record brain circuit activity that would be helpful to monitor neurodevelopment or to guide therapy in ASD. One such tool that will promote advances relevant to the BRAIN initiative is Clear, Lipid-exchanged, Anatomically Rigid, Imaging/immunostaining compatible, Tissue hYdrogel (CLARITY), a new technology that aids in the visualization of human brain structure as well as the localization of proteins, neurotransmitters, and gene expression patterns. This neurotechnology is already being used to study the brain of a person affected by autism.[65] Induced pluripotent stem cell (iPSC) technology is another revolutionary tool, which enables scientists to transform cells (drawn from simple skin biopsies) into nerve cells.[66,67] Such methods can be used to research biological phenotypes observed in autism (i.e., synaptic dysfunction),[37,68,69] examine specific genes and pathways that are differentially regulated, and screen drugs for their ability to ameliorate autistic phenotypes.[70] Breakthroughs in RNA sequencing (a technique that reveals which genes are being expressed) and epigenetics now allow powerful new studies of gene regulation in brain tissue. In the world of imaging, the NIH's Human Connectome Project aims to produce a detailed map of brain connections in those with ASD and to visualize how this map changes over time from infancy through childhood. These and other techniques bring together tremendously large amounts of data from a variety of tissues and cells to enable systems biology approaches to understand the connections between different systems, including genetics, brain circuits, the immune system, metabolism, and the microbiome. The richness of the data and the variety of tools needed call for a coordinated approach in which findings are replicated and the tools validated so that they can become clinically useful.

Question 2 Cumulative Funding Table

IACC Strategic Plan Objectives	Funding					
Year	2008	2009	2010	2011	2012	Total
Support at least four research projects to identify mechanisms of fever, metabolic and/or immune system interactions with the central nervous system that may influence ASD during prenatal-postnatal life by 2010 (Fever studies to be started by 2012). *IACC Recommended Budget: $9,800,000 over 4 years*	2.2 $3,377,568 18 projects	2.S.A $3,584,634 30 projects	2.S.A $4,972,407 37 projects	2.S.A $2,013,417 25 projects	2.S.A $3,049,827 26 projects	$16,997,853
	2.S.A. Funding: The recommended budget for this objective was met. **Progress:** Many projects were funded in this area (approximately 20-30 per year), but the field is still developing, and emphasis on this objective should continue in the future. Scientific advances have been made in linking maternal innate immune function and immune-system challenge to aspects of ASD. Methodological advances in the field include the development of animal models for study of the role of the immune system in ASD and PET ligands for imaging microglial activation. **Remaining Gaps, Needs, and Opportunities:** There is a need for a well-designed, multi-site clinical study of clinical effects of fever and to develop standard measures of fever and behavioral/cognitive outcomes. Questions about fever could be integrated into funded epidemiological studies. There is also interest in further work on metabolic and mitochondrial issues, but in order for this work to be done, there is a need for validation and standardization of measures for assessment of oxidative stress and mitochondrial function. More guidance is needed on the key questions for this field to answer – a workshop to define these methodologies may be helpful. One of the key questions is to determine whether it is the body temperature associated with fever or some consequence of immune activation and production of the febrile state that leads to amelioration of cognitive function.					
Launch three studies that specifically focus on the neurodevelopment of females with ASD, spanning basic to clinical research on sex differences by 2011. *IACC Recommended Budget: $8,900,000 over 5 years*	2.3 $0 0 projects	2.S.B $1,370,107 5 projects	2.S.B $1,096,678 5 projects	2.S.B $150,000 1 project	2.S.B $3,239,998 5 projects	$5,856,783
	2.S.B. Funding: The recommended budget was partially met. **Progress:** More than the minimum three studies recommended were launched, but further work is needed in this area. Studies have found that females with ASD often have a higher burden of ASD genetic risk mutations than males, suggesting a gender-associated protective effect in females. Research on factors protecting females from developing ASD symptoms even when challenged with genetic mutations that lead to ASD in boys may help to identify approaches to prevent development of ASD symptoms in both genders. **Remaining Gaps, Needs, and Opportunities:** Studies of protective and compensatory effects in females and differential response to treatment based on gender are promising areas that could help with future prevention and effective, personalized treatment efforts. Beyond genetic differences, it is important to determine whether other biological features, such as differences in neuropathology, are found in the two sexes.					

Table 2: Question 2 Cumulative Funding Table, see appendix for a color-coding key and further details.

Question 2 Cumulative Funding Table

IACC Strategic Plan Objectives	Funding					
Year	2008	2009	2010	2011	2012	Total
Identify ways to increase awareness among the autism spectrum community of the potential value of brain and tissue donation to further basic research by 2011. *IACC Recommended Budget: $1,400,000 over 2 years*	2.4 $0 0 projects	2.S.C $726,911 2 projects	2.S.C $17,000 1 project	2.S.C $22,000 1 project	2.S.C $90,120 1 project	$856,031
	2.S.C. Funding: The recommended budget was partially met. **Progress:** Loss of autism brain samples due to a freezer malfunction at a major brain bank in 2012 has caused a loss of progress in ASD research. Thus, there is a need for new samples to replace those that were lost and to begin expanding the amount of brain tissue available for ASD research. The Autism BrainNet initiative is a multi-site, privately funded effort that will target autism specifically and will include an autism-specific brain donation outreach campaign that addresses this objective. NIH launched the NIH Neurobiobank ($5 million), which includes samples for research on autism as well as other brain disorders, and has an associated online publication "Why Brain Donation? A Legacy of Hope" to increase awareness about brain donation. Both of these initiatives are not yet reflected in the Portfolio Analysis, because they began in 2013. In addition to these new brain banking efforts, the NICHD Brain and Tissue Bank produced a video for their website to generally increase awareness the potential value of brain and tissue donation to further basic research on neurodevelopmental and pediatric conditions. Since the effort is not autism-specific, it was not captured in the portfolio analysis. **Remaining Gaps, Needs, and Opportunities:** There is an ongoing and urgent need to raise awareness of the importance of brain and tissue donation for research, to standardize the methodology of collection and to increase the supply of such tissues. Autism BrainNet, a private outreach and postmortem brain donation program dedicated to research on autism and related disorders will integrate the Autism Tissue Program (ATP) with collection sites at Mount Sinai School of Medicine, the University of Texas Southwestern Medical School, and the University of California, Davis MIND Institute.					
Launch three studies that target improved understanding of the underlying biological pathways of genetic conditions related to autism (e.g., Fragile X, Rett syndrome, tuberous sclerosis complex) and how these conditions inform risk assessment and individualized intervention by 2012. *IACC Recommended Budget: $9,000,000 over 5 years*	N/A	2.S.D $9,171,542 48 projects	2.S.D $13,162,905 57 projects	2.S.D $12,360,956 64 projects	2.S.D $18,452,242 83 projects	$53,147,645
	2.S.D. Funding: The recommended budget was met. Significantly more than the recommended minimum budget was allocated to projects specific to this objective. **Progress:** A large number of projects were funded that address this objective. Investment in this area has doubled since 2009, and in 2013, NIH began funding an ACE center focused on tuberous sclerosis. Much is being learned about conditions related to autism that can be applied to autism. This objective is on track. **Remaining Gaps, Needs, and Opportunities:** The next step will be to translate findings in this area into clinically useful therapies.					

Table 2: Question 2 Cumulative Funding Table, see appendix for a color-coding key and further details.

Question 2 Cumulative Funding Table

IACC Strategic Plan Objectives	Funding					
Year	2008	2009	2010	2011	2012	Total
Launch three studies that target the underlying biological mechanisms of co-occurring conditions with autism, including seizures/epilepsy, sleep disorders, wandering/elopement behavior, and familial autoimmune disorders, by 2012. *IACC Recommended Budget: $9,000,000 over 5 years*	N/A	2.S.E $3,893,300 11 projects	2.S.E $4,611,058 14 projects	2.S.E $4,807,760 23 projects	2.S.E $3,218,960 22 projects	$16,531,078
	2.S.E. Funding: The recommended budget for this objective was met. **Progress:** More than twenty projects were funded that were specific to this objective. Scientific advances in this area include mechanistic and mutation linkages of epilepsy and ASD-like behaviors, as well as circadian rhythm disruptions downstream of ASD-associated mutations. **Remaining Gaps, Needs, and Opportunities:** While studies on co-occurring conditions have been initiated, a greater depth of understanding is needed. Further efforts are needed, especially on wandering, metabolic and immune conditions related to ASD, as well as a systems-biology approach to understand how these co-occurring conditions are related to ASD. In order to more accurately assess progress, wandering/elopement should be considered separately from seizures/epilepsy/sleep. Familial autoimmune disorders could be moved to 2.S.A to be grouped with other immune-related issues.					
Launch two studies that focus on prospective characterization of children with reported regression to investigate potential risk factors by 2012. *IACC Recommended Budget: $4,500,000 over 5 year*	N/A	2.S.F $0 0 project	2.S.F $401,595 2 projects	2.S.F $339,709 3 projects	2.S.F $251,830 2 projects	$993,134
	2.S.F. Funding: The recommended budget was partially met. **Progress:** The number of recommended projects has been met and progress is being made, but further work is needed to understand how autism develops. Some recent data suggest that regression may be more of a continuum than a distinct type of autism, and several studies have provided new descriptions of ASD developmental trajectories. However, other studies have found some differences between children with reported regression vs. children without reported regression. **Remaining Gaps, Needs, and Opportunities:** Further work is needed to better understand subtypes and potential biomarkers. High-risk siblings may present an opportunity for studying regression prospectively.					
Support five studies that associate specific genotypes with functional or structural phenotypes, including behavioral and medical phenotypes (e.g., nonverbal individuals with ASD and those with cognitive impairments) by 2015. *IACC Recommended Budget: $22,600,000 over 5 years*	N/A	2.S.G $5,903,875 21 projects	2.S.G $9,149,672 39 projects	2.S.G $11,105,408 45 projects	2.S.G $15,618,073 44 projects	$41,777,028
	2.S.G. Funding: The recommended budget was met. Significantly more than the recommended minimum budget was allocated to projects specific to this objective. **Progress:** Over 40 projects have been funded in this area, and the projects cover the areas described, so the objective appears to be on track. **Remaining Gaps, Needs, and Opportunities:** With so many studies initiated, the next step is to encourage multi-site collaboration in order to achieve the large number of subjects required for meaningful data interpretation.					

Table 2: Question 2 Cumulative Funding Table, see appendix for a color-coding key and further details.

Question 2 Cumulative Funding Table

IACC Strategic Plan Objectives	Funding					
Year	**2008**	**2009**	**2010**	**2011**	**2012**	**Total**
Complete a large-scale, multidisciplinary, collaborative project that longitudinally and comprehensively examines how the biological, clinical, and developmental profiles of individuals, with a special emphasis on females, youths, and adults with ASD, change over time as compared to typically developing people by 2020. *IACC Recommended Budget: $126,200,000 over 12 years*	**2.5** $8,523,806 49 projects	**2.L.A** $2,721,384 6 projects	**2.L.A** $2,283,875 6 projects	**2.L.A** $972,559 5 projects	**2.L.A** $6,160,017 9 projects	**$20,661,641**
	2.L.A. Funding: The recommended budget was partially met. **Progress:** Several projects have been funded in this area, and the ACE Network continues to collect data relevant to this objective. **Remaining Gaps, Needs, and Opportunities:** Though this research is underway, more clinical studies are needed over a longer trajectory to identify issues faced as people with ASD age, especially with regard to risk factors for other medical conditions. Another remaining need is that of standardization of data collection and analysis methods.					
Launch at least three studies that evaluate the applicability of ASD phenotype and/or biological signature findings for performing diagnosis, risk assessment, or clinical intervention by 2015. *IACC Recommended Budget: $7,200,000 over 5 years*	N/A	**2.L.B** $1,532,262 16 projects	**2.L.B** $450,271 2 projects	**2.L.B** $324,241 4 projects	**2.L.B** $1,321,632 8 projects	**$3,628,406**
	2.L.B. Funding: The recommended budget was partially met. **Progress:** Imaging studies have developed activity signatures of the ASD brain. While more than 3 studies were launched, more funding and work in this area are needed. **Remaining Gaps, Needs, and Opportunities:** This objective also requires standardization of data collection and analysis methods, as well as collaboration among investigators to pool data. Increased emphasis must be placed on conducting biological evaluations of very young children at risk for ASD and on collecting biological samples from these young children, to enable research into the establishment of biomarkers or risk markers in this population.					
Not specific to any objective (Core/Other Activities)	**2. Core/ Other Activities** $23,701,450 133 projects	**2. Core/ Other Activities** $34,348,932 163 projects	**2. Core/ Other Activities** $55,114,888 246 projects	**2. Core/ Other Activities** $41,027,141 227 projects	**2. Core/ Other Activities** $48,710,997 260 projects	**$202,903,408**
Total funding for Question 2†	**$40,621,403** 202 projects	**$63,252,949** 302 projects	**$91,260,349** 409 projects	**$73,123,190** 398 projects	**$100,113,696** 460 projects	**$363,353,007***

Table 2: Question 2 Cumulative Funding Table, see appendix for a color-coding key and further detail.

**This total reflects all funding for projects aligned to current objectives in the 2011 IACC Strategic Plan and incorporates funding for projects that may have been coded differently in previous versions of the Plan.*

†The totals reflect the funding and projects coded to this Question of the Strategic Plan in the particular year indicated at the top of the column. When reading each column vertically, please note that the projects and funding associated with each objective for the years 2008, 2009, and 2010 may not add up to the total at the bottom of the column; this is due to revisions of the Strategic Plan that caused some objectives to be shifted to other Questions under the Plan. The projects and funding associated with these reclassified objectives are now reflected under the Question in which they appear in the 2011 Strategic Plan.

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QUESTION 3

WHAT CAUSED THIS TO HAPPEN AND CAN IT BE PREVENTED?

INTRODUCTION

Aspirational Goal: Causes of ASD will be discovered that inform prognosis and treatments and lead to prevention/preemption of the challenges and disabilities of ASD.

The original version of the *IACC Strategic Plan*, published in 2009, identified nine objectives focused on research to identify and deepen the understanding of genetic and environmental causes of ASD. In 2009 and 2010, several new objectives were added. The new objectives emphasized the need to study how environmental autism risks may differ in vulnerable subgroups, and encouraged research that capitalized on new opportunities and approaches in areas such as epigenetics, the microbiome, animal models of ASD and bioinformatics. Over the past 5 years, a total of $380 million dollars has been invested to support research under Question 3. Significant advances have occurred in identifying several new genetic and environmental risk factors, and in the initiation and/or expansion of large epidemiologic studies, many of which are responsive to multiple *IACC Strategic Plan* objectives. Environmental exposure science within ASD studies, inclusion of diverse populations in etiological research, and the use of new animal models for gene/ environment research are areas that have not progressed as quickly and remain significant needs within the field. Continued investment is needed to follow-up on recent advances, to address a wide array of gap areas, and to determine the clinical and public health utility of both genetic and environmental findings. Leveraging the infrastructure of existing large population-based epidemiology studies that are well positioned to address several important questions about environmental risks for autism is a priority that will require significantly increased investment, in addition to continued efforts to obtain new cohort data to capture environmental risks during the relevant windows of susceptibility.

PROGRESS TOWARD THE STRATEGIC PLAN OBJECTIVES

The *2011-2012 IACC ASD Research Portfolio Analysis* reviewed projects funded by both government agencies and private foundations from 2008-2012. From 2008-2012, the total funding devoted to projects that address Question 3 was $381 million, and if just the years since the publication of the first *IACC Strategic Plan* in 2009 are considered, the funding for projects related to Question 3 was $298 million. Also in years 2009-2012, 96 percent of the total was invested in research gap areas identified by the 15 objectives in Question 3, while 4 percent of the total funding went toward research projects outside the *IACC Strategic Plan* objectives (in the core/other category).

All of the 15 specific objectives under Question 3 have shown progress in funded projects since the publication of the first *IACC Strategic Plan*. Four objectives addressing multi-site studies of prenatal environmental factors in high risk families, identification of genetic risk factors in people with ASD, large-scale gene-environment interaction studies, and a workshop on bioinformatics met or exceeded the recommended budget and fulfilled the recommended number of projects. Eleven objectives, concerning identification of genetic and epigenetic markers, environmental exposure risks, and study of special populations, partially met the recommended budget and had a number of projects underway.

PROGRESS IN THE FIELD OF GENETIC RISK FACTORS

During the past few years there has been a major revolution in ASD genetics research. Using the newest molecular and epidemiological methods, recent data continues to strongly support the role of genes in ASD, and the understanding of this role has been greatly refined. The emerging picture is one of profound complexity. Rather than an exclusive focus on one kind of variation, genetic variation at all scales (from changes at a single DNA base-pair, through small genetic insertions and deletions and larger copy number variations (CNVs), all the way up to extra chromosomes) must be considered, as all can contribute to ASD risk.[1,2] In addition, both common and rare variation (both mutations that are commonly shared across many individuals with ASD and mutations that are very rare or unique) have been found to play a role in ASD risk.[1–3]

The emergence of new, high- throughput genetic sequencing (HTS) technologies has provided an opportunity to rapidly identify rare and extremely rare genetic variation that occurs spontaneously (is not inherited) in single genes and can impact ASD risk. Data suggest that if these currently available technologies were to be used in the general ASD population, genetic changes that contribute to ASD risk could be identified in at least 30 percent of individuals with ASD.[4–11] While the sample sizes analyzed using HTS to date are still too small to identify many new, individual ASD genes, six or seven new ASD genes have been unambiguously identified from the first 1,000 individuals sequenced,[5–8,11–13] with several more likely candidate genes identified as well.[14] There are ongoing studies to examine data from a pool of 9,000 individuals with ASD, together with appropriate controls, for a total of at least 20,000 samples. It is anticipated that analysis of HTS data from this larger pool will double the number of known ASD genes, from the currently known genes that have been identified using other methods.[1]

Recent data also suggest that approximately 40-60 percent[15] of ASD risk can be attributed to inherited, common variation (single nucleotide polymorphisms/SNPs) and it is likely that in the future it will be possible to estimate ASD risk by analyzing multiple genetic markers,[16] as has been observed in other disorders. Common risk variants interact with other genes and also with the environment. Gene-environment (GxE) interactions are still suspected to be of major importance in ASD, but further work is needed to elucidate the nature of these interactions.[17,18] Based on the results of several studies, the number of genetic loci (or genetic "regions" that can include multiple genes) associated with ASD is now estimated to be near 1,000,[5,14,19] representing a surprisingly large proportion of genes in the genome (almost 5 percent of the 22,000 genes in the human genome). This suggests that many different genetic pathways may contribute to the development of ASD, and that further research on developmental trajectories (patterns of child development) could provide the potential to associate genetic changes with specific symptoms and behavioral phenotypes.[20,21]

New tools for identifying networks of functionally-related genes (groups of genes that work together to perform a function) that influence brain development, (i.e., those being used in the **BrainSpan** project[22,23]) have been applied in ASD. Results have shown that many of the identified risk genes map strongly to defined brain regions and cortical layers, act during specific developmental time windows within the prenatal period, and/or share the same functional pathways. The hope is that it will be possible to identify a smaller number of genes that are the "key drivers" of these pathways that could then become the priority targets for the development of new medicines.

PROGRESS IN THE FIELD OF ENVIRONMENTAL RISK FACTORS

In 2008, little was known about environmental risk factors for ASD. Given what had been revealed about ASD's genetic complexity at that time, it was suspected that environmental exposures and gene-environment interaction would likely be important to fully understanding ASD risk. **The California Autism Twin Study** published in 2011 demonstrated that the environmental component of ASD etiology is probably quite substantial.[24] Recent analysis of non-twin family data (from both simplex and multiplex families)[5,6,11,15] also supports the idea that mechanisms beyond inherited gene mutations and de novo, or spontaneous, mutations or copy number variants will be necessary for understanding the complex causes of ASD. The time around conception and during pregnancy are likely the most important time windows of heightened vulnerability for the development of the brain with supporting evidence from early reports linking autism symptoms to maternal ingestion of drugs such as thalidomide[25,26]and valproic acid,[26,27] and infection with congenital rubella,[28,29] as well as more recent reports showing that maternal intake of prenatal vitamins has a "protective" effect, reducing risk for ASD,[30–32] and that many genes that have been identified as linked to autism are expressed in the brain during fetal development.[22,23]

Over the past 5 years a modest investment has helped achieve good initial progress in identifying potential environmental ASD risk factors – especially considering the environment broadly as all influences beyond genetic predisposition. Along with the exposures listed above, factors associated with ASD protection or risk that have been replicated in two or more studies include: protective effect of prenatal vitamin intake,[30–32] and risks from prenatal maternal infection,[33,34] preterm birth,[35–38] advanced maternal and paternal age at conception[39–45] and short inter-pregnancy interval.[46,47] A recent study also showed elevated risk in mothers who used labor induction medications, but it is not clear whether the risk was

associated with induction itself or with conditions that may have created the need for use of induction medications.[48] Use of certain prescription medications by mothers during the prenatal period[49,50] has also been suggested as a potential risk factor for ASD, although currently there are conflicts in data from different reports and underlying conditions in the parent might explain these associations.[50,51] Ultrasound is another exposure that has been considered a possible risk, but recent studies have shown no association between ultrasound and ASD risk.[52,53] Recent reviews about potential environmental risk factors have compiled lists of exposures of interest for future studies.[54–56]

Particularly intriguing are the results of prenatal vitamin intake through supplements and diet, showing a 40 percent reduction in risk of ASD with prenatal vitamin supplements taken in the 3 months before or during the first month of pregnancy, but not during pregnancy months 2-9.[30] A trend of decreasing ASD risk as mothers consumed greater daily folic acid intake from foods, vitamins, and supplements in the first month of pregnancy was also reported.[31] The 40 percent reduction in risk for women who used folic acid supplements in the time around conception was replicated in a large Norwegian cohort study.[32] These findings raise challenging issues for public health education, given that a sizable fraction of pregnancies are not planned. If they represent causal associations, then by the time a woman recognizes she is pregnant, it may be too late for folic acid supplementation for the purpose of reducing ASD risk in her offspring. They also invoke a number of hypotheses related to epigenetic mechanisms in ASDs.

Among modifiable exogenous exposures, the largest number of studies to date has addressed associations of increased ASD risk with air pollution exposure during gestation and/or early infancy. Multiple studies have reported significant associations;[57–62] two studies examining ozone [60,62] and three that examined nitrogen dioxide (NO_2)[59,61,62] found significant associations with ASD. There is also now suggestive evidence that exposure to endocrine disrupting chemicals such as pesticides, including organophosphates and phthalates may be associated with ASD.[63–68] The role of heavy metals in ASD remains an open question, as to date, too few studies have been done to assess exposure to heavy metals during pregnancy, which is the most etiologically relevant window. Further work is needed on all of these exposures to more clearly establish associations and ensure no residual confounding due to socioeconomic factors, and if the association is causal, to determine in which periods the fetus/infant might be most susceptible. Also, replication of findings with direct individual-level exposure measures, perhaps using biomarkers, is needed. A useful future direction in the area of environmental exposures could be to focus on how shared properties of exposures (such as endocrine disruption) map to specific phenotypes of ASD.

Exposure assessment represents an ongoing challenge for discerning a role for the environment in ASD causation. Evidence points to pregnancy and the early postnatal period as critical windows of vulnerability, yet, until recently, few studies were collecting relevant data in real time during this period. To address this challenge, two studies using enriched risk designs (investigating subsequent pregnancies in families where one child has already been diagnosed with ASD), the Early Autism Risk Longitudinal Investigation (EARLI) and Markers of Autism Risk in Babies-Learning Early Signs (MARBLES), were launched with NIH support. These studies have captured important and unique pregnancy and birth data and biosamples not possible in other cohorts. However, their ultimate success depends on continued funding of these complex longitudinal projects. The most recent plans proposed for the Main Study of the NIH National Children's Study (NCS) may provide additional opportunities for exploring ASD risk with prevalent exposures, or ones that occur throughout pregnancy and can be measured at birth.

PROGRESS IN THE FIELD OF GENE-ENVIRONMENT INTERACTION

Although stressed as a critical area in ASD research, very few studies have focused explicitly on gene-environment interaction. This is in part due to lack of relevant and testable mechanistic hypotheses emerging from the basic sciences and also to the large logistical and resource challenges of assembling sufficiently-sized study populations with both adequate genetic and environmental data. Despite these obstacles, in the last 3 years several published examples provide empirical support for the long-suspected notion that the influence of environmental factors on ASD risk can be amplified in individuals with specific susceptibility genotypes. The first of these studies demonstrated that in populations that naturally have a lower level of folic acid due to a gene mutation that affects folate metabolism, the reduction in risk of ASD associated with folic acid supplementation during pregnancy is even stronger than that seen in the general population.[31] Another study reported that ASD risk associated with prenatal traffic-related air pollution exposure was greater among children with a specific gene mutation that has been linked to autism.[69] While these two findings suggest "proof of concept" regarding how genes may interact with environmental factors to increase autism risk, replication is needed. They also underscore the value of investments made to date in large and well-characterized study populations, and the parallel needs to continue expanding these efforts and to support infrastructure for specimen banking associated with such populations.

An area of both progress and opportunity for gene- environment research relates to epigenetics and ASD. As described in the previous chapter, epigenetics refers to modifications of DNA (such as methylation) that change over time and affect gene expression. The role of epigenetics in syndromic forms of autism is well established, and methylation analysis of blood and postmortem brain tissue now implicate epigenetics in the regulation of autism susceptibility genes. Most recently, a genome-wide examination of DNA methylation in a small sample of postmortem brains revealed several regions with consistent differences in methylation in ASD cases compared to controls.[70] Evidence continues to accrue regarding the ability of environmental factors such as nutrition,[71] drugs,[72] and psychosocial stress[73] to regulate transcription of genes through epigenetic modifications. This idea has not gained sufficient attention in ASD and merits additional research. Obstacles to further progress in elucidating the environmental epigenomics of ASD are the variability of epigenetic markers between and within tissues and over time. These factors make it difficult to use and interpret data from the kinds of biosamples that are typically available in human ASD studies (peripheral blood obtained after diagnosis), again highlighting the need for longitudinal pregnancy studies.

One final breakthrough is a mechanistic link between the environmental risk factor of paternal age and ASD risk, where a mechanism has been identified around the rate of de novo mutations. Several studies have shown that advanced paternal age at conception is associated with greater risk of ASD.[39,42–45,74,75] Separate studies have shown that older fathers produce sperm with greater numbers of *de novo* mutations,[76] while studies in animals have suggested that there are more profound epigenetic changes in sperm from older fathers.[74] The causes of these age-related changes in sperm are not yet known, but further exploration could provide key insights about the interface between genes and the environment.

PROGRESS TOWARD THE ASPIRATIONAL GOAL

Investments in the past 5 years have led to identification of new genetic and environmental factors contributing to ASD risk and identified the importance of the conception and gestational periods for the development of ASD. The new gene findings hold promise for a better understanding of the neurobiology of ASD and the development of novel pharmacotherapies. Rare genetic variants, as they are discovered, create both clinical and research opportunities. Genetic tests are now being routinely carried out in individuals who experience unexplained developmental delays. Chromosome microarray (CMA) is already recommended by the American Academy of Pediatrics (AAP) and the American College of Medical Genetics (ACMG) ,[77] and can inform some families about some ASD causes, rare but potentially serious comorbid medical conditions, and, in certain cases, the risk of ASD recurrence in future offspring.

In addition, because these rare variants are often associated with major neurophysiologic effects, they provide the opportunity to develop model systems in cells and in animals, where the basic pathobiology of ASD can be worked out, and where potential new medicines can be examined. This approach, carried out in cells in culture — including human neurons induced from individuals with genetic lesions — and in mice and rats, has led to novel treatment approaches. One of the most exciting developments in the past several years in ASD is the emergence of neurobiologically-defined new medicines for subtypes of ASD. Examples include ongoing trials in Fragile X syndrome, Rett syndrome, and Phelan-McDermid syndrome. All three of these result from clearly identified genetic mutations, and all are associated with very high risk of ASD. In some cases, the same drug is being tried as a treatment for individuals with ASD of unknown cause. Families that have a genetic diagnosis can now identify advocacy and family groups with similar mutations and can also choose to participate in relevant clinical trials. While these first trials are still at early stages, they represent the beginning of personalized medicine in ASD based on an individual's genetic findings.

The most recent findings available about the sibling recurrence risk for ASD have important clinical implications for families. Whereas earlier results from pooled baby siblings research samples suggest a recurrence risk of approximately 18 percent,[78] a more recent population-based registry study in Denmark found a substantively lower risk of about 7 percent.[79] The research sample rate may be an over-estimate due to selection bias, while the registry study may under-identify affected siblings (especially milder phenotypes). Consequently, the best estimate may lie somewhere between 7 and 18 percent. Notably, the Denmark study also found elevated recurrence among maternal half-siblings, which supports the idea of an etiologic role for maternal genetic factors, maternal intrauterine environment, and other prenatal environmental factors common across pregnancies.

Collectively, the candidate exposures studied to date in ASD represent the "first wave" of findings that were made possible by the initiation or continuation of large autism-focused studies such as Childhood Autism Risk from Genes and Environment (CHARGE) and the Center for Disease Control and Prevention (CDC)'s Study to Explore Early Development (SEED). The careful extension of existing population-based cohorts has also been important in understanding candidate exposures because these cohorts have enabled linkage to prospectively collected clinical records and biospecimens. In many cases, early research investments have focused on establishing study infrastructure and have provided only

limited support for analyses. The need to continue cultivating existing investments in this area cannot be overstated. While findings to date are not yet robust enough to inform public health action, the field is now well positioned to address questions regarding ASD-exposure relationships, as well as the identification of genetically, metabolically, or immunologically susceptible subsets of the population. SEED has completed the first phase of data collection for over 2,700 enrolled children, including genetic and environmental exposure data. These data are expected to be available for analyses in early 2014.

The progress achieved to date in the field of environmental epidemiology of ASD has occurred despite significant challenges in exposure measurement. To facilitate exposure measurement, Autism Speaks is funding the development and validation of a brief exposure questionnaire that was created by consensus by leading autism environmental science researchers that can be incorporated into a wide range of studies. Some remaining challenges include the limited amount and timing of collection of banked biospecimens. Also, analysis of non-persistent chemicals in samples collected after diagnosis does not reflect exposures occurring during early development. Consequently, many studies have relied on maternal recall of exposures, information available in medical records or various indirect methods of assigning exposures, such as using information about the known exposures associated with the residential location(s) where the mother resided during pregnancy.

These exposure assessment challenges are not unique to the field of ASD, and researchers in many other fields are working toward advancing exposure science. As these advances are made, it will be critically important to ensure that they are rapidly incorporated into ASD studies. Research on technologies to precisely monitor exposures in individuals, to accurately measure markers of exposure in banked blood and brain samples, and to consider the totality of an individual's exposures should be harnessed whenever possible to improve detection of environment-ASD relationships. Advances in the development and application of persistent biomarkers of exposure are especially needed so that analysis of current biospecimens can be used as a record for exposures occurring much earlier in development. Specimen banks such as newborn blood spots by some state governments, and cord blood or stem cells by commercial entities have tremendous potential for use in ASD research where they are available. Similarly, the development of biomarkers for exposure using strands from the often-saved first haircut, or using deciduous teeth may be worthwhile strategies for research investments.

There are several additional areas where more work is needed to meet Question 3 objectives. The first is use of animal models to explore gene-environment interaction. As noted under Question 2, there are now a substantial number of genetic mouse models that exhibit neuropathological and behavioral phenotypes that can be used to study ASD. Work on environmentally-induced models of ASD-like symptoms has been limited primarily to valproate and maternal infection, however, and there have been few efforts to use animal models to explore gene-environment interaction. Another strategy that warrants attention is the systematic evaluation/screening of candidate exposures for their effect(s) on molecular pathways that have been implicated by ASD genetic studies. For example, a recent study reported that defects in topoisomerases (enzymes involved in DNA replication, repair and epigenetic changes) may contribute to ASD by virtue of their importance in the expression of extremely long genes, which are overrepresented among known ASD risk genes.[80] This finding provides new leads for identifying exposures that may affect ASD risk through their impact on topoisomerase function. Further development and use of integrative bioinformatics tools that combine information about toxicants with the genes and pathways implicated in ASD provide another means for identifying and prioritizing candidate exposures for further study in ASD studies.

Finally, additional efforts are needed to address barriers to enrollment and retention of racially and ethnically diverse populations in order to ensure their representation in both epidemiologic and clinical studies. This information is critical for identifying vulnerable subgroups and informing public health prevention efforts. Enhancing the overall diversity of study populations should also prove helpful in detecting environment-ASD associations, as groups underrepresented in clinical studies are often those with disproportionate exposures.

Overall, while many advances have been made in the past 5 years in autism genetics and the study of environmental risk factors, including studies that have confirmed mid-pregnancy as a key time point of vulnerability for development of ASD, much work remains to be done to identify additional contributors and fully understand their complex interaction. Communication between researchers in the autism field and in other fields will be essential in order for advances in exposure science and genetic studies of other disorders to benefit the autism field. In addition, it will be critically important to maintain investment in and build upon existing infrastructure including birth cohorts, networks and databases to accelerate progress, and to ensure that risk is studied in underrepresented groups, in both girls and boys, and in relation to such factors as socioeconomic background and geography. A strengthened research base to address these issues will be essential to achieve the aspirational goal of discovering "causes of autism…that inform prognosis and treatments and lead to prevention/preemption of the challenges and disabilities of ASD."

Question 3 Cumulative Funding Table

IACC Strategic Plan Objectives	Funding					
Year	2008	2009	2010	2011	2012	Total
Coordinate and implement the inclusion of approximately 20,000 subjects for genome-wide association studies, as well as a sample of 1,200 for sequencing studies to examine more than 50 candidate genes by 2011. Studies should investigate factors contributing to phenotypic variation across individuals who share an identified genetic variant and stratify subjects according to behavioral, cognitive, and clinical features. *IACC Recommended Budget: $43,700,000 over 4 years*	3.2 $4,065,392 14 projects	3.S.A $13,926,663 11 projects	3.S.A $16,688,932 14 projects	3.S.A $2,207,214 7 projects	3.S.A $1,699,432 6 projects	$38,587,633
	3.S.A. Funding: The recommended budget was partially met, and is approaching the recommended budget. **Progress:** Progress has been made on this objective through the funding of several GWAS and sequencing projects. The current number of 6,000 GWAS subjects falls short of the goal of 20,000, but the number of whole exome sequences far exceeds 1,200, and could also reach 6,000 in the next year. Whole exome sequencing has identified 7-10 candidate genes, and promises to move closer to the goal of 50 in the future. Progress is being made in CNV studies. Overall, the work is on target. **Remaining Gaps, Needs, and Opportunities:** More subtyping and genotype-phenotype work outside of syndromic forms of autism, as well as natural history studies, are needed.					
Within the highest-priority categories of exposures for ASD, identify and standardize at least three measures for identifying markers of environmental exposure in biospecimens by 2011. *IACC Recommended Budget: $3,500,000 over 3 years*	3.3 $713,227 4 projects	3.S.B $0 0 projects	3.S.B $0 0 projects	3.S.B $0 0 projects	3.S.B $100,000 1 project	$813,227
	3.S.B. Funding: The recommended budget was not met; the funding allocated to projects specific to this objective falls far short of the recommendation. **Progress:** There has been progress on the understanding of exposures, but more work needs to be done to apply this directly to autism research. Progress has made through methodological advances embedded in epidemiological studies funded by NIEHS, but those projects are not captured by the Portfolio Analysis because they are not specific to autism. **Remaining Gaps, Needs, and Opportunities:** The primary obstacle to completion of this objective has been availability of funding to identify and validate exposure markers. There is a need for biomarkers of exposure; exposomics should be a priority area for future research.					
Initiate efforts to expand existing large case-control and other studies to enhance capabilities for targeted gene-environment research by 2011. *IACC Recommended Budget: $27,800,000 over 5 years*	3.4 $4,703,867 4 projects	3.S.C $8,033,454 9 projects	3.S.C $4,824,779 8 projects	3.S.C $5,714,408 10 projects	3.S.C $3,626,803 9 projects	$26,903,311
	3.S.C. Funding: The recommended budget was nearly met, but work still needs to continue on this objective. **Progress:** The funding allocated to this area so far has primarily supported building infrastructure that can now be expanded to include more subjects, more data, and more analytical projects. Studies such as the MARBLES (Markers of Autism Risk in Babies Learning Early Signs) cohort study and the CHARGE (Childhood Autism Risks from Genetics and the Environment) study are included under this objective. **Remaining Gaps, Needs, and Opportunities:** Continued benefit will be derived from past investments as these resources are expanded and pooled.					

Table 3: Question 3 Cumulative Funding Table, see appendix for a color-coding key and further details.

Question 3 Cumulative Funding Table

IACC Strategic Plan Objectives	Funding					
Year	2008	2009	2010	2011	2012	Total
Enhance existing case-control studies to enroll racially and ethnically diverse populations affected by ASD by 2011. *IACC Recommended Budget: $3,300,000 over 5 years*	3.5 $84,628 2 projects	3.S.D $103,827 3 projects	3.S.D $0 0 projects	3.S.D $0 0 projects	3.S.D $0 0 projects	$188,455
	3.S.D. Funding: The recommended budget was not met; the funding allocated to projects specific to this objective falls far short of the recommendation. **Progress:** The UCLA ACE center coded to 3.L.B. reflects some progress on this objective. CADDRE also includes racially diverse participants from multiple urban centers. Overall, however, both funding and outcomes related to this objective are far below the goal. **Remaining Gaps, Needs, and Opportunities:** There is a need for studies around high exposure, low socioeconomic status populations.					
Support at least two studies to determine if there are subpopulations that are more susceptible to environmental exposures (e.g., immune challenges related to infections, vaccinations, or underlying autoimmune problems) by 2012. *IACC Recommended Budget: $8,000,000 over 2 years*	N/A	3.S.E $1,739,200 13 projects	3.S.E $1,162,679 10 projects	3.S.E $419,215 5 projects	3.S.E $287,218 5 projects	$3,608,312
	3.S.E. Funding: The recommended budget was partially met **Progress:** Several projects were funded in this area, going beyond the minimum recommended by the committee, but the projects have been smaller than what was expected. However, even with smaller studies, a large amount of data has been collected relating to immunological conditions in children and mothers. **Remaining Gaps, Needs, and Opportunities:** More work is needed to analyze and interpret available data.					
Initiate studies on at least 10 environmental factors identified in the recommendations from the 2007 IOM report "Autism and the Environment: Challenges and Opportunities for Research" as potential causes of ASD by 2012. *IACC Recommended Budget: $56,000,000 over 2 years (revised in 2010)*	3.1 $7,600,673 19 projects	3.S.F $2,952,960 14 projects	3.S.F $166,362 5 projects	3.S.F $0 3 projects	3.S.F $75,000 1 project	$10,794,995
	3.S.F. Funding: The recommended budget was partially met. **Progress:** There has been a significant decrease in the number of studies related to this objective. **Remaining Gaps, Needs, and Opportunities:** Further work in this area is needed, and work should focus on identifying the directionality of associations between environmental factors and ASD (causal, reactive, or independent) in order to be applied to prevention and the development of therapeutics. Sophisticated methods that are being applied in other fields need to be brought into autism research.					

Table 3: Question 3 Cumulative Funding Table, see appendix for a color-coding key and further details.

Question 3 Cumulative Funding Table

IACC Strategic Plan Objectives	Funding					
Year	2008	2009	2010	2011	2012	Total
Convene a workshop that explores the usefulness of bioinformatic approaches to identify environmental risks for ASD by 2011. *IACC Recommended Budget: $35,000 over 1 year* **This objective was completed in 2011*	N/A	N/A	3.S.G $0 0 projects	3.S.G* $46,991 1 project	3.S.G* $0 0 projects	$46,991
	3.S.G. Funding: The workshop identified in this objective was funded and held by NIEHS in 2011. **Progress:** : A workshop on this topic, "Autism and the Environment: New Ideas for Advancing the Science," was convened by the National Institute of Environmental Health Sciences (NIEHS) in 2010. (a meeting report is available). Therefore, this objective has been completed. **Remaining Gaps, Needs, and Opportunities:** Next steps for this area include the need to develop an exposome. A forum for the sharing of new technologies and standardized assessments would also be useful in moving this field forward.					
Support at least three studies of special populations or use existing databases to inform our understanding of environmental risk factors for ASD in pregnancy and the early postnatal period by 2012. Such studies could include: · Comparisons of populations differing in geography, gender, ethnic background, exposure history (e.g., prematurity, maternal infection, nutritional deficiencies, toxins), and migration patterns; and · Comparisons of phenotype (e.g., cytokine profiles), in children with and without a history of autistic regression, adverse events following immunization (such as fever and seizures), and mitochondrial impairment. These studies may also include comparisons of phenotype between children with regressive ASD and their siblings. Emphasis on environmental factors that influence prenatal and early postnatal development is particularly of high priority. Epidemiological studies should pay special attention to include racially and ethnically diverse populations. *IACC Recommended Budget: $12,000,000 over 5 years*	N/A	N/A	3.S.H $1,527,866 13 projects	3.S.H $4,657,095 16 projects	3.S.H $4,096,317 13 projects	$10,281,278
	3.S.H. Funding: The recommended budget was partially met, and is approaching the recommended budget. **Progress:** The funded projects cover the objective well; there are 32 projects that are related to this objective, though more projects focus on use of databases than on special populations. A positive element of progress for this objective is the existence of large monitoring databases and projects that capitalize on those resources, such as iCARE and MINERvA. **Remaining Gaps, Needs, and Opportunities:** While progress is being made in this area, and it must be maintained in order to achieve this objective.					

Table 3: Question 3 Cumulative Funding Table, see appendix for a color-coding key and further details.

Question 3 Cumulative Funding Table

IACC Strategic Plan Objectives	Funding					
Year	2008	2009	2010	2011	2012	Total
Support at least two studies that examine potential differences in the microbiome of individuals with ASD versus comparison groups by 2012. *IACC Recommended Budget: $1,000,000 over 2 years*	N/A	N/A	**3.S.I** $53,960 3 projects	**3.S.I** $439,971 4 projects	**3.S.I** $255,332 6 projects	**$749,263**
	3.S.I. Funding: The recommended budget was partially met. **Progress:** The number of projects in this area has been growing, with 6 projects in 2012. The number of funded projects is large relative to the amount of funding, indicating that each of the projects is small, which suggests that these projects will not be sufficient in scope to complete this objective. **Remaining Gaps, Needs, and Opportunities:** The high cost of required technology could be a barrier to the completion of this objective. These smaller pilot studies are potentially underpowered. The question of sample availability is important for this objective, along with raising researcher awareness of sample repositories.					
Support at least three studies that focus on the role of epigenetics in the etiology of ASD, including studies that include assays to measure DNA methylations and histone modifications and those exploring how exposures may act on maternal or paternal genomes via epigenetic mechanisms to alter gene expression, by 2012. *IACC Recommended Budget: $20,000,000 over 5 years*	N/A	N/A	**3.S.J** $5,072,389 15 projects	**3.S.J** $5,341,237 19 projects	**3.S.J** $6,122,724 22 projects	**$16,536,350**
	3.S.J. Funding: The recommended budget was partially met, and the annualized recommended budget targets were met for all 3 years since the objective was introduced; therefore, the funding for this objective is on track. If this funding trend continues, the objective's recommended budget will be met within the recommended 5 year timeframe. **Progress:** More than the recommended number of projects have been funded, with 22 projects supported in 2012. This is a growing area of research, and the current momentum in this area should be maintained. **Remaining Gaps, Needs, and Opportunities:** An important technological need for this objective is the development of robust epigenetic measurements for small biological samples, such a blood spots. A possible barrier to research in this area is the availability and preservation quality of these samples. Large funded studies such as MARBLES might provide an opportunity to collect samples. If samples are made available, that may catalyze research in this area.					

Table 3: Question 3 Cumulative Funding Table, see appendix for a color-coding key and further details.

Question 3 Cumulative Funding Table

IACC Strategic Plan Objectives	Funding					
Year	2008	2009	2010	2011	2012	Total
Support two studies and a workshop that facilitate the development of vertebrate and invertebrate model systems for the exploration of environmental risks and their interaction with gender and genetic susceptibilities for ASD by 2012. *IACC Recommended Budget: $1,535,000 over 3 years*	N/A	N/A	3.S.K $733,922 5 projects	3.S.K $463,841 3 projects	3.S.K $90,000 3 projects	$1,287,763
	3.S.K. Funding: The recommended budget was partially met. However, the yearly funding decreased significantly from 2010-2012. It should be noted that this objective overlaps partially with 2.S.B., which is focused on research on sex differences in ASD, and 4.S.B., which focuses on development of animal models that can be used for understanding molecular and neural pathways that can be targeted by interventions. Genetic pathways that play a role in gender differences and other molecular and neural pathways may interact with environmental factors, so funding for these objectives could reflect progress on the goals of 3.S.K. **Progress:** Projects by Tychele Turner at Johns Hopkins and Donna Werling at UCLA that are using animal models to investigate sex differences in autism are coded to 2.S.B. The following 2010 workshop sponsored by NIEHS, Autism and the Environment: Advancing the Science, touched on this topic, but it was not the main focus of the workshop. **Remaining Gaps, Needs, and Opportunities:** The development of animal models for more broad ASD research is coded to question 4, and the use of such models to answer environmental exposure questions is a next step for this objective.					
Conduct a multi-site study of the subsequent pregnancies of 1,000 women with a child with ASD to assess the impact of environmental factors in a period most relevant to the progression of ASD by 2014. *IACC Recommended Budget: $11,100,000 over 5 years*	3.7 $2,742,999 1 project	3.L.A $3,740,812 2 projects	3.L.A $2,971,093 2 projects	3.L.A $2,864,377 1 project	3.L.A $2,875,202 2 projects	$15,194,483
	3.L.A. Funding: The recommended budget for this objective was met, but emphasis on this objective should continue in the future. **Progress:** The Group is concerned about the lack of continued funding for EARLI. More positively, projects analyzing the previously collected EARLI data are in process. Also, the MARBLES project contributes toward the goal of studying the interaction of genetic and environmental factors beginning during pregnancy, but, since it is not a multi-site study, and is also a continuation of an existing study funded as a pilot under a UC Davis Children's Center grant, funding for MARBLES is coded to 3.S.C., which overlaps somewhat with this objective. **Remaining Gaps, Needs, and Opportunities:** A barrier to this type of work is the extremely high cost of building the necessary infrastructure. With MARBLES and previously with EARLI, there has been some progress on infrastructure. It is important to maintain these cohorts where possible, to collect a wide range of samples, and to use them for multiple studies to capitalize on investments made.					

Table 3: Question 3 Cumulative Funding Table, see appendix for a color-coding key and further details.

Question 3 Cumulative Funding Table

IACC Strategic Plan Objectives	Funding					
Year	2008	2009	2010	2011	2012	Total
Identify genetic risk factors in at least 50% of people with ASD by 2014. *IACC Recommended Budget: $33,900,000 over 6 years*	3.8 $37,043,410 83 projects	3.L.B $49,905,587 79 projects	3.L.B $34,432,884 60 projects	3.L.B $25,383,346 59 projects	3.L.B $23,041,231 74 projects	$169,806,458
	3.L.B. Funding: The recommended budget was met. Significantly more than the recommended minimum budget was allocated to projects specific to this objective. **Progress:** Further work is needed to identify genetic risk factors in at least 50% of people. Currently, whole exome analysis predicts that a genetic risk factor can be identified for 20% of people; inclusion of CNV data might push this toward 30%. **Remaining Gaps, Needs, and Opportunities:** The initial budget recommendation for this objective was made based on the assumption that GWAS studies would provide risk factor identification, but sequencing has proven more fruitful. Since this technique is more expensive, a higher budget will be required to meet the goal of 50%.					
Determine the effect of at least five environmental factors on the risk for subtypes of ASD in the prenatal and early postnatal period of development by 2015. *IACC Recommended Budget: $25,100,000 over 7 years*	3.6 $1,803,628 13 projects	3.L.C $1,992,228 10 projects	3.L.C $820,320 10 projects	3.L.C $379,913 5 projects	3.L.C $353,000 5 projects	$5,349,089
	3.L.C. Funding: The recommended budget was partially met, and several projects were funded, but it appears there is a downward trend in funding for these projects over time. This objective partially overlaps with 3.L.A. **Progress:** Epidemiological studies coded to other objectives (e.g., EARLI) may also represent progress in this area. **Remaining Gaps, Needs, and Opportunities:** A barrier to the completion of this objective is the undefined nature of ASD subtypes, both phenotypically and etiologically, lack of prenatal samples, and the lack of longitudinal follow-up of at-risk subgroups. This field is still developing and needs support.					
Support ancillary studies within one or more large-scale, population-based surveillance and epidemiological studies, including United States populations, to collect data on environmental factors during preconception, and during prenatal and early postnatal development, as well as genetic data, that could be pooled (as needed) to analyze targets for potential gene/environment interactions by 2015. *IACC Recommended Budget: $44,400,000 over 5 years*	3.9 $17,297,788 29 projects	3.L.D $9,135,505 12 projects	3.L.D $11,464,011 10 projects	3.L.D $11,567,250 10 projects	3.L.D $13,549,160 12 projects	$63,013,714
	3.L.D. Funding: The recommended budget was met. Significantly more than the recommended minimum budget was allocated to projects specific to this objective. **Progress:** The funds allocated to this objective to date have been used for data collection and the development of infrastructure, with most of the studies coded to this area relating to CDC's CADDRE program. **Remaining Gaps, Needs, and Opportunities:** Continued funding will be needed to support data analysis. Both molecular and environmental data are needed.					

Table 3: Question 3 Cumulative Funding Table, see appendix for a color-coding key and further details.

Question 3 Cumulative Funding Table

IACC Strategic Plan Objectives	Funding					
Year	2008	2009	2010	2011	2012	Total
Not specific to any objective (Core/Other Activities)	**3. Core/ Other Activities** $6,791,008 52 projects	**3. Core/ Other Activities** $8,512,980 39 projects	**3. Core/ Other Activities** $1,312,450 7 projects	**3. Core/ Other Activities** $724,770 5 projects	**3. Core/ Other Activities** $315,607 3 projects	**$17,656,815**
Total funding for Question 3	**$82,846,620** 221 projects	**$100,043,216** 192 projects	**$81,231,647** 162 projects	**$60,209,628** 148 projects	**$56,487,025** 162 projects	**$380,818,136**

Table 3: Question 3 Cumulative Funding Table, see appendix for a color-coding key and further details.

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QUESTION 4

WHICH TREATMENTS AND INTERVENTIONS WILL HELP?

INTRODUCTION

Aspirational Goal: Interventions will be developed that are effective for reducing both core and associated symptoms, for building adaptive skills, and for maximizing quality of life and health for people with ASD.

A review of the state of the science in 2009 noted that many treatments were in use, but little rigorous evidence existed to support their safety or efficacy.[1] At that point, the Committee identified intervention research needs from two quite different approaches. One approach, dependent on progress in the basic and translational research areas covered under Questions 2 and 3, called for novel, targeted interventions based on an understanding of the molecular mechanisms of ASD. The other approach, related to the applied research and real-world deployment of tools and services covered in Questions 5 and 6, called for rigorous studies to test the efficacy and safety of interventions that were already in wide use, including behavioral and complementary medicine approaches.

Question 4 in the *2009 IACC Strategic Plan* included six objectives, with an additional six objectives (including some with multiple parts) added in the revisions in 2010 and 2011. Altogether, the most recent version of the *IACC Strategic Plan* recommended a wide range of studies under Question 4, including 19 randomized clinical trials, 20 model system studies to identify treatment targets, and one workshop. The total recommended budget was $283 million across all 12 objectives.

PROGRESS TOWARD THE STRATEGIC PLAN OBJECTIVES

The *2011 - 2012 IACC Portfolio Analysis* reviews ASD projects funded by both government agencies and private organizations from 2008 to 2012. Based on this analysis, the cumulative investment in projects categorized in Question 4 from 2008 to 2012 was $309 million. Focusing on 2009 to 2012, the period after publishing the *2009 IACC Strategic Plan*, the total investment was $255 million. This means that on average, the yearly investment in the research area targeted by Question 4 during this period was 18 percent higher than in 2008 ($54 million). It is important to note that from 2009 to 2012, roughly 90 percent of the investments assigned to Question 4 aligned with one of the 12 objectives, which address gap areas in the portfolio, and about 10 percent of the objectives address core/other activities that were not specific to any objective and may represent emerging areas of research not yet captured by the *IACC Strategic Plan* objectives.

Because most clinical trials require several years for completion, the snapshot of 2012 may be helpful for assessing the current cross-agency portfolio of activities relating to treatments and interventions for ASD. There were 269 projects funded in 2012 at a cost of $64 million, with 240 projects distributed among each of the 12 objectives and 29 projects ($3.9 million) assigned to core/other activities, thus demonstrating the broad range of research currently taking place in this area.

The research portfolio related to four of the objectives was considered to have met the recommended budget and number of projects, including those that called for randomized controlled trials (RCTs) addressing co-occurring conditions, development of model systems, early intervention trials, and studies on interventions for non-verbal/minimally verbal individuals. Eight objectives partially met their recommended number of projects and/or budgets. These objectives included testing safety and efficacy of interventions, investigating biological signatures, health promotion, medication trials, interventions to prevent recurrence in siblings, medications to treat co-occurring conditions, community studies evaluating intervention effectiveness, and a workshop on clinical subtypes and treatment personalization (with regard to the last objective, it was deemed only partially met because the relevant workshops and activities that took place were not exclusively focused on the topic mentioned in the objective, though some of the activities incorporate not only meetings/discussion, but also implementation of projects).

As noted above, there were 269 active projects in 2012 that were responsive to Question 4, with the large number of studies reflecting the wide variety of research into treatments and interventions for ASD. Despite the numerous avenues currently being pursued, however, many funded psychosocial, behavioral, medication and other biomedical intervention trials are being conducted with small budgets, suggesting that these projects are under-powered to provide the needed evidence for efficacy or safety. It is important to note that some of these projects are exploratory, and thus are appropriately funded with smaller budgets as an initial step, prior to larger scale investment if the strategies yield promising results. Additionally, the absence of therapeutic targets or consensus outcome measures makes interpretation of positive or negative results difficult, although as this field matures and the research moves forward, this problem is likely to resolve.

Again, reflecting the very early stage of intervention development for ASD, nearly one-third of the funding aligned with Question 4 was invested in one objective: the standardization and validation of model systems (such as cellular and animal models) to identify molecular targets or circuits for treatment development. Several objectives that address the assessment of current treatments received less investment. In particular, testing the safety and efficacy of widely-used treatments ($1.3 million in 2012) and studies of interventions for either secondary conditions ($1 million in 2012) or co-occurring conditions (less than $1 million in 2012) received relatively little investment, indicating a need to increase work in these areas. In developing the *IACC Strategic Plan*, the Committee emphasized the need for research to develop treatments for those most severely disabled by ASD, including those who are minimally verbal. Encouragingly, examination of the research portfolio showed strong growth in research on minimally verbal ASD, reflecting the interest of the research community in seeking to develop new approaches to help this population. Continued investment in this area will be vital to progress.

Overall, there has been considerable activity on Question 4 since the launch of the *IACC Strategic Plan* in 2009. While the overall financial investment roughly matches and, in many areas exceeds, the recommendations put forth in the *IACC Strategic Plan*, it is too early to assess the impact of these investments. Although clinical trials of pharmacological interventions for core symptoms of ASD are now underway, they require several years for completion, analysis, and reporting, resulting in very few published findings to date.[2] Preclinical studies, which have a shorter delivery time have, however, yielded some remarkable insights, especially on mice with mutations that model syndromic forms of ASD, such as Fragile X or Rett Syndrome.[3,4] In affected mice, experimental treatments reverse the syndrome both in development and in adulthood.[5] While these studies give hope, the relationship of syndromic autism (ASD caused by known genetic syndromes) to idiopathic autism (autism of unknown cause) is not clear. Furthermore, in many areas of neuroscience, efficacy of treatments in mice has not translated into efficacy of treatments in human patients. In summary, while there have been significant advances in the areas of genetics and neurobiological studies, the advances have not yet been translated into a full pipeline of molecular, cellular, and systems targets for interventions. The recent interest of pharmaceutical companies in investing in autism has been an encouraging development, as partnerships between government, nonprofit organizations and pharmaceutical companies will be essential to filling the pipeline toward development of new pharmacotherapies for ASD.

The clinical research agenda is also very much a work in progress. The development of Autism Speaks' Autism Treatment Network (ATN) and the entry of industry into this area are both promising changes, providing potential venues and support for future trials. While in 2008, only six clinical trials for ASD were listed in ClinicalTrials.gov, currently there are 92 ASD intervention trials recruiting subjects in the United States, including pharmacological studies to address core symptoms.

Recent developments in clinical trials on the use of the naturally occurring hormone oxytocin to address social impairments have yielded promising results. In an initial pilot RCT funded by Autism Speaks, researchers administered oxytocin nasal spray or a placebo to 25 children and teens twice a day for 2 months.[6] The children who received oxytocin showed greater improvement in social behaviors compared to those who received the inactive nasal spray. Preliminary results from a larger, follow-on, NIH-funded clinical trial have demonstrated that a single spray of intranasal oxytocin can normalize brain function when performing social tasks, suggesting that oxytocin may be able to enhance social function in children.[7] Further research on the efficacy of oxytocin therapy alone and in combination with behavioral therapy will be important areas for future study.

In addition to research on treating core symptoms, other efforts are providing insights into managing the symptoms associated with co-occurring conditions such as attention deficit hyperactivity disorder (ADHD),[8–10] epilepsy,[8,9,11,12] and disturbances in sleep,[13–17] immunity,[18,19] metabolism,[20–24] and gastrointestinal (GI)function.[25–28] Reflecting the growing focus on co-occurring conditions, in 2012, the Health Resources and Services Administration (HRSA) funded the Autism Intervention Research Network for Physical Health (AIR-P) and the ATN published empirically-validated physician guidelines for the assessment and treatment of GI, sleep, and ADHD symptoms in children with ASD.[17,27–34] In addition, the American Academy of Pediatrics (AAP) published guidelines for treatments of core symptoms, associated symptoms, and the use of complementary and alternative treatments.[35]

Several clinical trials of behavioral interventions were completed in the last 5 years with some notable successes. These early behavioral intervention trials demonstrated efficacy for significantly improving cognitive, language, and social abilities, as well as adaptive behavior, and have indicated that the improvements seen are maintained over time.[36–41] For example, the Early Start Denver Model (ESDM) has been shown to be effective in improving cognitive, language, social, and adaptive behaviors as well as in reducing the severity of ASD diagnosis.[36,41] In order to facilitate translation of the ESDM to the community, ongoing effort is focusing on alternate delivery of the intervention, such as through telehealth, community group settings, and parent-delivered approaches.[37,41] Another recent trial of a low intensity and brief intervention called JASPER (Joint Attention Symbolic Play Engagement and Regulation) demonstrated significant improvement compared with community treatment.[38] The relatively lower intensity of the intervention suggests that JASPER could be widely implemented.

Progress also is being made in educational intervention research. A recent comparative study of LEAP (Learning Experiences and Alternative Program for Preschoolers and their Parents), TEACCH (Treatment and Education of Autistic and Related Communication Handicapped Children), and non-model specific special education intervention approaches showed that in high-quality special education classrooms, all approaches were effective in improving symptom severity, as well as social, behavioral, and communication skills.[42] The study found that the quality of the classroom, rather than the specific intervention method, was the most important indicator of how much the child's symptoms improved. Future work on educational intervention approaches will be important not only to develop effective strategies, but also to learn which approaches will work best in specific subsets of children or in particular settings.

As progress on the development of interventions continues, research into biomarkers remains a high priority, and is vital to success in this field. First, identification of molecular and behavioral biomarkers of ASD would help to stratify the population so that treatments could be targeted to those who are most likely to benefit. For example, while as many as 50 percent of children will respond well to behavioral interventions, there is still a lack of biomarkers that can accurately predict response and help match individuals with appropriate treatments.

Additionally, biomarkers are essential as key indicators to establish when therapies are working. Biomarkers showing treatment response can be used to help researchers determine the best age and the best dose (in the case of behavioral interventions, low versus high intensity) at which to deliver therapy to achieve the maximum benefit in terms of brain and behavioral development of children with ASD. Along these lines, a recent study demonstrated that early intensive behavioral intervention correlated with positive change in EEG activity that was associated with improvements in social behavior, providing the first demonstration of a physiological biomarker to indicate the effect of a behavioral treatment.[43]

Additional biomarkers of treatment success are needed. Until it becomes possible to biologically measure treatment response, negative results from pharmacological and behavioral interventions will be difficult to interpret and positive results may not definitely indicate the requisite dose or duration of treatment. In addition to an improved ability to measure the initial response to treatments, there is also a need for longitudinal studies to evaluate the long-term outcomes of treatments and interventions, including measures of quality of life.[44] In summary, autism treatment research remains a young field that shows promise, and the focus must now be on identification of consensus outcome measures (including biomarkers) that are both robust and sensitive to change.

A wide range of treatments with varying degrees of evidence to support them are widely used for ASD. The "practice to research" approach, in which information on interventions that are already in use is collected from large health care systems, registries, from clinical networks such as the ATN, and through virtual, self-reporting networks such as the Interactive Autism Network (IAN), could prove useful for assessing current interventions in real-world settings. If fully developed for ASD, the practice to research approach promises to be a fruitful strategy for collecting data on treatment effectiveness, leading more quickly to randomized clinical trials.

New technologies, including devices to serve as social prosthetics (to provide social feedback or information) or tools for communication assistance, are exciting opportunities for the next generation of interventions in ASD. For example, the National Science Foundation (NSF) currently funds a project to develop a robot designed to act as a social therapy tool, providing an opportunity for individuals with ASD to practice social interactions in a safe and comfortable way without the complexities that are found in human interactions. New technologies are also being used to improve communication abilities of those people with ASD who are minimally verbal. In the future, devices will likely be used in combination with behavioral interventions and medications to create personalized treatments. The combinations of devices, behavioral interventions, and medications will be a profound challenge for research design and regulatory approval, but may prove most useful for children and adults with complex needs.

Along with progress in developing interventions for ASD, there will continue to be a need for access to reliable information about interventions that can be accessed by providers and families considering intervention choices. Encouragingly, the past 5 years have seen the publication of several systematic reviews of interventions as well as the launch of new tools, such as a publicly accessible "Interventions, Treatments and Therapies for Autism" database that provides lay-friendly information about autism interventions (supported by Research Autism in the United Kingdom).[45–47]

PROGRESS TOWARD THE ASPIRATIONAL GOAL

Interventions that are effective for reducing both core and associated symptoms, for building adaptive skills, and for maximizing quality of life and health for people with ASD, will likely need a stronger foundation from the preceding *IACC Strategic Plan* questions; in particular, information about the stratification of ASD into subtypes (so that interventions can be tailored) and a deeper understanding of the biology of ASD (so that interventions can be effective). While in the past, serendipitous findings based on clinical observation have led to treatments for neuropsychiatric disorders without

a deep understanding of the underlying biology, it is anticipated that investment in understanding the mechanisms underlying ASD will facilitate the development of the next generation of treatments. In addition, continued improvement of behavioral, educational and technological interventions will be important. Early intervention to restore a normal developmental trajectory must remain a high priority.

There are now several medications that are being tested in RCTs that are expected to be completed in 2014 or 2015. However, to date, progress on reducing core symptoms has been most evident with early behavioral interventions. The efficacy of these treatments is powerful evidence that ASD core symptoms can be treated, even if medications or devices which might be more rapid and more accessible have yet to be developed. Looking forward, future clinical trials will need to assess quality of life measures as well as reducing symptoms. In addition, effort should be made to scale up interventions that are effective in lab settings so that they may serve the broader community.

Progress has also been made in the development of treatments for several co-occurring conditions, and this continues to be an important avenue of ASD research. Associated conditions and symptoms such as epilepsy, ADHD, anxiety and depression are already being treated effectively, with both medications and behavioral interventions, although more work to improve these approaches and explore the combination of medical and behavioral approaches is needed. Recent guidelines on the management of co-occurring conditions such as sleep disturbances, ADHD, and gastrointestinal (GI) issues are a clear sign of progress for families and providers,[17,27–30,32–34] with the hope that more evidence-based guidelines will be developed in the future.

Future efforts will need to address the needs of the ASD population across the lifespan. Much of the effort to develop treatments to date has focused on children, yet based on the larger proportion of life that is spent in adulthood, it is possible that the number of adults with ASD may be much larger than the number of children with ASD. Future studies must include development of treatments and interventions for individuals of all ages, including adults and adolescents, as well as children. In addition, treatments must address the needs of the entire spectrum, including those who are minimally verbal individuals and those with intellectual disabilities. Furthermore, interventions must be tailored to the needs of individuals from diverse communities in a manner that is culturally responsive, and parents need to have access to high quality sources of information about available interventions.

While the field of ASD intervention has made important strides in the past 5 years, the need for a wider variety of effective intervention options to meet varying needs remains an outstanding goal. Partnerships between government and private organizations and involvement of families and individuals affected by ASD in research will be essential as the community continues to work toward the aspirational goal of developing interventions that will help all people with ASD to build adaptive skills and maximize quality of life and health.

Question 4 Cumulative Funding Table

IACC Strategic Plan Objectives	Funding					
Year	2008	2009	2010	2011	2012	Total
Support at least three randomized controlled trials that address co-occurring medical conditions associated with ASD by 2010. *IACC Recommended Budget: $13,400,000 over 3 years*	**4.2** $4,583,171 5 projects	**4.S.A** $4,733,841 6 projects	**4.S.A** $3,787,700 4 projects	**4.S.A** $1,826,542 4 projects	**4.S.A** $2,174,124 3 projects	**$17,105,378**
	4.S.A. Funding: The recommended budget for this objective was met. **Progress:** More than three projects were funded, including trials of sleep, anxiety, seizure and gastrointestinal (GI) interventions, meeting the objective. Additional work will be needed in the future to fully address these conditions. **Remaining Gaps, Needs, and Opportunities:** Sleep issues, anxiety, hyperactivity and GI issues are key co-occurring medical conditions in patients with ASD. Although there is much more known today about sleep initiation than what was understood 5 years ago, there is little understanding of what interventions/treatments are effective for sleep maintenance or night awakening. There is not much known concerning anxiety treatments for those with ASD, and challenges exist regarding the adaptation of anxiety treatments from outside ASD patient groups. Research into interventions for hyperactivity may be transferred from populations outside of those with ASD (i.e., ADHD). Though there has been an increased awareness of gastrointestinal difficulties and common symptoms among people with ASD, little is known about the etiology of autism-related GI issues. More research on the etiology of GI issues will be needed to develop appropriate treatments/ interventions.					
Standardize and validate at least 20 model systems (e.g., cellular and/or animal) that replicate features of ASD and will allow identification of specific molecular targets or neural circuits amenable to existing or new interventions by 2012. *IACC Recommended Budget: $75,000,000 over 5 years*	**4.5** $15,879,827 42 projects	**4.S.B** $20,162,709 70 projects	**4.S.B** $23,229,501 92 projects	**4.S.B** $21,606,118 89 projects	**4.S.B** $21,232,514 94 projects	**$102,110,669**
	4.S.B. Funding: The recommended budget was met. Significantly more than the recommended minimum budget was allocated to projects specific to this objective. **Progress:** More than 90 projects were supported to develop animal models. **Remaining Gaps, Needs, and Opportunities:** Planning Group members discussed whether the amount of investment in this area is appropriate when compared to investments in clinical trials and other later stage studies. Invited experts suggested that the current stage of scientific research in ASD requires pre-clinical research to identify targets from animal and cellular models. Similar to cancer treatment development pathways, which spanned 20-30 years, research in ASD must invest in model systems to understand the fundamental biology from which translation to the clinic can be built. The translational validity of research in non-human animals cannot be determined until human trials are conducted, thus the need for rapid progress to clinical studies in humans is important.					

Table 4: Question 4 Cumulative Funding Table, see appendix for a color-coding key and further details.

Question 4 Cumulative Funding Table

IACC Strategic Plan Objectives	Funding					
Year	2008	2009	2010	2011	2012	Total
Test safety and efficacy of at least five widely used interventions (e.g., nutrition, medications, assisted technologies, sensory integration, medical procedures) that have not been rigorously studied for use in ASD by 2012. *IACC Recommended Budget: $27,800,000 over 5 years*	4.6 $641,285 8 projects	4.S.C $3,252,941 29 projects	4.S.C $1,509,745 18 projects	4.S.C $2,254,724 18 projects	4.S.C $1,288,226 17 projects	$8,946,921
	4.S.C. Funding: The recommended budget was partially met. **Progress:** Several projects were funded in this area, but more work is needed, as this is an area of significant public interest. **Remaining Gaps, Needs, and Opportunities:** Experts discussed the best balance between developing new treatments and testing current treatments that lack evidence, especially when funds are limited and conclusive clinical trials are expensive. The group noted that interventions for minimally verbal children are needed; some projects on assistive communication technologies, robotics and speech processing technology to assist with social communication training are funded, but more are needed. There are other projects related to minimally verbal autism in objective 4.S.G. Small pilot studies on nutritional therapies (i.e., GFCF diet studies) have been conducted with inconclusive outcomes, demonstrating the necessity for further exploration of nutritional interventions. Future emphasis on scientific investment in sensory integration and assisted technologies is needed.					
Complete two multi-site randomized controlled trials of comprehensive early intervention that address core symptoms, family functioning and community involvement by 2013. *IACC Recommended Budget: $16,700,000 over 5 years*	4.7 $4,236,869 5 projects	4.S.D $7,540,613 9 projects	4.S.D $10,306,148 18 projects	4.S.D $11,156,647 20 projects	4.S.D $8,848,130 21 projects	$42,088,407
	4.S.D. Funding: The recommended budget was met. Significantly more than the recommended minimum budget was allocated to projects specific to this objective. **Progress:** In 2011 and 2012, ~20 trials were supported, including a mix of trial sizes. **Remaining Gaps, Needs, and Opportunities:** There is a need for both small, pilot studies and larger, robustly powered studies in this area. Several larger studies in the past few years (e.g., Early Start Denver Model) have emerged, but most studies in this area are generally smaller than in other fields of medicine and therefore lack the power to be informative if negative or definitive if positive. This objective also cites "family functioning" and "community living," which may have significant overlap with objectives in Questions 5 and 6 of the *Strategic Plan*.					

Table 4: Question 4 Cumulative Funding Table, see appendix for a color-coding key and further details.

Question 4 Cumulative Funding Table

IACC Strategic Plan Objectives	Funding					
Year	2008	2009	2010	2011	2012	Total
Convene a workshop to advance the understanding of clinical subtypes and treatment personalization (i.e., what are the core symptoms to target for treatment studies) by 2011. *IACC Recommended Budget: $50,000* ** This objective was partially completed in 2011*	N/A	4.S.E $0 0 projects	4.S.E $0 0 projects	4.S.E* $26,000 1 project	4.S.E* $0 0 projects	$26,000
	4.S.E. Funding: The recommended budget was partially met, but was not put toward a single dedicated workshop. **Progress:** Two workshops and other activities that have partially addressed this issue have taken place, but to date there has not been a dedicated workshop on this issue, so this objective is marked "yellow." **Remaining Gaps, Needs, and Opportunities:** Autism Speaks held two relevant workshops. The first, that took place on January 2011, "Outcome Measures for Clinical Trials with Individuals with ASD: Challenges and Opportunities," was focused on developing strategies for advancing clinical trials of medications for ASD core and associated symptoms. The second, "Translational Medicine Research in ASD: Challenges and Opportunities," that also took place in January 2011 focused on the basic science needed to discover and develop new treatments. Biomarkers and treatment personalization were among the topics discussed in both workshops. The EU-AIMS public-private consortium in Europe is working toward "developing and validating translational approaches for the advancement of novel therapies to treat ASD." Identification of biomarkers of subtypes of ASD and personalization of interventions are within the consortium's goals. Joint meetings between EU-AIMS and the Foundation for NIH Biomarkers Consortium, another recently-formed consortium around biomarkers and personalized treatments, are ongoing to determine the opportunities for collaboration on identifying surrogate markers for ASD treatment studies. Thus, while a dedicated workshop on clinical subtypes has not taken place, some of the present activities are discussing and implementing projects related to this topic.					
Launch randomized controlled trials of interventions including biological signatures and other measures to predict response, and monitor quality of life and functional outcomes in each of the following groups: · Five trials in infants and toddlers by 2013. *IACC Recommended Bud* · Three trials in school-aged children and/or adolescents by 2013. *IACC Recommended Budget: $18,000,000 over 5 years (revised in 2010)* · Three trials in adults by 2014. *IACC Recommended Budget: $18,000,000 over 5 years* *Total IACC Recommended Budget: $66,000,000 over 5 years*	4.3 & 4.4 $12,109,516 16 projects & 30 projects	4.S.F $9,791,270 42 projects	4.S.F $7,575,212 30 projects	4.S.F $5,445,599 23 projects	4.S.F $6,255,438 21 projects	$41,177,035
	4.S.F. Funding: The recommended budget was partially met. **Progress:** The investment in projects under this objective is making good progress toward the recommended amount, with more than 20 projects funded in 2011 and 2012. **Remaining Gaps, Needs, and Opportunities:** Current projects in this area are restricted to small pilot studies, which are essential to establishing a foundation prior to expansion to larger scale work. Thus, increased investment in this area is important. It should be noted that most RCTs in the future will incorporate some aspect of biological signatures (thus potentially presenting a challenge to future coding of projects).					

Table 4: Question 4 Cumulative Funding Table, see appendix for a color-coding key and further details.

Question 4 Cumulative Funding Table

IACC Strategic Plan Objectives	Funding					
Year	2008	2009	2010	2011	2012	Total
Support at least five studies on interventions for nonverbal individuals with ASD by 2012. Such studies may include: · Projects examining service-provision models that enhance access to augmentative and alternative communication (AAC) supports in both classroom and adult service-provision settings, such as residential service-provision and the impact of such access on quality of life, communication, and behavior; · Studies of novel treatment approaches that facilitate communication skills in individuals who are nonverbal, including the components of effective AAC approaches for specific sub-populations of people with ASD; and · Studies assessing access and use of AAC for children and adults with ASD who have limited or partially limited speech and the impact on functional outcomes and quality of life. *IACC Recommended Budget: $3,000,000 over 2 years*	N/A	N/A	**4.S.G** $1,907,721 11 projects	**4.S.G** $2,830,851 13 projects	**4.S.G** $4,841,831 16 projects	**$9,580,403**
	4.S.G. Funding: The recommended budget was met. Significantly more than the recommended minimum budget was allocated to projects specific to this objective. **Progress:** Between 11 and 16 studies were funded annually in the years 2010-2012, but results will not be available for at least two years. **Remaining Gaps, Needs, and Opportunities:** The field of research on non-verbal patients with ASD is growing, yet still requires significant work and future investment. ASD research has historically concentrated on verbal individuals and adults, which highlights the need for increased research on minimally verbal populations.					
Support at least two studies that focus on research on health promotion and prevention of secondary conditions in people with ASD by 2012. Secondary conditions of interest include weight issues and obesity, injury, and co-occurring psychiatric and medical conditions. *IACC Recommended Budget: $5,000,000 over 3 years*	N/A	N/A	**4.S.H** $225,877 2 projects	**4.S.H** $222,265 1 project	**4.S.H** $956,827 4 projects	**$1,404,969**
	4.S.H. Funding: The recommended budget was partially met. **Progress:** A small number of projects, but more than the recommended minimum, were funded, but further work is needed to address some of the specific issues described in the objective. **Remaining Gaps, Needs, and Opportunities:** Overlap in interpretation between "co-occurring" and "secondary" conditions presents a challenge in evaluating this objective. There is likely overlap between projects that may fit this objective and those in 4.S.A. Areas of health promotion and disease prevention should be emphasized in this objective, as those are distinct from issues mentioned in other objectives in this Question. It was noted that 4.S.H's emphasis on prevention and health promotion may also overlap with 5.S.D and 5.L.D on "health and safety and mortality" issues.					

Table 4: Question 4 Cumulative Funding Table, see appendix for a color-coding key and further details.

Question 4 Cumulative Funding Table

IACC Strategic Plan Objectives	Funding					
Year	2008	2009	2010	2011	2012	Total
Complete at least three randomized controlled trials on medications targeting core symptoms in people with ASD of all ages by 2014. *IACC Recommended Budget: $22,200,000 over 5 years*	**4.8** $1,380,376 12 projects	**4.L.A** $1,168,146 10 projects	**4.L.A** $1,924,932 11 projects	**4.L.A** $1,527,858 12 projects	**4.L.A** $3,713,783 14 projects	**$9,715,095**
	4.L.A. Funding: The recommended budget was partially met. **Progress:** 10-14 studies have been funded, which is more than the minimum recommended, and momentum within the pre-clinical phases of this objective is currently building. It should be noted, however, in that many of these studies are small trials or pilot studies. **Remaining Gaps, Needs, and Opportunities:** Though there is little evidence that CNS drug development in animals will translate to humans, either in terms of toxicity or efficacy, there is still a need for investment in well-established animal model studies to identify promising molecular, cellular, or systems targets before mounting randomized clinical trials in humans. However, existing drugs for other indications may be adapted to ASD without extensive pre-clinical work, and there is also evidence for proof of concept studies for ASD (particularly those addressing core symptoms). It is also critically important to develop appropriate outcome measures for use in trials.					
Develop interventions for siblings of people with ASD with the goal of reducing the risk of recurrence by at least 30% by 2014. *IACC Recommended Budget: $6,700,000 over 5 years*	**4.9** $14,256 1 project	**4.L.B** $132,263 2 projects	**4.L.B** $307,349 3 projects	**4.L.B** $14,256 2 projects	**4.L.B** $362,987 2 projects	**$831,111**
	4.L.B. Funding: The recommended budget was not met; the funding allocated to projects specific to this objective falls far short of the recommendation. **Progress:** Only a small number of projects has been funded, and the intent of the objective has not been met to date. Research on siblings is still at an early stage, and the results, just beginning to be published, will inform future progress. **Remaining Gaps, Needs, and Opportunities:** Results from studies within this objective will emerge in the near future. Greater understanding of the mechanisms underlying sibling development of ASD will be key before any targeted early interventions may be developed for this population.					
Conduct at least one study to evaluate the safety and effectiveness of medications commonly used in the treatment of co-occurring conditions or specific behavioral issues in people with ASD by 2015. *IACC Recommended Budget: $10,000,000 over 5 years*	N/A	**4.L.C** $1,061,222 7 projects	**4.L.C** $2,302,240 7 projects	**4.L.C** $2,834,887 8 projects	**4.L.C** $277,072 3 projects	**$6,475,421**
	4.L.C. Funding: The recommended budget was partially met. **Progress:** A small number (3-7) of studies of pharmacological interventions for co-occurring conditions was funded. There exist many studies examining drugs that are in active use for ADHD that are now being adapted to ADHD-ASD patient groups. **Remaining Gaps, Needs, and Opportunities:** There currently is much need for greater understanding of drug efficacy in ASD populations.					

Table 4: Question 4 Cumulative Funding Table, see appendix for a color-coding key and further details.

Question 4 Cumulative Funding Table

IACC Strategic Plan Objectives	Funding					
Year	2008	2009	2010	2011	2012	Total
Support at least five community-based studies that assess the effectiveness of interventions and services in broader community settings by 2015. Such studies may include comparative effectiveness research studies that assess the relative effectiveness of: · Different and/or combined medical, pharmacological, nutritional, behavioral, service-provision, and parent- or caregiver-implemented treatments; · Scalable early intervention programs for implementation in underserved, low-resource, and low-literacy populations; and · Studies of widely used community intervention models for which extensive published data are not available. Outcome measures should include assessment of potential harm as a result of autism treatments, as well as positive outcomes. *IACC Recommended Budget: $37,500,000 over 5 years*	N/A	N/A	**4.L.D** $8,756,832 32 projects	**4.L.D** $6,296,024 32 projects	**4.L.D** $10,186,313 45 projects	**$25,239,169**
	4.L.D. Funding: The recommended budget was partially met, and the annualized recommended budget targets were met for all 3 years since the objective was introduced. Therefore, the funding for this objective is on track. **Progress:** 30-45 studies have been supported, which is greater than the recommended minimum of at least five studies. Considerable work has been done under this objective, but these projects do not cover the full scope of interventions in the community. Comparing the large number of studies to the funding suggests that many small studies are being funded rather than fewer large ones. **Remaining Gaps, Needs, and Opportunities:** Emphasis on both the evaluation of interventions in controlled/academic settings prior to community based studies and the translation of interventions to community-based settings is key. Understanding of "Type 2 Translation," or transfer of research from academic settings to real-world settings is important, considering barriers to transferring academic-based interventions to clinical groups and communities. Investment is still necessary in the academic setting before successful translation to community-based interventions can occur. For successful T2 translation to underserved communities, cost effectiveness and case coordination or case management is often helpful with uptake. This objective also overlaps considerably with objectives in Question 5. It is important to explore which supports are specifically executed at the community level (vs. home, schools, etc.), and to determine how they are best designed.					
Not specific to any objective (Core/Other Activities	**4. Core/ Other Activities** $14,075,905 54 projects	**4. Core/ Other Activities** $15,560,011 59 projects	**4. Core/ Other Activities** $6,290,633 49 projects	**4. Core/ Other Activities** $4,777,350 37 projects	**4. Core/ Other Activities** $3,862,655 29 projects	**$44,566,554**
Total funding for Question 4†	**$53,968,973** 178 projects	**$63,403,014** 234 projects	**$68,123,890** 277 projects	**$60,819,121** 260 projects	**$63,999,900** 269 projects	**$309,267,132***

Table 4: Question 4 Cumulative Funding Table, see appendix for a color-coding key and further details.

**This total reflects all funding for projects aligned to current objectives in the 2011 IACC Strategic Plan and incorporates funding for projects that may have been coded differently in previous versions of the Plan.*

† The totals reflect the funding and projects coded to this Question of the Strategic Plan in the particular year indicated at the top of the column. When reading each column vertically, please note that the projects and funding associated with each objective for the years 2008, 2009, and 2010 may not add up to the total at the bottom of the column; this is due to revisions of the Strategic Plan that caused some objectives to be shifted to other Questions under the Plan. The projects and funding associated with these reclassified objectives are now reflected under the Question in which they appear in the 2011 Strategic Plan.

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QUESTION 5

WHERE CAN I TURN FOR SERVICES?

INTRODUCTION

Aspirational Goal: Communities will access and implement necessary high-quality, evidence-based services and supports that maximize quality of life and health across the lifespan for all people with ASD.

The *2009 IACC Strategic Plan*, which was revised in 2010 and 2011, delineated nine objectives related to Question 5, which include four short-term objectives and five long-term objectives to address gaps in current policy and services research that will benefit the autism community. These objectives call for studies and demonstration projects addressing issues such as: ways to improve access to services in traditionally underserved populations, developing successful models for self-directed care, evaluating how best to coordinate services across multiple state and local agencies, studying and improving health and safety and reducing mortality in individuals with ASD, implementing and disseminating interventions that have been proven efficacious, and evaluating cost effectiveness of services. The total recommended budget was $71 million across all nine objectives for this question.

PROGRESS TOWARD THE STRATEGIC PLAN OBJECTIVES

The 2011-2012 *IACC Portfolio Analysis* reviewed projects funded by both government agencies and private foundations from 2008 – 2012. Based on this analysis, the cumulative investment from 2008 – 2012 in projects categorized to Question 5 was $124 million. Approximately 70 percent of the investments assigned to Question 5 were in gap areas addressed by the Question 5 objectives, while 30 percent were in areas covered by the core/other category, which may represent areas of ongoing, mainstream efforts or emerging research areas that have not been captured in the *IACC Strategic Plan* objectives.

Of the nine specific objectives under Question 5, three objectives addressing access to services and implementation of evidence-based interventions in diverse populations, and evaluation of training for service and support providers, met or exceeded the recommended budget and fulfilled the recommended number of projects. The objective regarding studies to address dental health issues of people with ASD met the recommended number of projects, but the projects were done with less funding than was projected in the budget recommendation and only covered dental services for children. Four specific objectives were far below the recommended budget and number of projects. These include objectives regarding evaluation of state and local coordination of community-based services, projects to examine health, safety, and mortality issues, testing evidence based services for community living settings, and evaluation of programs to increase health and safety. Additionally, one objective, on studies to examine how self-directed community-based services impact individuals across the ASD spectrum, did not have any funding in the past 2 years, though there were some projects in this objective category in earlier years. The committee felt, however, that even with the earlier projects, they did not adequately cover some of the key community-based services, such as those related to employment and housing.

Overall, considerable progress was made in some areas of the services research field related to these nine Question 5 objectives. A growing body of research examines the best strategies to implement evidence-based autism interventions in diverse community settings—especially schools. Large-scale randomized implementation and effectiveness trials have shown that, with appropriate organizational and individual supports, evidence-based interventions developed in academic research settings can be implemented with fidelity in community settings and result in more positive outcomes than standard community care.[1] Implementation science (the study of approaches to delivery of services) is developing within the autism field. It will be important for the autism field to rapidly assimilate new developments from the general implementation science field, such as methods for addressing organizational, provider and consumer level factors to improve services and outcomes, in order to optimize delivery of autism interventions in community settings.

In a related development, the National Professional Development Center on Autism Spectrum Disorders, supported by the United States Department of Education (ED), now provides community education and service providers with **free information on evidence-based practices** for children and adolescents with ASD. The center has also made great progress on the development of **web based training programs** for the dissemination of early educational intervention best practices to states. This provides an opportunity for research examining the effects of such resources on implementation in both rural and urban settings. In the medical arena, with support from Autism Speaks and the Health Resources and Services Administration (HRSA), a wide range of physician and parent tool kits,[2] and the first empirically-supported

physician guidelines for the treatment of gastro-intestinal conditions,[3,4] sleep conditions,[5,6] and attention deficit hyperactivity disorder (ADHD)[7,8] are now available, defining standards of care and increasing the ability of practitioners to appropriately treat these conditions in service delivery settings. In the realm of safety issues, the Department of Education issued a resource document for restraint and seclusion in 2012 that provided guidance to schools on limiting restraint and seclusion while promoting positive behavioral supports and interventions as a safe and effective alternative. [9] Additionally, the first research studies of ASD-associated wandering have been done[10,11] and progress has been made by the National Autism Association in developing toolkits and information for preventing wandering and by the Department of Justice and the National Center for Missing and Exploited Children on quickly and appropriately responding to ASD wandering incidents to reduce injury and mortality.[12,13]

The passage and implementation of the Affordable Care Act (ACA) creates the opportunity for states to include behavioral treatments for individuals with ASD as part of their essential health benefits. This determination was based on the growing body of evidence supporting the efficacy of behavioral interventions and provides an example of how scientific advances can support policy changes that benefit the community. The extent to which states will include behavioral treatment coverage within their plans and the effects of the adoption of these benefits on treatment and outcomes remains unclear. Additionally, more than 30 states have explicitly listed autism as a related condition or explicitly included autism in the definition of people served under the State's Medicaid Home and Community Based Services waiver for people with intellectual disabilities, and 10 states offer waivers that specifically cover Applied Behavioral Analysis (ABA). Similar policy changes have been taking place in the military. As of July 25, 2013, TRICARE, the medical benefit plan of the military health system, extended coverage of ABA to non-active duty family members in addition to active duty family members that previously had coverage for this service.

Since 2010, the Centers for Medicare & Medicaid Services (CMS) has undertaken several activities that have provided new information about ASD services available in the community. In 2010, CMS issued a report entitled *Autism Spectrum Disorders (ASDs) Services Final Report on Environmental Scan* that describes the results of an extensive literature review of the scientific evidence regarding the efficacy, effectiveness, safety, and availability of ASD-related services and supports, including those funded through federal sources, that support daily living for people of all ages with ASD. [14] In 2011, CMS also issued a report on a nine-state study entitled, *Report on State Services to Individuals with Autism Spectrum Disorders (ASD)*, which assessed the implementation of evidence-based promising practices through the lens of state experience, summarizing the current state of ASD-related services covered by Medicaid and other sources in each of the nine states.[15] The report describes the types of services and supports provided by state and local governments, the sources of funding for programs, and the policy, staffing and implementation issues that states and localities encounter in the administration of programs that serve people with ASD. CMS also issued a report, *Autism Spectrum Disorders (ASD): State of the States of Services and Supports for People with ASD*, in 2014. This study assessed existing state programs and supports for families living with ASD in 50 states and the District of Columbia, providing a comprehensive view of services that received support from various federal sources and were made available through state programs across the country.

Internationally, there is also increased focus and funding aimed at monitoring and improving access to services for people with ASD. In 2012, the United Nations (UN) General Assembly unanimously passed a resolution, "Addressing the socioeconomic needs of individuals, families and societies affected by autism spectrum disorders, developmental disorders and associated disabilities," calling on governments to monitor and report as well as improve access to

healthcare, education, training, and intervention programs for persons with ASD and other developmental disabilities.[16] In 2013, the executive board of the World Health Assembly, governing body of the World Health Organization (WHO), adopted the resolution "Comprehensive and Coordinated Efforts for the Management of Autism Spectrum Disorders."[17] The resolution was co-sponsored by more than 50 countries and supported by all, including the United States.

A wealth of descriptive studies over the last five years has quantified the economic and health impact of autism on families. In one recent study, the economic cost of autism in the United States was updated, showing a substantial increase in cost across a variety of domains. The overall cost of ASD in the US is now estimated at $137 billion per year and the cost of providing care for each person with an ASD ranges from $1.4 million to $2.3 million over their lifespan, a number that is impacted by intellectual disability of the person.[18] This is a dramatic increase from the 2007 estimate of $35 billion per year. Drivers of costs associated with ASD included special education services[19] and parental productivity loss.[20] These costs were substantially smaller, however, than those related to residential care and individual productivity loss for individuals with ASD in adulthood.

Recent research has also provided a much better and more sophisticated understanding of disparities in the delivery of care to children and adults with ASD. Studies have moved beyond examining disparities in age of diagnosis to examine disparities in components of the diagnostic experience and in service use post-diagnosis.[21,22] Recent findings suggesting that the lifespan of people with ASD is similar to that of typically-developing peers (except in cases where comorbid conditions and accidents cause premature mortality) point to the need for more research to understand and address both comorbid conditions and the challenges of aging with ASD.[23]

PROGRESS TOWARD THE ASPIRATIONAL GOAL

Health disparities in the diagnosis and treatment of autism now are well described but poorly addressed. Studies must move from observational to experimental, in which strategies to reduce disparities are developed and tested. One issue of particular importance may be whether improving quality of care in traditionally underserved geographic regions is enough to ameliorate disparities, or if instead interventions targeted toward specific cultural and ethnic groups are needed. The Committee highlighted the need for the research portfolio to focus on developing practical, affordable and culturally-competent services and support approaches that can be used in a variety of settings, and for these approaches to be able to be adapted to the required scale to meet community needs.

While considerable strides have been made toward understanding the best ways to implement evidence-based practices in community settings, there is much work left to do in bringing interventions to scale. One barrier to studies that address related issues is the lack of strong, ongoing community-academic partnerships. These partnerships are necessary to conduct field research on effectiveness, implementation and scale-up of evidence-based practices. The Department of Education Institute of Education Science (IES) offered a partnership Request For Applications (RFA) in 2013 and NIMH previously supported a Research Infrastructure Support Program (RISP) mechanism to develop and maintain this type of

infrastructure. On a related note, most implementation or effectiveness studies have examined one intervention at a time in single service systems. Many, if not most, individuals with ASD receive multiple services concurrently in response to complex needs. Methods are needed to account for, and perhaps coordinate or simplify this complexity.

Progress in this area also has been hampered by some significant measurement issues. Currently there are few instruments that are appropriate for use at the population level to measure either availability or quality of services, or outcomes of these services. State agencies already may collect some of these important measures or may have the infrastructure to do so, suggesting the need for a different type of public-academic partnership. This measurement is urgently needed to provide a benchmark for the success of different programs at improving the health of the population and to identify models of excellence.

One important recent development is the investment by the NIH in a series of three initiatives to support research on services implementation across the lifespan, with the goals of addressing the challenges of improving outcomes for children, adolescents and adults. The first initiative targets models for coordination of ASD identification, evaluation, and early intervention services for children with ASD within the first two years of life, including tests of the feasibility and effectiveness of interventions across settings.[24] The second focuses on models to assist adolescents with ASD to transition to adult supports and services while preventing lapses in services and supports, enhancing functioning across settings, and maintaining or improving ASD symptoms, general health, safety, and quality of life.[25] The third addresses development of adult ASD service strategies that concern areas of employment and training, social relationships, physical and mental health, and independent functioning, including community housing and safety, alone or in combination, with the ultimate goal of improving behavioral, functional and health outcomes.[26] Awards for all three initiatives are expected in 2014.

In the past several years, while important strides have been made in estimating the economic impact of autism, there is still a need for more information on the cost effectiveness of services that can help support policy decisions. New cost effectiveness research should take a lifespan approach to assess long-term costs and benefits. Economic cost is not the only cost however, and should not be examined at the expense of other potential benefits of intervention. The concept of "social return on investment" may be an important one to examine. One possibility to address both types of return on investment is to take advantage of ongoing or recently completed randomized trials to continue to follow both the experimental and control conditions to determine the long-term impacts of these interventions.

In the past 5 years, the IACC and private organizations have helped raise a new level of public awareness of safety issues such as seclusion, restraint and wandering that have had significant impact on the ASD community.[27,28] Some initial steps toward disseminating information and data gathering activities have begun, but much more progress is needed in order to reduce the number of incidents, injuries and deaths associated with these preventable circumstances.

Overall, there are many opportunities for increased investment in ASD services research to fill important gaps in knowledge about what services are needed, how to best deliver them, which services work for which communities and strategies to increase uptake of best practices across settings. With infusion of additional support, infrastructure such as state demonstration programs that have been established within the past 5 years could provide an important opportunity for new research partnerships that could yield valuable information about services approaches in real-world settings. Such innovative approaches and resulting research data will be needed in the future to support progress toward the IACC Question 5 aspirational goal of creating an environment where "communities will access and implement necessary, high-quality, evidence-based services and supports that maximize quality of life and health across the lifespan for all people with ASD."

Question 5 Cumulative Funding Table

IACC Strategic Plan Objectives	Funding					
Year	2008	2009	2010	2011	2012	Total
Support two studies that assess how variations in and access to services affect family functioning in diverse populations, including underserved populations, by 2012. *IACC Recommended Budget: $1,000,000 over 3 years*	5.2 $0 0 projects	5.S.A $499,999 1 project	5.S.A $2,061,834 9 projects	5.S.A $1,351,793 8 projects	5.S.A $1,364,087 6 projects	$5,277,713
	5.S.A. Funding: The recommended budget was met. Significantly more than the recommended minimum budget was allocated to projects specific to this objective. **Progress:** The initial target of two studies was met, with 1-9 projects supported per year, but more work is still needed in this area. **Remaining Gaps, Needs, and Opportunities:** The projects under this objective cover several topics related to family functioning and health disparities, but not the full breadth of the gaps mentioned in the objective. This objective, as written, may be too broad. Work is still needed to understand why underserved populations have poorer outcomes and what can be done to close the gaps. We need to understand what portfolio of services will result in the best outcomes for different populations. To address these questions, a qualitative approach (i.e., needs assessment or survey) may be needed to understand the context of barriers faced by different groups. Research on disparities needs to move beyond observational studies to experimental designs to see what approaches work best in different populations and settings.					
Conduct one study to examine how self-directed community-based services and supports impact children, youth, and adults with ASD across the spectrum by 2014. *IACC Recommended Budget: $6,000,000 over 3 years*	N/A	5.S.B $446,340 6 project	5.S.B $291,635 6 projects	5.S.B $0 1 project	5.S.B $0 0 projects	$737,975
	5.S.B. Funding: The recommended budget was partially met. **Progress:** More work is needed in this area to achieve the goals set forth by the objective. While more than the number of studies called for have been supported, the area is underfunded (the projects have been small) and the projects do not examine all areas targeted in the objective. **Remaining Gaps, Needs, and Opportunities:** Several of the funded projects relate to recreational activities, but more projects that focus on issues such as housing, employment, and quality of life (self-direction) are needed. Issues such as housing and employment may not be reflected in the portfolio data because the agencies and organizations included in the analysis may not have these topics as a primary focus, and many housing and employment-related efforts may not be specific to ASD. This area may benefit from a "practice to research" approach where already-operating programs can be evaluated for efficacy and this may help to develop more easily implementable services. Work is also needed to determine what outcome measures are informative and useful. Another issue is the scalability, as many vocational projects are very small and intensive and this is not an effective model for broad implementation. Potential funding mechanisms for these evaluations include the Dept. of Education Institute of Educational Science program for partnering researchers and educators and the NIMH Research Initiative for Scientific Enhancement (RISE) R25 program.					

Table 5: Question 5 Cumulative Funding Table, see appendix for a color-coding key and further details.

Question 5 Cumulative Funding Table

IACC Strategic Plan Objectives	Funding					
Year	2008	2009	2010	2011	2012	Total
Implement and evaluate five models of policy and practice-level coordination among State and local agencies to provide integrated and comprehensive community-based supports and services that enhance access to services and supports, self-determination, economic self-sufficiency, and quality of life for people with ASD across the spectrum and their families, (which may include access to augmentative and alternative communication [AAC] technology), with at least one project aimed at the needs of transitioning youth and at least one study to evaluate a model of policy and practice-level coordination among State and local mental health agencies serving people with ASD, by 2015. *IACC Recommended Budget: $25,000,000 over 5 years (revised in 2011)*	N/A	5.S.C $0 0 projects	5.S.C $4,225,315 15 projects	5.S.C $600,000 3 projects	5.S.C $600,000 2 projects	$5,425,315
	5.S.C. Funding: The recommended budget was partially met. **Progress:** Progress has been made but the objective is not fully achieved, as it is underfunded and the projects do not cover all of the issues mentioned in the objective. **Remaining Gaps, Needs, and Opportunities:** Studying services coordination is very difficult and it is hard to define outcomes. State to state dissemination is very limited and fragmented. Also, state policies often are translated to practice very differently in different areas and counties. State and local services programs also suffer from a lack of knowledge in how to engage and sustain community partnerships. A pairing of existing state and local services programs (including those that may be participating in federally-funded state demonstration programs) with research funding for evaluation would be the most cost-effective way to collect and analyze data about the implementation of models of coordination. For example, building research projects onto existing state demonstration programs and supporting the development of partnerships between academic researchers and state agencies to study models of policy implementation would be ways to advance this type of research.					
Support two studies to examine health, safety, and mortality issues for people with ASD by 2012. *IACC Recommended Budget: $4,500,000 over 3 years*	N/A	N/A	5.S.D $159,135 3 projects	5.S.D $0 1 project	5.S.D $5,000 1 project	$164,135
	5.S.D. Funding: The recommended budget was not met; the funding allocated to projects specific to this objective falls far short of the recommendation. **Progress:** More work is needed on this objective; studies have been funded in this area (e.g., wandering, victimization), but they are small and they do not address all issues within this objective. **Remaining Gaps, Needs, and Opportunities:** There may be some projects in other *Strategic Plan* Questions that are related to this objective (i.e., the Utah epidemiological study coded to Question 7 that examines health risks and causes of mortality). There is ongoing data mining of existing data sets to identify risks, new methods of prevention, methods of recovery, and best practices. Best practices need to be developed to respond to wandering (prevention, response, and search). A "practice to research" model, where data are collected in the process of delivering services, would also be appropriate. One issue that is underrepresented in the portfolio is sexual/reproductive health communication for adolescents and adults with ASD. In general, adult needs are not well-represented in the current research.					

Table 5: Question 5 Cumulative Funding Table, see appendix for a color-coding key and further details.

Question 5 Cumulative Funding Table

IACC Strategic Plan Objectives	Funding					
Year	2008	2009	2010	2011	2012	Total
Test four methods to improve dissemination, implementation, and sustainability of evidence-based interventions, services, and supports in diverse community settings by 2013. *IACC Recommended Budget: $7,000,000 over 5 years*	5.4 $125,838 2 projects	5.L.A $5,460,809 10 projects	5.L.A $7,747,912 22 projects	5.L.A $5,840,814 24 projects	5.L.A $7,210,677 32 projects	$26,386,050
	5.L.A. Funding: The recommended budget was met. Significantly more than the recommended minimum budget was allocated to projects specific to this objective. **Progress:** This is a very broad objective, and a lot of research is being supported in this area. More work is needed, however, to cover the range of topics addressed in the objective. **Remaining Gaps, Needs, and Opportunities:** Specifically, the requirement of projects looking at diverse community settings has not been met. Most of the projects listed are not focused on dissemination or may be using a model that is not well-translated to autism. Dissemination should be part of a grant application and this should be rigorously enforced. An opportunity in this area would be to create and support training institutes within existing networks that are focused on implementation and dissemination.					
Test the efficacy and cost-effectiveness of at least four evidence-based services and supports for people with ASD across the spectrum and of all ages living in community settings by 2015. *IACC Recommended Budget: $16,700,000 over 5 years*	5.3 $0 0 projects	5.L.B $103,722 5 projects	5.L.B $0 0 projects	5.L.B $0 0 projects	5.L.B $499,995 1 project	$603,717
	5.L.B. Funding: The recommended budget was not met; the funding allocated to projects specific to this objective falls far short of the recommendation. **Progress:** There are ongoing projects under this objective with regard to efficacy but not cost-effectiveness. More work is needed and in general, the intention of this objective has not been achieved. **Remaining Gaps, Needs, and Opportunities:** Cost-effectiveness evaluations have to be paired with randomized controlled trials (RCTs). Efforts should be made to build onto existing efforts by adding cost-effectiveness evaluation to existing RCTs. Administrative supplements may help to achieve those additions. There are not well established autism-specific measures of cost-effectiveness. Some barriers to achieving this objective include the need for a long follow up period, which often is not possible due to the cost of running longer term trials. Also, these projects often do not receive favorable scores during grant review because review favors tightly controlled experimental designs rather than experimentation in real-world conditions.					

Table 5: Question 5 Cumulative Funding Table, see appendix for a color-coding key and further details.

Question 5 Cumulative Funding Table

IACC Strategic Plan Objectives	Funding					
Year	2008	2009	2010	2011	2012	Total
Evaluate new and existing pre-service and in-service training to increase skill levels in service providers, including direct support workers, parents and legal guardians, education staff, and public service workers, to benefit the spectrum of people with ASD and to promote interdisciplinary practice by 2015. *IACC Recommended Budget: $8,000,000 over 5 years*	N/A	**5.L.C** $132,494 6 projects	**5.L.C** $36,433,257 83 projects	**5.L.C** $6,048,734 30 projects	**5.L.C** $3,724,262 29 projects	**$46,338,747**
	5.L.C. Funding: The recommended budget was met. Significantly more than the recommended minimum budget was allocated to projects specific to this objective. **Progress:** Many projects have been funded in this area. However, there is an ongoing need for support of efforts in this area. **Remaining Gaps, Needs, and Opportunities:** Significant workforce needs remain, especially with regard to paraprofessionals. With all studies in this objective, there remains an issue of scale. Most training programs are designed for small groups. In order for training to be effective at the community level, it has to be able to scale up for broad dissemination, so training programs need to be evaluated for their potential to be scaled up. Comparative effectiveness studies of training models are needed to illuminate whether or not providers need more training, which populations require which training methods, and which training methods are most effective.					
Evaluate at least two strategies or programs to increase the health and safety of people with ASD that simultaneously consider principles of self-determination and personal autonomy by 2015. *IACC Recommended Budget: $2,000,000 over 2 years*	N/A	N/A	**5.L.D** $296,840 5 projects	**5.L.D** $279,999 4 projects	**5.L.D** $54,999 3 projects	**$631,838**
	5.L.D. Funding: The recommended budget was small yet was partially met. **Progress:** Though more than the two studies recommended as a minimum have been funded in this area, more work is needed. This objective overlaps significantly with 5.S.D and also with 4.S.H. In the future, perhaps these objectives should be collapsed and combined. **Remaining Gaps, Needs, and Opportunities:** Obesity is an important issue related to this objective that is currently not represented to a great extent in the portfolio. It is therefore an area where, moving forward, there should be more focus.					

Table 5: Question 5 Cumulative Funding Table, see appendix for a color-coding key and further details.

Question 5 Cumulative Funding Table

IACC Strategic Plan Objectives	Funding					
Year	2008	2009	2010	2011	2012	Total
Support three studies of dental health issues for people with ASD by 2015. This should include: · One study on the cost-benefit of providing comprehensive dental services, including routine, non-emergency medical and surgical dental services, denture coverage, and sedation dentistry to adults with ASD as compared to emergency and/or no treatment. · One study focusing on the provision of accessible, person-centered, equitable, effective, safe, and efficient dental services to people with ASD. · One study evaluating pre-service and in-service training program to increase skill levels in oral health professionals to benefit people with ASD and promote interdisciplinary practice. *IACC Recommended Budget: $900,000 over 3 years for each sub-objective ($2,700,000 total)*	N/A	N/A	**5.L.E** $196,457 2 projects	**5.L.E** $443,860 3 projects	**5.L.E** $307,784 2 projects	**$948,101**
	5.L.E. Funding: The recommended budget was partially met. **Progress:** While several important projects have been funded in this area, there is a gap in projects that focus on dental services for adults and training for dentists working with autistic adults. **Remaining Gaps, Needs, and Opportunities:** While the funded studies focus on behavior management, a more comprehensive health focus is needed to address the dental needs of children and adults with ASD. This objective is very specific, but there are other important primary health care needs for people with ASD that need to be addressed. In the future, perhaps this topic could be collapsed under a broader general objective that addresses primary health care needs (combined with 5.S.D, 5.L.D). If a new objective were to be written, other important primary care issues such as mental health services should be included.					
Not specific to any objective (Core/Other Activities	**5. Core/ Other Activities** $1,247,714 5 projects	**5. Core/ Other Activities** $2,004,687 8 projects	**5. Core/ Other Activities** $13,436,737 66 projects	**5. Core/ Other Activities** $11,553,704 63 projectss	**5. Core/ Other Activities** $9,060,297 62 projects	$37,303,139
Total funding for Question 5†	**$1,685,222** 13 projects	**$8,648,050** 36 projects	**$64,849,122** 211 projects	**$26,118,904** 137 projects	**$22,827,101** 138 projects	**$123,816,730**

Table 5: Question 5 Cumulative Funding Table, see appendix for a color-coding key and further details.

**This total reflects all funding for projects aligned to current objectives in the 2011 IACC Strategic Plan and incorporates funding for projects that may have been coded differently in previous versions of the Plan.*

† The totals reflect the funding and projects coded to this Question of the Strategic Plan in the particular year indicated at the top of the column. When reading each column vertically, please note that the projects and funding associated with each objective for the years 2008, 2009, and 2010 may not add up to the total at the bottom of the column; this is due to revisions of the Strategic Plan that caused some objectives to be shifted to other Questions under the Plan. The projects and funding associated with these reclassified objectives are now reflected under the Question in which they appear in the 2011 Strategic Plan.

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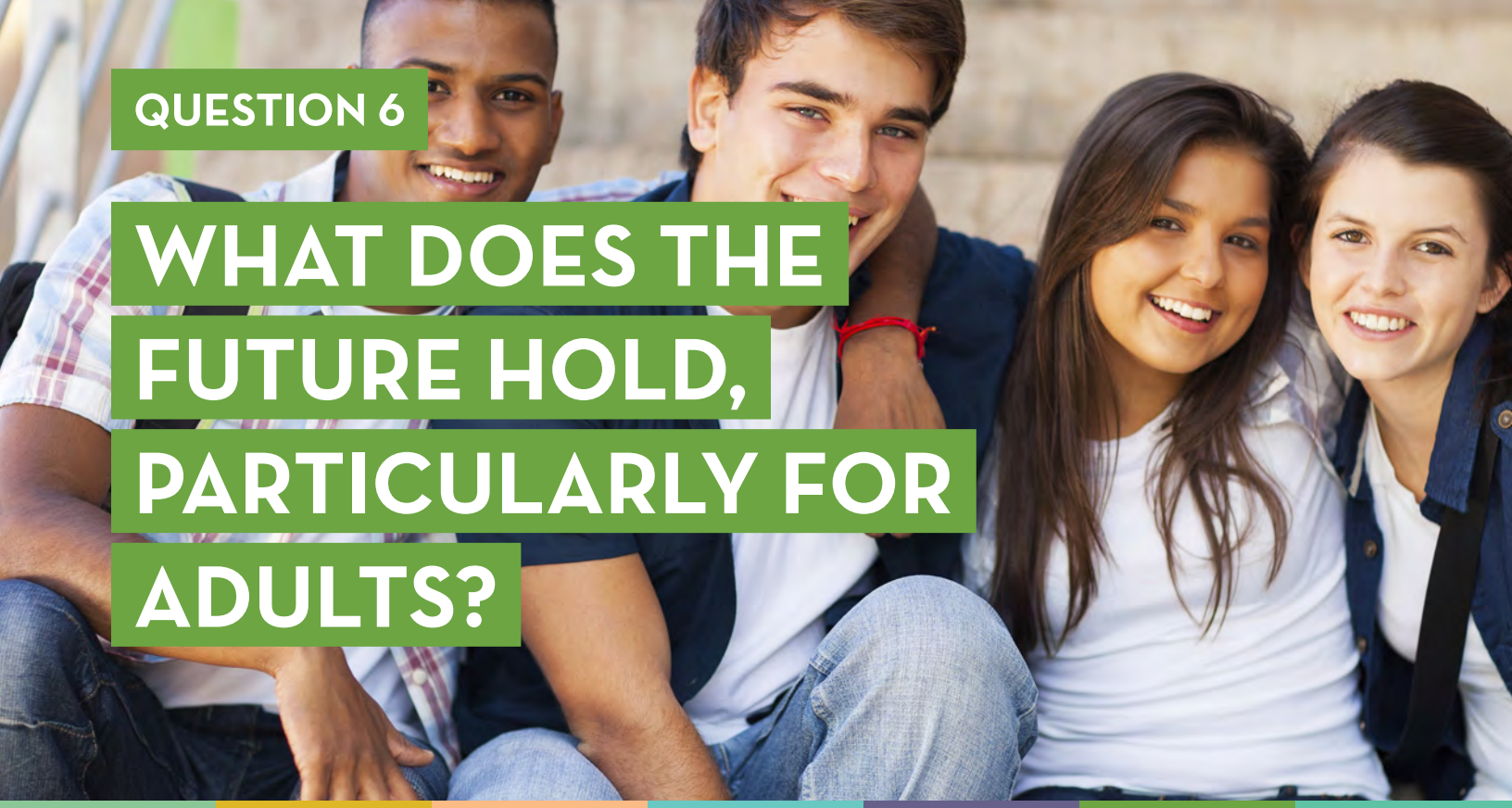

QUESTION 6

WHAT DOES THE FUTURE HOLD, PARTICULARLY FOR ADULTS?

INTRODUCTION

Aspirational Goal: All people with ASD will have the opportunity to lead self-determined lives in the community of their choice through school, work, community participation, meaningful relationships, and access to necessary and individualized services and supports.

Positive, early childhood experiences can help increase the likelihood of better outcomes in adulthood. However, gains that were hard-won in childhood are at risk of losing traction during the period of new challenges associated with the transition to adulthood. The nature and availability of supportive services change dramatically as youth age out of eligibility for special education.[1,2] Families and adults on the autism spectrum need to navigate an entirely new terrain of services. The social-ecological context of development, which encompasses how individuals interact with the communities and systems around them, also changes radically upon leaving secondary school.

Adulthood brings new challenges related to the attainment and performance of social roles, shifts in family roles and relationships as parents age, and coping with the accumulation of a lifetime of financial and psychological stressors. Co-occurring mental health conditions also present an area of great challenge for many adults on the autism spectrum.[3,4] For some, adulthood may also introduce new abilities, declining impairment severity, discovery of new ways to participate and contribute in communities, and new opportunities for achieving health and well-being. For others, particularly those with significant intellectual impairment, severe behavioral and communication

challenges persist into adulthood, often with additional complications such as epilepsy.[5] As in other stages of life, there must be a wide variety of approaches available to adults to reflect the broad diversity of challenges found in home and community contexts and to support improved outcomes for people across the entire autism spectrum.

The *2009 IACC Strategic Plan* emphasized the need for research on individual-level interventions to improve outcomes for adults with ASD. This remains an important area for research, and some progress has been made. However, there have been important changes in thinking over the past few years about how best to support the success of adults on the autism spectrum. There have been calls for research performed in real-world settings that focuses on outcomes related to quality of life, and interventions that target the social environment and not just the individual. There also has been a growing recognition of the need for researchers to build the evidence base through partnerships with community agencies and businesses that are developing promising innovations rather than in academic research settings.

PROGRESS TOWARD THE STRATEGIC PLAN OBJECTIVES

The *2009 IACC Strategic Plan*, including revisions in 2010 and 2011, called for eight objectives within Question 6 that the Committee viewed as gap areas. Under this question there are four short-term objectives and four long-term objectives that highlight the need for research about transitioning youth, adult diagnosis, and adult interventions. The total recommended budget was $54 million across all eight objectives for this question.

Of the eight objectives under Question 6, three objectives address the impact on quality of life for adults utilizing various services, including aspects of the service delivery system such as educational and health services , specialized training for direct care providers, and interventions and services received during childhood. The recommended number of projects was fulfilled for these objectives and the recommended budgets were partially met. Two objectives regarding the evaluation of existing disability programs for their effectiveness in meeting the needs of transitioning youth and adults and the development of community-based interventions partially met the recommended budget levels and had active projects underway to accomplish the objective. Another two objectives, with projects to develop methods to identify adults and link them to services, and to conduct implementation research of services for adults, were far below the recommended budget and number of projects. Finally, one objective to conduct comparative effectiveness research to examine community-based interventions, services, and supports for adults has had only 2 projects in the past 5 years, and in the most recent 2 years did not have any funding or projects. The Committee raised the question of whether there are yet enough empirically solid adult interventions to make it possible to conduct comparative effectiveness studies.

The Committee noted that an overarching issue in the current organization of the *IACC Strategic Plan* objectives was that grouping of several distinct topics into each objective made it challenging to assess progress, and that future iterations might potentially benefit from further division into discrete topics such as community housing, life transitions, employment, and services/supports for older adults.

There have been several notable advances in research in this area over the past 5 years. A number of studies have begun describing young adult outcomes,[6] service needs and access,[7] and service program models.[2] Systematic reviews have

examined extant research on services and interventions.[8] Examples of community-based participatory research have also emerged, such as adaptation of surveys to allow for more active participation of adults with ASD in reporting on health care experiences.[9] In one such survey, when compared with the general population, adults with ASD reported several concerns such as lower satisfaction with patient-provider communication and higher odds of unmet physical and mental healthcare needs, providing useful information about specific parts of the healthcare experience that can be improved.[9]

Despite these advances, the rate of production of scientific knowledge about the experience of autism in adulthood remains very low. The generalizability of findings from many of these studies is limited by small sample sizes, lack of information about the socioeconomic and ethnic-racial characteristics of study subjects, and issues with research design and methodology.[8,10,11] The quality of studies conducted through 2011 regarding vocational programming,[12] pharmacology,[13] social skills interventions,[10] and psychosocial interventions,[14] remains in an emergent state.

The growing number of adults with autism due to increased awareness and diagnosis, as well as the transition of children and adolescents into adulthood has reinforced the sense of urgency around research that can guide national policy recommendations for supports and models of employment, community living, and continued education. Much growth in ASD program innovations is occurring outside of the traditional academic realm,[15] and this body of practice-based knowledge should be incorporated along with more traditional research efforts as an important driver of future investigations.

PROGRESS TOWARD THE ASPIRATIONAL GOAL

Longitudinal data on life course pathways and outcomes, evaluation of service innovations in partnership with community agencies, understanding the positive contributions people on the autism spectrum can make to society, financial impacts on families, and improved ability to measure outcomes at the population level are all areas of research where work is required to continue progress toward the aspirational goal. The majority of a typical lifespan is spent in adulthood. However, this is the stage of life that is still the least understood in ASD. In recent years, awareness of the needs of adults on the autism spectrum has increased to some extent, and more data on services gaps and outcomes have become available. For example, results of a recent meta-analysis suggest that adults with ASD experience a lower quality of life than adults without ASD, and that this trend extends into older adulthood.[16]

Given the relatively limited existing data, more research focus should be directed toward understanding how ASD unfolds across the lifespan by conducting longitudinal studies that extend into adulthood. Longitudinal studies have paid dividends in basic science knowledge for other developmental disorders like Fragile X syndrome and Down syndrome and have the potential to yield similar benefits for autism. In addition, more detailed studies of the needs of adults on the spectrum are required to better understand the nature of these needs and to determine which services will best support individuals across the lifespan with the greatest return on investment for society.

Several seminal studies have been published that provide basic epidemiological description of the prevalence and

correlates of various outcomes of the transition into early adulthood, along with risks and protective factors. Through these, we are learning more about the high prevalence of co-occurring health and psychiatric disabilities in adults,[4,17] and the need for physicians with specialized training to provide care for adults with ASD.[7] Analysis of state developmental disability services data found the rate of self-injurious and destructive behaviors was twice as high in middle-aged adults with ASD and intellectual impairment compared to those with only intellectual disability, signaling the urgency of treatment and policy to address severe behavioral problems.[18] A follow-up to a 1980s statewide autism prevalence study in Utah to investigate mortality among individuals with ASD found that elevated mortality risk associated with ASD appeared to be related to the presence of co-occurring medical conditions and intellectual disability rather than ASD itself, suggesting the importance of access throughout life to coordinated medical care for this high risk sub-population.[19]

Cohort studies have revealed a high rate of complete disconnection of young adults from any work or education during the first several years after high school – greater than 50 percent during the first 2 years after exiting high school.[20] The rate of disconnection was higher compared to youth with other disabilities even after adjusting for correlates. The latest research data indicate that outcomes are particularly poor for young adults from socially disadvantaged families and for those who have greater levels of impairment.[20–22]

Employment has been a particular area of research focus. One recent study found that for adults with ASD, the rate of ever having a paid job in the first 8 years after high school is about 50 percent - much lower than among youth with other types of disability.[22,23] In addition, the types of jobs were limited in range, and average rate of pay was not adequate to support independent living.[22,23] The study also found that even among people with ASD who had severely impaired conversational abilities, approximately one-fifth did become employed, highlighting the potential for employment even among those with high levels of impairment.[22] In another study, researchers found that adults with ASD who engaged in work had greater vocational independence and were more likely to have fewer maladaptive behaviors and improved activities-of-daily-living skills 5 years later.[23,24] Research findings also suggest that vocational outcomes are better for individuals who do not work in sheltered workshop settings prior to participating in supported employment.[25] Recent work toward development of vocational indexes that can facilitate standardized measurement of a full range of vocational and educational outcomes will enhance researchers' ability to study trajectories of development during adulthood and measure the impact of interventions and services aimed at promoting independence.[26]

Over the past 5 years, more knowledge has been gained about the social and mental health issues faced by adults on the autism spectrum. Research suggests that the experience of social isolation is more pronounced in young adults with ASD than those with other types of disabilities.[27,28] Increased levels of loneliness appear to have a negative effect on mental well-being.[29] With regard to residential status, research has found that young adults on the autism spectrum are more likely to have lived at home, to never have lived elsewhere on their own, and to have required more supervision compared to adults with other disability types.[21]

In the arenas of intervention and services research, which are more thoroughly addressed in Questions 4 and 5 of the *2013 IACC Strategic Plan Update*, much research has focused on psychosocial interventions with noted improvement with use of methods like applied behavior analysis and social cognition training.[14,30] Development and adaptation of social skills interventions for people with severe intellectual disability is a continuing need.[10]

WHAT GAPS HAVE EMERGED IN THE PAST TWO YEARS?

Several gaps—and opportunities—have become clear in the past two years. Using the World Health Organization (WHO)'s biopsychosocial framework for understanding disability, several areas for further ASD adults services research efforts can be defined.[31] Overall, currently there is a limited knowledge base regarding the needs of adults on the autism spectrum as they relate to severity of impairment at all levels. The Committee noted particular urgency for increasing research directed at understanding and meeting the needs of those on the more severely-affected end of the autism spectrum, and for the development of services approaches and service delivery models that will improve quality of life for adults with severe disability. These include approaches to address issues of employment, housing, health, social life, recreation and other issues that influence how a person with ASD integrates into adult society.

Research gaps within the medical/health arena (the "biological" level of analysis in the WHO framework) include the limited understanding of the course of co-occurring health conditions through adulthood, limited research on the course of neurological development in later stages of life, and limited studies of the long-term outcomes associated with use of various types of interventions. Programs of research addressing questions about the maturation and aging process in disability conditions such as Fragile X syndrome and Down syndrome may represent opportunities for asking similar scientific questions about the process of aging in ASD.

Gaps in the mental and behavioral health arenas (the "psychological and behavioral" level of analysis in the WHO framework) include continued difficulty describing the heterogeneity of the autism spectrum in ways that are informative for treatment planning and policy making. Developing strategies for intervening in complex cases with both severe developmental and mental health challenges remains an area where the knowledge base needs to be expanded. With increasing awareness of co-occurring conditions that affect people with ASD and recent data suggesting that co-occurring conditions such as epilepsy can be a cause of elevated mortality, it is important to understand the pattern of emergence of these conditions in order to anticipate and work toward prevention of the secondary effects of these added challenges. There is a strong need for more studies that characterize the heterogeneity of development and outcomes in ASD in middle and later stages of adulthood.

There also continue to be major gaps in knowledge at the "social and population health" levels of analysis. There is limited knowledge of the ways in which people on the autism spectrum contribute to communities and society. Strategies being examined in health and mental health services research, such as peer mentoring and navigation, may represent opportunities for adaptation. A growing autism self-advocacy movement increases opportunities for collaborative research partnerships. With respect to adults who remain dependent on their families for care, very little is known about the needs of these individuals and what approaches will provide the greatest help to families planning for the transition when parents are no longer able to care for their dependent adult child.

Identification and surveillance of autism in adults, and development of screening and diagnostic tools for use in adult populations also remain important needs. There is an ongoing study to adapt the Autism Diagnostic Observation

Schedule (ADOS) modules 1 and 2 for use in adults, but multiple projects testing different approaches would be optimal. It is important for the tools that are being developed to be efficient so they can be readily employed in large, community based settings. There is also a need for screening and diagnostic tools to be adaptable to different settings and cultural contexts, including international settings. For example, a study conducted in 2012 illuminated the need for adaptation of diagnostic tools for Latino populations.[32] Along with the development of screening and diagnostic tools, attention needs to be focused on ensuring that there is an available network of services for those who receive a diagnosis and that diagnosis does not inadvertently result in a loss of services and supports.

Outcome measures are needed for quality of life in adults with ASD. It is important to understand what outcomes are meaningful to adults with ASD and their families. Person-centered outcomes strategies and measures should be developed. Achieving validity and reliability of such measures across the lifespan and full range of the autism spectrum remains a significant challenge.

ASD affects multiple domains and many adults are simultaneously involved in different types of services and interventions. Research is needed to better understand the challenges entailed in navigating the service system and how family finances are impacted over the lifespan. Most research remains focused on one intervention at a time, not taking into account the complexity of systems of care in real-world settings. There is little understanding of how nonprofit and government service providers and systems are adapting to the growing number of adults on the spectrum. Advances in conceptualizing and measuring social return on investment and patient preferences could be adapted to build a stronger basis upon which to study the population-level benefits of societal investment in adult services.

As mentioned in the preceding chapter on Question 5, NIH has recently launched a series of three initiatives to support research on services implementation across the lifespan, with the goals of addressing the challenges of improving outcomes for people with ASD across the lifespan. Of relevance to Question 6, one of the initiatives focuses on models to assist adolescents with ASD to transition to adult supports and services while preventing lapses in supports and services, enhancing functioning across settings, and maintaining or improving ASD symptoms, general health, safety, and quality of life.[33] Another addresses development of adult ASD service strategies that concern areas of employment and training, social relationships, physical and mental health, and independent functioning including community housing and safety, alone or in combination, with the ultimate goal of improving behavioral, functional and health outcomes.[34] Awards are expected in 2014.

Some exciting developments in other sectors and fields may hold promise for adaptation and examination in the context of ASD research. Much growth in ASD program innovation is occurring outside of the traditional academic realm, highlighting a need for more community-based research and research on promising practices that can be replicated and adapted in various settings. There is growing interest in social networks and health outcomes, especially because of the concerns of many parents about what will happen to their child after they are gone. Significant advances have been made in other fields in investigating complex systems, social networks, and factors related to successful knowledge translation and program implementation. Much could be gained by fostering transdisciplinary research to leverage these and other advances being made in other fields. The field of continuous quality improvement is receiving a lot of attention in health services research; the corresponding potential for building practice-based evidence remains largely untapped in ASD, providing an opportunity for future studies.

A number of states have created dedicated autism agencies or bureaus and state-level ASD advisory commissions. There is a growing interest among these stakeholders in improving systems for collecting data about services and outcomes. Combined with technological advances in data aggregation and mining, there is an opportunity to pilot test methods for obtaining these data using community-, state-, and national level population indicators of unmet needs, services access, and outcomes.

SUMMARY AND RECOMMENDATIONS

Since the release of the *IACC Strategic Plan* in 2009, the adult services research field has made some important advances, including gathering of new data on the services available across the states, information about how adults are interacting with the service system, and data on the service needs of adults on the autism spectrum. Data have shown tremendous gaps in the service system that need to be addressed by innovative services approaches that are cost-effective and can be adapted to use in a broad variety of settings. While recent systematic reviews about adult interventions and services have noted the need to increase the evidence base to support access to services,[14] the research field is beginning to yield promising randomized controlled trial results[35] that have already influenced service provision in many states and service providers and businesses have been rolling out innovative promising practices. Moving forward, partnerships between academic researchers and state, local and private service providers will play an important role in building a body of practice-based evidence that can support effective service provision strategies. This work may also be helpful in filling the gap in effective methods for measuring population level outcomes that can indicate whether efforts implemented at agency and community levels are translating to improvements in the well-being of the population. While adult services remain a major frontier in autism research, increased investment in this area holds great potential to strengthen the service system with approaches and practices grounded in a strong evidence base, with the ultimate goal of providing all people with ASD with access to the services and supports they need to maximize their health, fully participate in community life, and live self-determined lives.

Question 6 Cumulative Funding Table

IACC Strategic Plan Objectives	Funding					
Year	2008	2009	2010	2011	2012	Total
Launch at least two studies to assess and characterize variation in the quality of life for adults on the ASD spectrum as it relates to characteristics of the service delivery system (e.g., safety, integrated employment, post-secondary educational opportunities, community inclusion, self-determination, relationships, and access to health services and community-based services) and determine best practices by 2012. *IACC Recommended Budget: $5,000,000 over 3 years*	6.2 $0 0 projects	6.S.A $20,000 1 project	6.S.A $283,837 2 projects	6.S.A $542,193 6 projects	6.S.A $1,013,156 10 projects	$1,859,186
	6.S.A. Funding: The recommended budget was partially met. **Progress:** More than (the recommended minimum of) two projects have been funded in this area, though the end goal of determining best practices has not yet been met. Still, this area is moving in the right direction as funding and projects have increased over time. **Remaining Gaps, Needs, and Opportunities:** There is a great need to develop standardized measures for quality of life for people with ASD, across both range of ability and lifespan.					
Evaluate at least one model, at the State and local level, in which existing programs to assist people with disabilities (e.g., Social Security Administration, Rehabilitation Services Administration) meet the needs of transitioning youth and adults with ASD by 2013. *IACC Recommended Budget: $5,000,000 over 3 years*	N/A	6.S.B $0 0 projects	6.S.B $700,000 2 projects	6.S.B $700,000 2 projects	6.S.B $700,000 2 projects	$2,100,000
	6.S.B. Funding: The recommended budget was partially met. **Progress:** More than (the recommended minimum of) one project was funded, meeting the initial target of this objective. **Remaining Gaps, Needs, and Opportunities:** Current projects relate to vocational rehabilitation, as called for in the objective, but no projects address Social Security programs, which remain a need. Also, looking at one model is too limited in scope, and stronger partnerships among programs would be beneficial for this objective. In the future, perhaps this objective could be expanded to include more projects and/or funding to examine other models.					
Develop one method to identify adults across the ASD spectrum who may not be diagnosed, or are misdiagnosed, to support service linkage, better understand prevalence, and track outcomes with consideration of ethical issues (insurance, employment, stigma) by 2015. *IACC Recommended Budget: $8,400,000 over 5 years*	N/A	6.S.C $0 0 projects	6.S.C $28,000 1 project	6.S.C $28,000 1 project	6.S.C $0 1 project	$56,000
	6.S.C. Funding: The recommended budget was not met; the funding allocated to projects specific to this objective falls far short of the recommendation. **Progress:** The objective called for a minimum of one project, and one small project to adapt the ADOS modules 1 and 2 for use in adults has been supported in this area, but most likely multiple projects testing various approaches, followed by intense efforts to refine the instruments, would be needed to develop a set of tools that could be used in different settings to diagnose adults. **Remaining Gaps, Needs, and Opportunities:** In addition to developing tools that can be used for diagnosis in adults, it is critical to ensure that diagnosis links to a plan for intervention and /or service provision for diagnosed adults, resulting in improved outcomes.					

Table 6: Question 6 Cumulative Funding Table, see appendix for a color-coding key and further details.

Question 6 Cumulative Funding Table

IACC Strategic Plan Objectives	Funding					
Year	2008	2009	2010	2011	2012	Total
Conduct at least one study to measure and improve the quality of lifelong supports being delivered in community settings to adults across the spectrum with ASD through provision of specialized training for direct care staff, parents, and legal guardians, including assessment and development of ASD-specific training, if necessary, by 2015. *IACC Recommended Budget: $4,500,000 over 3 years*	N/A	6.S.D $0 0 projects	6.S.D $619,163 3 projects	6.S.D $0 2 projects	6.S.D $0 1 project	$619,163
	6.S.D. Funding: The recommended budget was not met; the funding allocated to projects specific to this objective falls far short of the recommendation. **Progress:** While more than one project has been funded, and the objective called for one project at minimum, the current funding and projects for this objective are not likely to meet the intent of the objective. Also, the few projects funded do not address the full range of issues mentioned in this objective. **Remaining Gaps, Needs, and Opportunities:** The projects under this objective focus on secondary students and transition age youth and there are no projects focusing on older adults. No new projects were funded in 2011 and 2012, though the goals of this objective are similar/overlapping to those of 5.L.C, and projects coded there may also represent progress on this objective. There is a need for effective training for healthcare staff and guardians that can be delivered cost-effectively on a large scale.					
Develop at least two individualized community-based interventions that improve quality-of-life or health outcomes for the spectrum of adults with ASD by 2015. *IACC Recommended Budget: $12,900,000 over 5 years*	6.5 $2,471,000 1 project	6.L.A $509,965 2 projects	6.L.A $2,285,071 18 projects	6.L.A $2,154,170 15 projects	6.L.A $616,119 11 projects	$8,036,325
	6.L.A. Funding: The recommended budget was partially met. **Progress:** Between 11 and 18 projects were supported each year between 2010 and 2012. Progress is being made; however, a sustained effort is needed to fully achieve the goals set forth by this objective. Funding for projects specific to this objective was substantially lower in 2012 than previous years, which is a concern. **Remaining Gaps, Needs, and Opportunities:** Work focused on adults with ASD lags behind that focused on children and adolescents. This objective is similar to 6.S.A – it might be helpful to separate the outcomes of interest to better assess progress. Also, quality of life outcome measures are needed to know if interventions are working.					
Conduct one study that builds on carefully characterized cohorts of children and youth with ASD to determine how interventions, services, and supports delivered during childhood impact adult health and quality of life outcomes by 2015. *IACC Recommended Budget: $5,000,000 over 5 years*	N/A	6.L.B $718,290 2 projects	6.L.B $1,280,790 3 projects	6.L.B $1,348,557 4 projects	6.L.B $639,346 2 projects	3,986,983
	6.L.B. Funding: The recommended budget was partially met. **Progress:** More than the minimum of one recommended project was funded. However, the projects have not answered all of the questions regarding long-term outcomes of interventions, services and supports received during childhood and more research is needed in this area. **Remaining Gaps, Needs, and Opportunities:** More than one study would be useful for this objective, including a focus on the benefits of early intervention. The barrier of the high cost of conducting these types of studies could be mitigated by capitalizing on partnerships between groups and on existing infrastructure.					

Table 6: Question 6 Cumulative Funding Table, see appendix for a color-coding key and further details.

Question 6 Cumulative Funding Table

IACC Strategic Plan Objectives	Funding					
Year	**2008**	**2009**	**2010**	**2011**	**2012**	**Total**
Conduct comparative effectiveness research that includes a cost-effectiveness component to examine community-based interventions, services, and supports to improve health outcomes and quality of life for adults on the ASD spectrum over age 21 by 2018. Topics should include: · Community housing for people with ASD; · Successful life transitions for people with ASD, including from post-secondary education to adult services, employment, sibling relationships, and day programs; and · Meeting the service and support needs of older adults with ASD. *IACC Recommended Budget: $8,000,000 over 5 years*	N/A	**6.L.C** $0 0 projects	**6.L.C** $774,644 2 projects	**6.L.C** $0 0 projects	**6.L.C** $0 0 projects	**$774,644**
	6.L.C. Funding: The recommended budget was not met; the funding allocated to projects specific to this objective falls far short of the recommendation. **Progress:** Not nearly enough funding and projects have been devoted to this objective much more work needs to be done. **Remaining Gaps, Needs, and Opportunities:** Projects regarding service and support needs of older adults are needed; however, there is a question about whether there are yet enough empirically sound adult interventions to make it possible to do comparative effectiveness studies. It could be useful to separate out specific populations, topics (housing, transitions, etc.) or outcomes in order to better assess progress. A characterization of current resources and how well they're working is needed for this objective, which is the goal of the newly released report from The State of the States project. The current focus of the field on the transition to adulthood should be expanded to include the full lifespan.					
Conduct implementation research to test the results from comparative effectiveness research in real-world settings, including a cost-effectiveness component to improve health outcomes and quality of life for adults over 21 on the ASD spectrum by 2023. *IACC Recommended Budget: $4,000,000 over 5 years*	N/A	**6.L.D** $0 0 projects	**6.L.D** $0 0 projects	**6.L.D** $75,000 2 projects	**6.L.D** $60,000 3 projects	**$135,000**
	6.L.D. Funding: The recommended budget was not met; the funding allocated to projects specific to this objective falls far short of the recommendation. **Progress:** There is an inadequate amount of projects and funding for this objective. The funded studies are economic analyses, but there is a lack of comparative effectiveness research in adults that is ready to be tested in real-world settings, and thus, there are no projects that move to this next level. **Remaining Gaps, Needs, and Opportunities:** There is a huge gap in adult prevalence research, and in identifying relevant real-world settings for adults with ASD. Identifying the needs of adults with ASD remains important (a needs assessment is needed), and research involving ASD subjects beyond the age of 18 is both lacking and vital.					
Not specific to any objective (Core/Other Activities)	**6. Core/ Other Activities** $467,683 2 projects	**6. Core/ Other Activities** $159,444 2 projects	**6. Core/ Other Activities** $671,619 3 projects	**6. Core/ Other Activities** $50,000 3 projects	**6. Core/ Other Activities** $830,556 4 projects	**$2,179,302**
Total funding for Question 6†	**$9,796,491** 9 projects	**$1,407,699** 7 projects	**$6,643,124** 34 projects	**$4,897,920** 35 projects	**$3,859,177** 34 projects	**$19,746,603***

Table 6: Question 6 Cumulative Funding Table, see appendix for a color-coding key and further details.

**This total reflects all funding for projects aligned to current objectives in the 2011 IACC Strategic Plan and incorporates funding for projects that may have been coded differently in previous versions of the Plan.*

†The totals reflect the funding and projects coded to this Question of the Strategic Plan in the particular year indicated at the top of the column. When reading each column vertically, please note that the projects and funding associated with each objective for the years 2008, 2009, and 2010 may not add up to the total at the bottom of the column; this is due to revisions of the Strategic Plan that caused some objectives to be shifted to other Questions under the Plan. The projects and funding associated with these reclassified objectives are now reflected under the Question in which they appear in the 2011 Strategic Plan.

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QUESTION 7

WHAT OTHER INFRASTRUCTURE AND SURVEILLANCE NEEDS MUST BE MET?

INTRODUCTION

Aspirational Goal: Develop and support infrastructure and surveillance systems that advance the speed, efficacy, and dissemination of ASD research.

The original *IACC Strategic Plan*, launched in 2009, was structured around only six Questions. In 2010, the IACC recognized that grouping the topics of research infrastructure, workforce, and ASD surveillance into a separate chapter would highlight these issues that are critically important to research success and help the committee track investments and evaluate progress in this area in the same organized, rigorous manner that is used in the rest of the *IACC Strategic Plan*. Over the past 5 years, a total of $158 million dollars has been invested in building and maintaining the ASD research infrastructure to support needed research and surveillance efforts. Many of the original infrastructure needs identified in 2009 have been accomplished, but continued investment is critical in order to develop, maintain, and build on these valuable new resources.

PROGRESS TOWARD THE STRATEGIC PLAN OBJECTIVES

The *IACC ASD Research Portfolio Analyses* reviewed projects funded by both government agencies and private foundations from 2008-2012. From 2009-2012, the total funding devoted to projects pertaining to Question 7 was $158 million. On average for each year from 2010-2012, the funding levels for this Question were doubled from the 2009 level ($16 million) and the number of funded projects was also more than twice as high. Additionally, in years 2009-2012, 27 percent of the total funding went toward core/other research projects that were not aligned with the research gaps covered by the 16 objectives in Question 7.

Of the 16 specific objectives within Question 7, 8 objectives addressing basic and clinical data sharing and dissemination, workforce expansion, and model-systems resources met or exceeded the recommended budget and fulfilled the recommended number of projects. Four objectives, concerning documenting the services available in each state, expanding biobanks, and expanding surveillance infrastructure partially met the recommended budget and had a number of projects underway. Four more objectives did not have any funding or projects. Two of these objectives, focused on a needs assessment for database linkage and a funding mechanism for rapid replication of research results, remain a high priority. The objective concerning development of a web tool for prevalence estimates was fulfilled through several projects that encompassed multiple conditions including autism; the intended goal was achieved, although it was done outside the autism portfolio. The intent of the objective to disseminate best practices in service provision through the publication of "Promising Practices" papers was not completed; this goal may have been superseded by other types of best practice dissemination methods (e.g., web pages, tool kits, presentations at conferences), so the objective in its current form was not viewed by the Committee as a high priority to continue.

INFRASTRUCTURE

Over the past 5 years there has been a significant rise in data sharing among researchers, increased availability of biological samples, expanded surveillance efforts, substantial investment in building the ASD research workforce and major improvement in dissemination of research results to the community.

Databases have been developed to house and provide researchers with access to valuable research data collected from those affected by autism as well as neurotypical subjects. In addition, in 2011 the NIH Office of Autism Research Coordination (OARC) developed and launched a new database, the *IACC Portfolio Analysis Web Tool*, that gathers data on federal and non-profit supported ASD research-related projects together into one place, enabling broad public access to detailed information about these projects, as well as searching, sorting and graphics to facilitate further analysis and monitoring of progress over time.

The Interactive Autism Network (IAN), developed by the Kennedy Krieger Institute, is a tool designed to match scientists with research subjects to enhance the pace of research. The IAN network has also greatly facilitated rapid research on issues of symptom severity and intervention. For example, in 2011 when concerns about the impacts of autistic wandering behavior were brought to the IACC's attention through a public presentation at an IACC meeting, members of the IACC and other organizations were able to work with the IAN network within a period of three months to launch and complete a study involving over 1,200 children utilizing the IAN database. Results of the study indicated that almost 50 percent of children with ASD had wandered.[1] In conjunction with this rapid study, a new International Classification of Diseases (ICD-9) code to track autistic wandering in health records was almost immediately implemented and the American Academy of Pediatrics (AAP) issued new guidelines that included wandering in patient-family anticipatory guidance, alerting parents of children with ASD to the prevalence of wandering so that they could take preventive measures.[2]

The National Database for Autism Research (NDAR), funded by the NIH, is a rich resource that includes genomic data and imaging studies as well as other types of data for use in ASD research. NDAR has become the standard data repository for the ASD research community. In January 2010, the NIH began including an expectation for data sharing in most of its awards, requiring that human subject data be deposited in a broadly accessible database. In 2012, 81 percent of NIH-funded human subjects grants were contributing data to NDAR. NDAR also supports data sharing from other funders of autism research including the Autism Science Foundation, the Centers for Disease Control and Prevention (CDC), the Department of Defense (DoD), and the State of New Jersey. NDAR has also now linked to IAN and the Autism Speaks supported Autism Genetic Resource Exchange (AGRE) and Autism Tissue Program (ATP), enabling researchers to access data in those repositories.

To date, NDAR has facilitated the sharing of data on 70,000 research subjects with much more expected in the next 24 months. Also, the rich "omics" (genomics, proteomics, transcriptomics, metabolomics, etc.) and imaging datasets have been de-identified and protected in the computational cloud, enabling an unprecedented array of resources, techniques and computational software to be used collaboratively by the research community. The results of such efforts along with categorization of data into common concepts like IQ, language, and executive function enable users to query and pull down data from across multiple sources and disciplines, maximizing the utility of the data and driving scientific discovery. NDAR data have been cited in publications, and access requests have been substantial. Over 300 researchers at 75 laboratories from 10 countries applied for and were granted access to NDAR in 2013.

Aggregated data in NDAR, among its federated partners and the labs sharing data are available to the general public (see NDAR Query).[3] NDAR now supports harmonized receipt of all human subjects research data, including clinical, imaging, genomics, proteomics, electroencephalogram (EEG), eye tracking, and task- based functional magnetic resonance imaging (fMRI) data. Figure 1 provides a summary of the shared research subjects data now available in NDAR. The NIMH Repository and Genomics Resource (NIMH-RGR) is another key resource that has played an important role in supporting research by providing access to biological samples from more than 150,000 well- characterized, high quality patient and control samples from a wide-range of mental disorders, including autism. The number of samples in the NIMH Genomics Repository has increased to more than 27,000, many with extensive phenotype/genotype information. The NIMH repository has also started collecting induced pluripotent stem cell (iPS) lines and fibroblasts. In terms of DNA, this represents a two-fold increase since 2008.

In addition to genomics and cell line samples, brain tissue is another critically important resource needed to further autism research. Unfortunately, brain tissue samples have actually declined in number during the past 5 years due to a freezer malfunction in 2012 that resulted in the loss of more than half of the existing samples from the largest autism brain repository in the United States. The brains lost have not yet been replaced in terms of numbers, and it may take several years to fully recover. In 2013, only nine new ASD brains were added to existing repositories. Despite these challenges and setbacks, there is a concerted effort both publicly and privately to increase the number of brain tissue samples. In 2013, NIH launched a new NIH Neurobiobank initiative. This repository will collect and standardize brain tissue samples for research on ASD as well as other brain disorders. The initiative includes a publication to increase awareness of brain donation, "Why Brain Donation? A Legacy of Hope." In addition, a group of private funders including the Autism Science Foundation, Autism Speaks, the Nancy Lurie Marks Family Foundation, and the Simons Foundation, recently launched the Autism BrainNet, a multi-site effort to increase the numbers of ASD-specific brain samples. Their efforts will also include an ASD-specific outreach and education plan to encourage tissue donation.

Launch of NDAR Increases Number of Research Subjects Whose Data are Shared

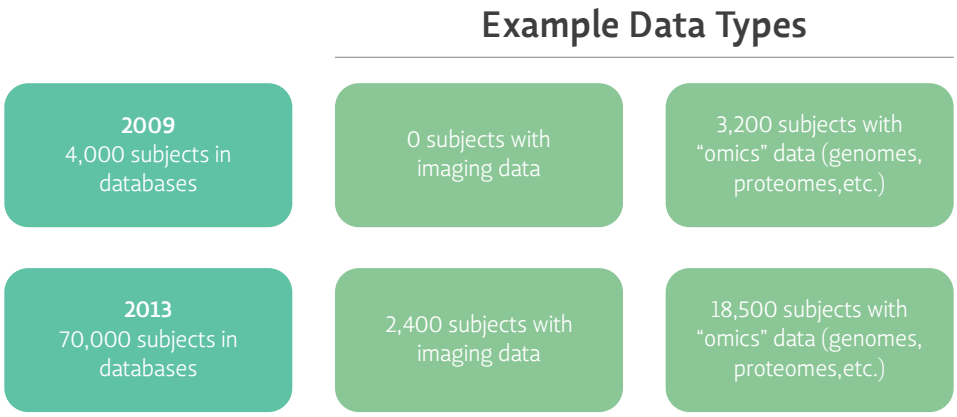

Figure 1. In 2009, essentially all human subjects data being shared within the autism research community were contained in two separate databases—the Autism Speaks AGRE and ATP data repositories—and totaled approximately 4,000 subjects. In 2009, NDAR was collecting data, but its data sharing capabilities were not launched until 2010. Since the launch, NDAR has continued to both collect and make data available to researchers. By 2013, the total number of research participants for whom data were available for study through NDAR had dramatically increased, with data now available for 70,000 subjects. This includes data collected by NDAR as well as the AGRE and ATP datasets, all of which are now available through NDAR. In addition, by 2013 a wide variety of data types was available, with many subjects in the databases having multiple data types available. Examples of the kinds of data shared through NDAR include imaging data, genomes, proteomes, clinical data, and exposures data.

NIMH Repository and Genomics Resource (NIMH-RGR) Sample Summary (2008-2013)

Phenotypic category	# Subjects with DNA/LCL/CPL[1] samples	# Subjects with samples and phenotypic[2] data in distribution[3] (% non-caucasian[4])	# Total affected cases in distribution (independent cases[5])	# Multiplex families (Trios)	# Subjects with fibroblast lines (iPSC[6]) in distribution
Autism (2013)	28,288	15,676 (17%)	6,278 (4,222)	1,553 (3,387)	21 (25)
Autism (2012)	27,240	14,628 (17%)	5,938 (3,906)	1,530 (3,179)	0 (0)
Autism (2011)	25,890	9,822 (24%)	4,252 (2,479)	1,431 (1,860)	0 (0)
Autism (2010)	23,421	8,601 (20%)	3,842 (2,128)	1,386 (1,630)	0 (0)
Autism (2009)	19,824	6,434 (19%)	3,001 (1,598)	1,125 (1,209)	0 (0)
Autism (2008)	14,887	6,434 (19%)	3,001 (1,598)	1,125 (1,209)	0 (0)

Table 7. Summary of sample number and type for Autism specific samples included in the NIMH Genomics Repository. [1] LCL, Lymphoblastoid Cell Line; CPL, Cryopreserved Lymphoblasts [2] Phenotypic data includes clinical interviews, DIGS (Diagnostics Interview for Genetics Studies) & DSM variables. Samples include unaffected family members. [3] Distributions are NIMH sample collections with phenotypic data available for distribution to authorized investigators. [4] Non-Caucasians include Black, Hispanic, American Indian and Asian. [5] Subjects are unrelated. [6] Induced pluripotent stem cell lines produced by NIMH Genomics Repository Stem Cell facility.

SURVEILLANCE

Updated estimates published in 2012 from the CDC's ASD and Developmental Disability Monitoring Network (ADDM) indicate that 1 in 88 children has been identified with ASD, based on an average taken across multiple ADDM network study sites across the United States.[4] The ADDM network, which uses a methodology based on review of health and education records, has been the CDC's primary United States surveillance initiative. It currently includes 12 sites, and data are now available over multiple years, which enables researchers to examine prevalence trends as well as characteristics that are changing in the population and average age at diagnosis. The ADDM infrastructure has laid the foundation to expand surveillance to younger children in six ADDM sites. In addition, ADDM investigators have initiated data linkage and analytic projects to better understand characteristics of the population of children with identified ASD. These include evaluations of perinatal characteristics, parental age, medication use, participation in the juvenile justice system, hazardous air pollutant exposures, phenotypic characteristics, and changes in prevalence over time, among others. The ADDM Network has established a system to provide updated ASD prevalence estimates and has enabled a better understanding of the needs of the community. In addition to ADDM, the National Survey of Children's Health (NSCH), using telephone survey methodology, reported ASD prevalence estimates that were consistent with ADDM estimates.[5] The 2009-2010

National Survey of Children with Special Healthcare Needs infrastructure was used for the 2010 follow-up study, "Survey of Pathways to Diagnosis and Services," to better understand how children with ASD are identified and treated.[6] A workshop was held in 2011 to summarize the state of the science and needs in evaluating trends in ASD prevalence.[7]

There are also many private organizations, and groups outside the United States monitoring prevalence and service data. Autism Speaks has supported a population-based screening effort at an ADDM Network site to evaluate how many children with ASD are potentially being missed by current ascertainment methods. Autism Speaks has also initiated the Global Autism Public Health Initiative (GAPH) to support awareness and epidemiologic studies of ASD in sites around the world. There have also been efforts in the United Kingdom to examine the prevalence of ASD. A study in children using a comprehensive diagnostic assessment method found a prevalence of 1.16 in 100, and a study in adults using a population based survey and diagnostic assessment approach found a similar prevalence of .98 in 100.[8–10] In South Korea, a population based study that used diagnostic assessments found a prevalence of 1 in 38, and that two-thirds of cases of ASD identified were unrecognized and untreated, highlighting a need for improved screening, diagnosis and services.[11]

There is increasing international focus on surveillance of prevalence and services. In 2012, the United Nations (UN) General Assembly unanimously passed a resolution, "Addressing the Socioeconomic Needs of Individuals, Families and Societies Affected by Autism Spectrum Disorders, Developmental Disorders and Associated Disabilities," calling on governments around the world to monitor and report as well as improve access to healthcare, education, training, and intervention programs for persons with ASD and other developmental disabilities.[12] In 2013, the executive board of the World Health Assembly, governing body of the World Health Organization (WHO), adopted a complementary resolution, "Comprehensive and Coordinated Efforts for the Management of Autism Spectrum Disorders."[13] These resolutions indicate growing commitment to address ASD on a global level.

Health disparities are another area of high interest within the field of surveillance. ADDM Network study results initially showed autism prevalence in some minority groups was lower than in in whites, but more recent data have begun to close the gaps with prevalence in minorities and whites becoming more similar, suggesting that the difference is not in actual prevalence but instead may reflect differences in diagnosis (e.g., later diagnosis, missed diagnosis, etc. in minority communities).[4,14–16] More research is needed to better understand the role of cultural issues, access to services and other issues in this phenomenon.

ASD is also being studied in immigrant populations to learn more about ASD in diverse populations. In 2013, results from a study of ASD prevalence among diverse populations of children in Minneapolis, Minnesota, collaboratively supported by CDC, NIH, Autism Speaks, and the Association of University Centers on Disabilities (AUCD), showed that while Somali children had a similar prevalence of autism to white children and a higher prevalence than in non-Somali black children or Hispanic children, that the prevalence of intellectual disability among children with ASD was much higher in Somalis.[17] Additional studies will be needed to understand the reasons for these differences. A study by Swedish researchers investigated the relationship between parental immigration status and risk of ASD, taking into consideration the importance of region of origin, timing of immigration and autism subtypes.[18] They found that children of immigrant parents were at increased risk of ASD with intellectual disability, especially when parents immigrated from countries with a low human development index. That risk was also higher when immigration occurred around pregnancy, but elucidation of the reasons for these differences will require further research.

Despite efforts to track the age of diagnosis and increased capability to diagnose ASD earlier, the average age of diagnosis in the United States has remained relatively constant. The proportion of children being diagnosed earlier has improved, however, with ADDM data indicating that the proportion of children diagnosed by age 3 increased from 12 percent in 2002 to 18 percent in 2008.[4] In addition, due to changes in diagnostic criteria and greater community awareness, more cases are being identified when they were initially missed. As the prevalence of ASD has increased, a greater number of children have been identified with ASD — specifically those with ASD without intellectual disability and, as mentioned earlier, among racial and ethnic minority groups. Children without intellectual disability or with fewer ASD characteristics tend to be identified at later ages. Thus, while more children are being identified, much work needs to be done to identify children with ASD and other developmental delays earlier and more equitably so that all of those in need of services can be connected to appropriate services and supports as early as possible.

The surveillance infrastructure may present opportunities for more in-depth data collection related to services, treatment, and co-occurring conditions to complement data currently collected and identify opportunities for improving diagnosis and treatment of children with ASD. A future challenge to the accuracy of trends in prevalence may result from the implementation of the new *DSM-5* diagnostic criteria for ASD. Because ADDM has collected detailed descriptions of the clinical findings for each child, the system is poised to evaluate how prevalence estimates may be influenced by these updated criteria.

Future efforts must focus on encouraging more families from diverse backgrounds to participate in ASD research, join registries, and donate biological samples. Also, as the ability to collect and link data grows, it is crucial to pay greater attention to issues of privacy, security, and ethical use of data.

PROGRESS TOWARD THE ASPIRATIONAL GOAL

Progress toward the Question 7 aspirational goal to "develop and support infrastructure and surveillance systems that advance the speed, efficacy and dissemination of ASD research" has been rapid over the past 5 years. As demonstrated by the above tables, the numbers of shared subjects and samples have doubled at minimum, and in some cases increased by orders of magnitude. This increase in the availability of resources advances the speed and efficacy of ASD research. The sharing of these resources through initiatives such as NDAR, IAN, and AGRE demonstrate effective dissemination of resources, and fuel the cycle of increased research speed and efficacy. In terms of research infrastructure, the aspirational goal will be met as long as current support is continued and current momentum is maintained.

Surveillance systems have also progressed over the past 5 years, allowing the tracking of prevalence, age of diagnosis, and other trends over time. As awareness of ASD has grown in the community and diagnostic criteria have broadened, more children have been identified with ASD, especially those without intellectual disability and among racial and ethnic minority groups, who tend to be identified at later ages. Thus, while more children are being identified, advances leading to earlier identification for children across all cultural backgrounds and across the entire spectrum and will be critical to ensure that all of those in need of services can receive them as early as possible. With the surveillance infrastructure now

in place, there is an opportunity to use it for more in-depth data collection related to services, treatment, and co-occurring conditions to complement data currently collected and identify opportunities for improving diagnosis and treatment of children with ASD.

The progress toward meeting the goal of dissemination and communication of autism research findings has been significant. Many government and private organizations and groups including Simons Foundation, Autism Speaks, Autism Science Foundation, Interactive Autism Network, NIH and the CDC regularly share lay-audience friendly summaries of recent research findings and new interventions to raise community awareness. Future efforts must focus on encouraging more families from diverse backgrounds to participate in ASD research, join registries, and donate biological samples. Throughout the process of ASD surveillance and infrastructure expansion, it will also be important to maintain focus on ethical issues surrounding the privacy of research participants and security of data. The initial steps toward the aspirational goal to "develop and support infrastructure and surveillance systems that advance the speed, efficacy, and dissemination of ASD research" have begun, but continued investment and broader outreach will be needed to ensure that the benefits of ASD research and access to the highest quality interventions, services, and supports are attainable for all communities across the United States and around the globe.

Question 7 Cumulative Funding Table

IACC Strategic Plan Objectives	Funding					
Year	2008	2009	2010	2011	2012	Total
Conduct a needs assessment to determine how to merge or link administrative and/or surveillance databases that allow for tracking the involvement of people living with ASD in health care, education, and social services by 2009. *IACC Recommended Budget: $520,000 over 1 year*	6.4 $0 0 projects	7.A $0 0 projects	7.A $0 0 projects	7.A $0 0 projects	7.A $0 0 projects	$0
	7.A. Funding: There has been no specific funding for projects addressing this objective. **Progress:** The Planning Group is not aware of any efforts (projects or funding) that have been made to address this objective since it was created. **Remaining Gaps, Needs, and Opportunities:** A needs assessment remains necessary due to issues surrounding patient privacy in linked databases and also to determine how tracking the involvement of people with ASD in health care, education, and social services is possible with existing tools and resources. It remains to be decided whether this should be a government-led effort or a public/private partnership. Such resources could be utilized by both the research and services provision communities.					
Conduct an annual "State of the States" assessment of existing State programs and supports for people and families living with ASD by 2011. *IACC Recommended Budget: $300,000 each year (revised in 2010)*	5.1 $311,670 6 projects	7.B $7,061 1 project	7.B $197,128 1 project	7.B $88,154 1 project	7.B $0 1 project	$604,013
	7.B. Funding: The recommended budget was partially met. **Progress:** Centers for Medicare & Medicaid Services (CMS) conducted a "State of the States" project and released a report summarizing the results of the study in 2014. The book *Autism Services Across America* by Dr. Peter Doehring also reviews existing programs and services across the states. **Remaining Gaps, Needs, and Opportunities:** The initial State of the States study, overseen by CMS, was completed and published in 2014, but the objective calls for an annual study. Since the first study required multiple years to complete and since it is not clear if services will change enough yearly to warrant an annual study, this objective should be revisited with CMS to understand whether an annual study is the best approach.					
Develop and have available to the research community means by which to merge or link databases that allow for tracking the involvement of people in ASD research by 2010. *IACC Recommended Budget: $1,300,000 over 2 years*	6.1 $6,767,808 4 projects	7.C $1,665,180 2 projects	7.C $2,785,368 5 projects	7.C $1,387,146 7 projects	7.C $985,158 6 projects	$13,590,660
	7.C. Funding: The recommended budget was met. Significantly more than the recommended minimum budget was allocated to projects specific to this objective. **Progress:** IAN and Group Health Cooperative Autism Registry are two examples of projects that are responsive to this objective. This objective should be considered to be met, with funding exceeding the recommended budget and a large number of diverse projects addressing this issue. NDAR, IAN and AGRE are all publicly available databases. **Remaining Gaps, Needs, and Opportunities:** To advance this objective we need to encourage patients and families to join the registry. Compared to registry numbers for cystic fibrosis (100%), autism is behind at ~4% of patients enrolled in a registry. A table of the numbers of registrants by year would be an informative figure. We need more organized systems to improve participation.					

Table 8: Question 7 Cumulative Funding Table, see appendix for a color-coding key and further details.

Question 7 Cumulative Funding Table

IACC Strategic Plan Objectives	Funding					
Year	2008	2009	2010	2011	2012	Total
Establish and maintain an international network of biobanks for the collection of brain tissue, fibroblasts for pluripotent stem cells, and other tissue or biological material, by acquisition sites that use standardized protocols for phenotyping, collection, and regulated distribution of limited samples by 2011. · This includes support for post-processing of tissue, such as genotyping, RNA expression profiling, and MRI. · Protocols should be put into place to expand the capacities of ongoing large-scale children's studies to collect and store additional biomaterials, including newborn bloodspots, promoting detection of biological signatures. · Support should also be provided to develop an international web-based digital brain atlas that would provide high-resolution 3-D images and quantitative anatomical data from tissue of patients with ASD and disease controls across the lifespan, which could serve as an online resource for quantitative morphological studies, by 2014. *IACC Recommended Budget: $82,700,000 over 5 years (revised in 2011)*	2.1 & 2.6 $5,018,579 1 project & 1 project	7.D $436,815 2 projects	7.D $7,814,918 6 projects	7.D $8,531,425 6 projects	7.D $2,950,550 5 projects	$24,752,287

7.D. Funding: The recommended budget was partially met. In terms of autism-specific projects, $24.7 million has been spent to date. Including non-autism-specific projects called for in the objective (i.e., the brain atlas), $59.6 million has been spent to date.

Progress: NIH launched a new multi-disorder Neurobiobank initiative in 2013. The $5 million effort encompasses autism and other brain disorders, and is not included in the 2008-2012 projects examined by the committee for this update because it began in 2013. A private effort, the Autism BrainNet, is also underway, with several collection/storage/distribution sites governed by a scientific board which distributes samples based on scientific merit of proposed projects to use the tissue. Though these two efforts represent progress, more work is needed to increase the amount of tissues available and to ensure good stewardship of these resources. The BrainSpan Atlas, supported by the Allen Brain Institute and a consortium of government and private funders, was completed and launched in 2011 and provides a powerful new resource for data on gene expression in the brain during development, but the project is not reflected in the 2008-2012 funding figures because it is not autism specific. In 2009, NIH supported the atlas with $18.4 million dollars and in 2010, NIH provided $16.5 million. The NIMH Repository and Genomics Resource is another resource that has continued to grow to meet the needs of researchers in many fields, including ASD research. Current sample numbers in the repository are: 28,300 DNA samples, with 15,700 samples that have been processed and prepared for distribution and 6,300 cases of autism represented. There are 21 fibroblast lines and 25 induced pluripotent stem cell lines.

Remaining Gaps, Needs, and Opportunities: While progress has been made in establishing, maintaining and expanding tissue resources for research, this is still an area of enormous need. Currently there may be fewer brain samples available for study than there were at the inception of the ***Strategic Plan*** due to the failure of a freezer at a major brain bank in 2012, which resulted in the loss of a large number of ASD brain specimens. There is also still a need for tissue and brains from neurotypical controls. Compared to other disorders, the number of tissue samples available for ASD research is quite low.

Table 8: Question 7 Cumulative Funding Table, see appendix for a color-coding key and further details.

Question 7 Cumulative Funding Table

IACC Strategic Plan Objectives	Funding					
Year	2008	2009	2010	2011	2012	Total
Begin development of a web-based toolbox to assist researchers in effectively and responsibly disseminating their findings to the community, including people with ASD, their families, and health practitioners by 2011. *IACC Recommended Budget: $400,000 over 2 years*	N/A	7.E $330,662 2 projects	7.E $390,134 1 project	7.E $533,354 1 project	7.E $0 1 project	$1,254,150
	7.E. Funding: The recommended budget was met. Significantly more than the recommended minimum budget was allocated to projects specific to this objective. **Progress:** The goal of objective has been achieved in terms of efforts to help researchers more effectively disseminate their findings to the community online and in lay-friendly formats, but not through a web-based toolbox. For example, several agencies, organizations and groups (CDC, NIH, Simons Foundation, Autism Speaks, ASF, IAN) publish lay-friendly summaries of recent scientific findings online, as well as lay-friendly versions of their reports. In addition, the "Data from Papers" feature in NDAR connects readers from the Pubmed citation of a study to the actual data deposited in the database. **Remaining Gaps, Needs, and Opportunities:** Though agencies and organizations are making active efforts to assist researchers with disseminating findings to the community via the web, access to information about research findings remains limited for those communities that are resource-poor and do not have internet access. In addition, the lack of open access to most peer-reviewed journals limits the public's ability to access fully detailed information about new findings.					
Create funding mechanisms that encourage rapid replication studies of novel or critical findings by 2011. *No recommended budget assigned by the IACC*	N/A	7.F $0 0 projects	7.F $0 0 projects	7.F $0 0 projects	7.F $0 0 projects	$0
	7.F. Funding: There has been no specific funding for this objective. **Progress:** There are no projects categorized to this objective. The Planning Group discussed the issue that creation of funding mechanisms is not likely to be achieved through grant funding, and therefore would not be reflected in the grant portfolio. **Remaining Gaps, Needs, and Opportunities:** The Committee still feels that this objective is relevant and that it is not too early to begin replication studies. In the databases there are 70,000 subjects, 7,000 exomes and 2,500 MRIs that can be used for replication analysis. The intent of the objective was to quickly replicate findings related to potential treatments, but to date, no special fast-track funding mechanisms have been established to support this.					
Develop a web-based tool that provides population estimates of ASD prevalence for States based on the most recent prevalence range and average identified by the ADDM Network by 2012. *IACC Recommended Budget: $200,000 over 2 years*	N/A	7.G $0 0 projects	7.G $0 0 project	7.G $0 0 project	7.G $0 0 project	$0
	7.G. Funding: Autism tracking data is captured in CDC's environmental tracking tool, which became available to the public in 2012, and is not reflected in the autism grant portfolio figure because it is a general tool that encompasses multiple disorders and conditions. **Progress:** The intent of this objective has been accomplished through the CDC project and can be considered completed. **Remaining Gaps, Needs, and Opportunities:** No new needs or opportunities in this area were identified.					

Table 8: Question 7 Cumulative Funding Table, see appendix for a color-coding key and further details.

Question 7 Cumulative Funding Table

IACC Strategic Plan Objectives	Funding					
Year	2008	2009	2010	2011	2012	Total
Create mechanisms to specifically support the contribution of data from 90% of newly initiated projects to the National Database for Autism Research (NDAR), and link NDAR with other existing data resources by 2012. *IACC Recommended Budget: $6,800,000 over 2 years*	N/A	7.H $1,932,996 2 projects	7.H $2,453,253 3 projects	7.H $1,517,596 1 project	7.H $3,679,808 5 projects	$9,583,653
	7.H. Funding: The recommended budget for this objective was met. **Progress:** The objective to create mechanisms to support the contribution of data from newly initiated projects to NDAR has been met, and NDAR has linked with several other existing data sources such as the ATP, AGRE and IAN. In 2012, 81% of NIH-funded extramural studies were contributing data to NDAR. All NIH grants have terms that require linking of data to NDAR. **Remaining Gaps, Needs, and Opportunities:** Infrastructure will need continued development to enable greater availability of standardized data and analytical tools for cloud computing. IAN data collection could be expanded to include locations of residence to enable geographic data collection on environmental exposures.					
Supplement existing ADDM Network sites to use population-based surveillance data to conduct at least five hypothesis-driven analyses evaluating factors that may contribute to changes in ASD prevalence by 2012. *IACC Recommended Budget: $660,000 over 2 years*	N/A	7.I $6,715,815 15 projects	7.I $6,137,128 13 projects	7.I $4,928,453 13 projects	7.I $6,028,878 13 projects	$23,810,274
	7.I. Funding: The recommended budget was met. Significantly more than the recommended minimum budget was allocated to projects specific to this objective. (Note that the funding amount for this objective reflects the full funding of the ADDM sites and not just the supplements.) **Progress:** The research goals in the objective have been achieved. Initially, supplements were needed to support these analyses, but now the ADDM sites are well established and are conducting some analyses using funds from the ADDM grants themselves, while outside supplements are supporting other additional analyses. **Remaining Gaps, Needs, and Opportunities:** Supplements remain an opportunity to capitalize on this infrastructure.					

Table 8: Question 7 Cumulative Funding Table, see appendix for a color-coding key and further details.

Question 7 Cumulative Funding Table

IACC Strategic Plan Objectives	Funding					
Year	2008	2009	2010	2011	2012	Total
Develop the personnel and technical infrastructure to assist States, territories, and other countries that request assistance describing and investigating potential changes in the prevalence of ASD and other developmental disabilities by 2013. *IACC Recommended Budget: $1,650,000 over 3 years*	N/A	7.J $494,449 11 projects	7.J $170,490 4 projects	7.J $545,414 6 projects	7.J $159,610 4 projects	$1,369,963
	7.J. Funding: The recommended budget was met. In addition, the Autism Speaks Global Health Initiative projects address this objective, though they have been coded to their specific scientific areas and are not represented in this funding amount. Also, the CDC provides personnel and help to States, territories and countries as requested, but the budget for that assistance is not reflected in the portfolio analysis figures because this work is not done through grants. **Progress:** Progress has been made in addressing this need, but not all responsive projects were reflected in the funding amount because some of them were conducted through sources not captured in the portfolio analysis (non-autism specific funding sources) or the projects were assigned according to their scientific topics rather than to this objective. In addition to providing supplemental funding for ADDM site surveillance, Autism Speaks funds projects on surveillance conducted by sites outside of the ADDM network, such as the Kwa-Zulu-Natal Autism Study in South Africa. **Remaining Gaps, Needs, and Opportunities:** While progress has been achieved, ongoing efforts are needed in this area.					
Encourage programs and funding mechanisms that expand the research workforce, enhance interdisciplinary research training, and recruit early-career scientists into the ASD field by 2013. *IACC Recommended Budget: $5,000,000 over 3 years*	N/A	7.K $2,527,472 7 projects	7.K $7,358,427 34 projects	7.K $4,813,286 27 projects	7.K $10,003,091 25 projects	$24,702,276
	7.K. Funding: The recommended budget was met. Significantly more than the recommended minimum budget was allocated to projects specific to this objective. Many of the fellowship grants are coded according to the specific topic of the research conducted and thus are not represented in this funding figure. **Progress:** In 2008, NIH supported 46 autism related training/fellowship grants ($5.1 million), and in 2012 NIH supported 78 such grants ($7.7 million). **Remaining Gaps, Needs, and Opportunities:** This objective should continue to be encouraged with a possible future emphasis on services-based research.					

Table 8: Question 7 Cumulative Funding Table, see appendix for a color-coding key and further details.

Question 7 Cumulative Funding Table

IACC Strategic Plan Objectives	Funding					
Year	2008	2009	2010	2011	2012	Total
Expand the number of ADDM sites in order to conduct ASD surveillance in children and adults; conduct complementary direct screening to inform completeness of ongoing surveillance; and expand efforts to include autism subtypes by 2015. *IACC Recommended Budget: $16,200,000 over 5 years*	N/A	7.L $699,304 2 projects	7.L $1,429,602 8 projects	7.L $705,552 6 projects	7.L $847,002 6 projects	$3,681,460
	7.L. Funding: The recommended budget was partially met, but it is noted that the full funding of the ADDM sites is reflected in Objective 7.I. and thus there may be under-representation of funding in this category. **Progress:** Supplements have been provided to six ADDM sites by CDC to collect data from a younger cohort (4-year-olds) in addition to the 8 year olds currently studied; two other ADDM sites have received supplements from CDC to conduct surveillance studies among 15 to 18 year olds. Despite these expansions, further work is needed to better understand prevalence in both younger and older populations. A current project at UNC is reassembling those who participated in TEACCH to conduct a study of long-term outcomes. Also, Paul Shattuck has published studies on young adults with disabilities seeking services that have revealed a significant drop in services use and access post-high school, along with an increased likelihood to remain living with a parent or guardian. In addition, the Utah cohort (mentioned in Question 6) has been used for studies related to adults with autism, with a recent paper identifying health risks and causes of mortality. **Remaining Gaps, Needs, and Opportunities:** While subtypes were included as part of this objective, with the changes in the DSM to eliminate subtypes, this portion of the objective may no longer be relevant. In the future it may be more useful to collect data on characteristics of children and adults with ASD who participate in studies.					
Support 10 "Promising Practices" papers that describe innovative and successful services and supports being implemented in communities that benefit the full spectrum of people with ASD, which can be replicated in other communities, by 2015. *IACC Recommended Budget: $75,000 over 5 years*	N/A	7.M $0 0 projects	7.M $0 0 project	7.M $0 0 projects	7.M $0 0 projects	$0
	7.M. Funding: There has been no specific funding for this objective. **Progress:** CMS is no longer supporting the program that produced the earlier promising practices papers; it is possible that other methods of disseminating best practices information are now being used. **Remaining Gaps, Needs, and Opportunities:** Best practices information dissemination is still a high priority, but there may be other means by which this is being done. The focus should be on achieving dissemination rather than on the particular method used. Perhaps this objective should be revisited and replaced with a version that reflects current needs and practices or combined with another objective as appropriate in the future.					

Table 8: Question 7 Cumulative Funding Table, see appendix for a color-coding key and further details.

Question 7 Cumulative Funding Table

IACC Strategic Plan Objectives	Funding					
Year	2008	2009	2010	2011	2012	Total
Enhance networks of clinical research sites offering clinical care in real-world settings that can collect and coordinate standardized and comprehensive diagnostic, biological (e.g., DNA, plasma, fibroblasts, urine), medical, and treatment history data that would provide a platform for conducting comparative effectiveness research and clinical trials of novel autism treatments by 2012. *IACC Recommended Budget: $1,850,000 over 1 year*	N/A	N/A	7.N $6,662,790 3 projects	7.N $7,419,887 22 projects	7.N $5,270,828 22 projects	$19,353,505
	7.N. Funding: The recommended budget was met. Significantly more than the recommended minimum budget was allocated to projects specific to this objective. **Progress:** Autism Speaks' ATN is a care network that also has research capabilities. The ATN has a collection of biological samples collected from patients who have sought care at the ATN. However, these samples are not targeted toward research use because the samples are not broadly shared like those from other repositories and the samples were not collected systematically. As the ATN has progressed in its work, it has shifted away from the goal of creating a repository to a new focus on developing clinical guidelines, especially in the area of co-occurring conditions. Several guidelines have been published. Another network, the IAN, has piloted a new rapid method of conducting "virtual" clinical trials of low-risk or "safe" treatments. For example, IAN conducted a trial on omega 3 fatty acids – a commonly used dietary supplement - across 40 states in 10 weeks, demonstrating the value of using interactive research networks for these types of trials. **Remaining Gaps, Needs, and Opportunities:** Clinical and patient social networks represent new ways to conduct research ("practice to research"), as well as a path for evaluating interventions that do not require extensive safety testing (e.g., alternate diets or technological interventions) quickly using large social networks.					
Create an information resource for ASD researchers (e.g., PhenX Project) to share information to facilitate data sharing and standardization of methods across projects by 2013. • This includes common protocols, instruments, designs, and other procedural documents and should include updates on new technology and links to information on how to acquire and utilize technology in development. • This can serve as a bidirectional information reference, with autism research driving the development of new resources and technologies, including new model systems, screening tools, and analytic techniques. *IACC Recommended Budget: $2,000,000 over 2 years*	N/A	N/A	7.O $605,338 3 projects	7.O $1,070,941 3 projects	7.O $728,000 1 project	$2,404,279
	7.O. Funding: The recommended budget for this objective was met. **Progress:** A small number of projects specific to this objective were funded. In addition, there are other projects that are responsive to the goals of this objective, but are coded elsewhere. For example, NDAR has developed a data dictionary that is now widely used across the research community to standardize data terminology so that data can be uniformly shared among researchers. Funding for this project is not reflected in the total for this objective because NDAR is coded elsewhere. NDAR also has a human subject common identifier that is now broadly used by the community. **Remaining Gaps, Needs, and Opportunities:** Funding is necessary to develop standardized methods and protocols. This is a long term project and will need to be approached carefully.					

Table 8: Question 7 Cumulative Funding Table, see appendix for a color-coding key and further details.

Question 7 Cumulative Funding Table

IACC Strategic Plan Objectives	Funding					
Year	**2008**	**2009**	**2010**	**2011**	**2012**	**Total**
Provide resources to centers or facilities that develop promising vertebrate and invertebrate model systems, and make these models more easily available or expand the utility of current model systems, and support new approaches to develop high-throughput screening technologies to evaluate the validity of model systems by 2013. *IACC Recommended Budget: $1,100,000 over 2 years*	N/A	N/A	**7.P** $1,588,780 1 project	**7.P** $0 0 projects	**7.P** $0 0 projects	**$1,588,780**
	7.P. Funding: The recommended budget for this objective was met. **Progress:** The project in the Portfolio Analysis that addresses this objective is a NIMH intramural project to produce transgenic mouse models of mental and neurodevelopmental disorders, including ASD. In addition, when mouse models are made under grants and projects coded elsewhere in the portfolio, they are shared via Jackson Laboratories, and that funding is not reflected here. **Remaining Gaps, Needs, and Opportunities:** Emphasis on providing means to encourage development and sharing of animal models, and development of assays that can be used in animal models is still required to advance basic and translational ASD research.					
Not specific to any objective (Core/Other Activities)	N/A	**7. Core/ Other Activities** $1,000,000 2 projects	**7. Core/ Other Activities** $13,253,709 26 projects	**7. Core/ Other Activities** $12,314,084 18 projects	**7. Core/ Other Activities** $16,863,272 23 projects	**$43,431,065**
Total funding for Question 7†	N/A	**$15,809,755** 46 projects	**$50,847,065** 108 projects	**$43,855,291** 111 projects	**$47,516,197** 112 projects	**$170,126,365***

Table 8: Question 7 Cumulative Funding Table, see appendix for a color-coding key and further details.

**This total reflects all funding for projects aligned to current objectives in the 2011 IACC Strategic Plan and incorporates funding for projects that may have been coded differently in previous versions of the Plan.*

† The totals reflect the funding and projects coded to this Question of the Strategic Plan in the particular year indicated at the top of the column. When reading each column vertically, please note that the projects and funding associated with each objective for the years 2008, 2009, and 2010 may not add up to the total at the bottom of the column; this is due to revisions of the Strategic Plan that caused some objectives to be shifted to other Questions under the Plan. The projects and funding associated with these reclassified objectives are now reflected under the Question in which they appear in the 2011 Strategic Plan.

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CONCLUSION

PROGRESS

The *2013 IACC Strategic Plan* Update details the progress that has been made on the scientific questions and investment recommendations of the *IACC Strategic Plan*. Of the 78 specific *IACC Strategic Plan* objectives, 73 have fully met or partially met the recommended budget. Overall, approximately $1.5 billion in public and private research funding has been dedicated to ASD projects over the past 5 years, with an average funding increase of 39 percent across the *IACC Strategic Plan* Questions for the period following its initial release in 2009. This increased investment has brought forth a range of scientific advances in all areas of the *IACC Strategic Plan*.

The state of the science has dramatically changed in the ASD field since 2008, reflected in a significant increase over time in the number of journal publications related to ASD research.[1] While biological differences in individuals with ASD were hypothesized earlier, now there are data demonstrating specific changes in the genome and epigenome,[2–20] gene expression,[21,22] cell structure and function,[23–29] brain connectivity,[30–32] and behavior[33–35] that have been linked to the causes and underlying biology of ASD. Over the past 5 years, genetic studies have revealed that genetic variation ranging from changes in single bases to alteration of large regions of DNA or even extra chromosomes can contribute to ASD risk, and that both inherited and spontaneous mutations can play a role.[2–4] Several environmental factors have emerged as potential contributors to ASD risk in the past five years, including: prenatal maternal infection,[36,37] preterm birth,[38–41] advanced maternal and paternal age at conception,[42–48] short inter-pregnancy interval,[49,50] as well as some data suggesting that exposure to air pollution,[51–56] phthalates[57–59] and pesticides[60–62] during pregnancy may also increase risk. Vitamin intake, particularly folic acid,[63–65] during the pre-conception period has been identified as a possible protective factor against ASD risk, while both the genetic and environmental data now point to the early months of gestation as a critical period for the development of ASD.

Advances in screening tools such as the Modified Checklist for Autism in Toddlers (M-CHAT) and the Infant-Toddler checklist, with an emphasis on early and repeated screenings, now make it possible to set a realistic future goal to identify 95 percent of children with ASD before the age of 24 months.[66–69] New technologies to detect differences in eye-tracking patterns, and new research on white matter tract development and posture control in infants also introduce the potential to detect ASD as early as 2-6 months of age.[30,33–35] This ability for early ASD detection, however, will depend on large community-based validation studies of screening in the general population and only will become clinically useful if efficient, cost effective tools can be designed around these new capabilities. It will also be critical to ensure that following a positive early screening result, parents readily seek diagnosis and intervention, and that there are effective early interventions available. Recent clinical trials of behavioral interventions have demonstrated their positive impact on outcomes and have begun to provide the evidence base needed to support the widespread use of these advances in the community.[70–75] However, more needs to be done to make these therapies affordable and scalable to large and diverse community settings, and efforts are needed to increase the number of children who progress from identification in early screens to diagnosis and early intervention. Disparities in access to diagnosis and treatment based on resources, ethnicity, and gender remain another significant challenge.

Studies of animals that carry gene mutations that, in humans, cause syndromic forms of autism have demonstrated that in animals symptoms can be reversed both in early development and in adulthood.[76,77] While these studies may not directly translate to humans, they indicate that some symptoms of autism may be amenable to treatment even later in life, they identify possible drug targets, and they provide a pathway for developing treatments for the core symptoms of ASD. Clinical trials in toddlers have demonstrated the value of early behavioral intervention, with gains in behavior and function as well as the first demonstration of measurable changes in brain activity in response to intervention.[70–75,78] Several trials are currently underway, ranging from exploratory trials of novel interventions to tests of treatments that are already in current use in the community. Over the past 5 years, a large clinical network has been developed, several pharmaceutical companies have become engaged in ASD research, and new technologies have emerged that may prove transformative. This field still requires standardized, sensitive outcome measures and biomarkers that can both stratify the heterogeneous ASD population and serve as rapid indicators of clinical response.

Recent studies have revealed the tremendous service needs within the community, with data showing that young adults transitioning out of the educational system frequently lose their services access and often have limited opportunities for employment and independent housing.[79–82] While more data are required on the needs of adults with ASD so that services can be more appropriately targeted, there is already an opportunity to collect data on the effectiveness of current services being delivered in the community through projects such as federally-funded state demonstration projects. In some cases, it may also be possible to do comparative studies that could begin to make improvements in services for adults in the near term.

One of the most encouraging signs of progress has been the expansion of research infrastructure over the past 5 years, helping the scientific community embrace a culture of data integration and sharing. Several large scale government-funded research centers, privately funded efforts, and some public-private collaborative projects have been built in the past 5 years. The National Database for Autism Research (NDAR), an NIH-funded hub that stores and shares aggregate data, from exomes to images, has grown to include over 70,000 human subjects. Efforts such as the government-funded NIH Neurobiobank and the privately-funded Autism BrainNet have been established to try to expand the supply of available brain and other tissue samples for ASD and brain disorder research. In addition, the Interactive Autism Network (IAN) and Autism Genetic Resource Exchange (AGRE) give families the opportunity to share data and participate in new models of more rapid, interactive clinical trials, expanding the possibilities for future research.

Relative to many other areas of biomedical research, ASD science is still a young field. While the past 5 years have seen rapid growth and substantial scientific progress, the Committee recognizes the large gap that still remains between advances made in research settings and practical benefits that are ready to be delivered to individuals and families living with ASD today. We remain far from the overall intention of the *IACC Strategic Plan* to foster research that will yield tangible improvements in quality of life for people with ASD across all settings and communities. An intensified effort will be needed to ensure that recent promising discoveries are rapidly translated into clinical practice and services that will improve quality of life for individuals with ASD.

In conducting this review, the Committee recognized several core needs that spanned across multiple areas on the research portfolio:

- ***Scaling Up***

  Many of the screening tools, interventions, and services approaches that have been developed to date are effective in research settings and when tested in small groups. In order for these tools and approaches to have the potential to impact the community, they must be scaled up to be useable in the full range of community settings. In addition, providers and families need to be educated and empowered to disseminate and implement research findings in the community, ensuring the highest quality of services.

- ***Population Inclusion***

  Screening tools are frequently tested in the siblings of children with ASD because they are at elevated risk of developmental concerns, including ASD. In order to ensure that screening and diagnostic tools are developed and validated for use in broader populations, it will be important to include children in the general population (with no family history of ASD), adolescents, and adults in future screening and diagnostic tool development research. For other studies, many participants have mild disability and are in areas with good access to medical care. It is vital that participants across the full range of ASD disability, across all periods of the lifespan, and from underserved populations are included so that tools developed will have broad applicability.

- ***Practice to Research***

  In the arenas of interventions and services, there are already many practices that are being utilized within the community, and there are interactive virtual networks of individuals and families available, providing an opportunity to study the use of these interventions and services in a real-world setting. More academic and community partnerships and new clinical trial approaches are needed to leverage these resources and gain valuable insight into what approaches are effective in community settings. The new Congressionally-established Patient Centered Outcomes Research Institute (PCORI) may be an opportunity for such studies.

- ***Addressing Heterogeneity***

  The heterogeneity of ASD, which is a spectrum composed of different conditions sharing some core features but resulting from different underlying biology and causes, and presenting with varying levels of severity in several different domains, remains a challenge. The development of predictive and early efficacy biomarkers that can identify subtypes of ASD that will respond to different treatments will be essential to move to a precision medicine approach for ASD.

- ***Leveraging Existing Infrastructure***

  In the past 5 years, both public and private resources have been invested in establishing infrastructure for surveillance, clinical research, environmental studies, and sample and data sharing. To fully utilize these resources and gain the maximum value from these investments, agencies and organizations should consider building new studies onto these existing resources.

- ***Applying Strategies from Other Fields***
  Scientific disciplines relevant to autism are making considerable advances in the study of other health conditions. Over the past 5 years, there has been much success in learning about ASD biology from research on related disorders. Similarly, ASD researchers may be able to adopt successful strategies from other disease fields to solve issues such as how to detect trace chemicals in small biosamples effectively or how to best reach underserved populations with tools and services. Finally, the data collected by longitudinal studies and the data available through NDAR need to be exhaustively analyzed.

- ***Standardized Outcome Measures***
  In order to truly determine the effectiveness of interventions and the outlook across the lifespan, measurements of outcomes that are responsive to interventions and quality of life measures that can help determine the effectiveness and impact of services must be identified and standardized.

FUTURE DIRECTIONS

History may identify the past 5 years as an inflection point for our understanding of ASD. Increased investments from both private and government sources, improved resources for research, and expanded communities of scientists entering this field all provide hope that recent progress will accelerate. Many new areas of science, from the microbiome to social prosthetics, may transform our understanding of ASD with entirely new tools for interventions. One of the greatest challenges will be finding the right balance between science that can immediately improve quality of life for individuals with ASD and science that seeks to gain fundamental knowledge about ASD with the promise of prevention or cure in the future. The ASD community has a diversity of views on how to set this balance, with some focused on identifying the causes with the goal of preventing ASD, reducing disability or finding a cure, while others focus on accommodation, inclusion, and acceptance. In the near term, science can serve both sets of goals to develop a deeper understanding of the many forms of ASD and enhance interventions, services, and supports that can offer individuals with ASD opportunities for independence and full participation in community life.

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APPENDIX:

ASD Research Progress on IACC Strategic Plan Objectives: Summary of Years 2008 to 2012

The tables include data (project numbers and funding) from Federal and private funders of ASD research for years 2008 through 2012, as aligned with the objectives of the *2011 IACC Strategic Plan*. They also include summaries (based on discussions during the 2013 IACC Strategic Plan Update Workshop) of progress on reaching the goals of each objective, as well as remaining gaps, needs, and opportunities. Please note the following:

During the updating of the *Strategic Plan* from 2008 to 2010, the wording and numbering of objectives changed. Data included in each *Portfolio Analysis Report* from 2008 to 2012 was categorized at the time with respect to the most recent iteration of the *Strategic Plan* where the objectives had changed. For the purpose of this five-year comparison, data from the Portfolio Analyses conducted in 2008 and 2009 were aligned with the most recent objectives, found in the ***2011 Strategic Plan***. The full wording of the 78 objectives listed in the *2011 Strategic Plan* is depicted in the left column of the table.

The middle five columns of the table contain the data (project numbers and funding) for each individual year from 2008 to 2012, with the objective number (as it appeared in the annual Portfolio Analysis) listed above it. The IACC recommended budget listed below the project data represents the most updated budget listed in *2011 Strategic Plan*. If the recommended budget has been revised since 2008, the year the revision took place is found in parentheses following the budget figure. Therefore, if there is no mention of a revision, the IACC recommended budget has remained constant from 2008 to 2011. The annual project status for each objective from 2008 to 2012 is indicated within the table by colored highlighting of the objective number. An objective is considered active if its status is green or yellow, and inactive if its status is red.

- Any objective colored green has funding which is greater than or equal to the recommended funding for that year (determined by annualizing the recommended budget associated with that objective); any objective colored yellow has active projects, but with funding that totals less than the annualized recommended amount; while any objective colored red has no active projects.[1]
- Objectives whose overarching aim (e.g., the ultimate goal of the research as opposed to the number of projects called for in the objective) were achieved/partially achieved either in a previous year, or with funding that was not captured in the portfolio analyses,[2] are colored pale green/pale yellow.

[1]Please note that while the green, yellow and red indicators suggest a funding status for each year and that looking across all years may give some indication of a trend, that some agencies and organizations provide all the funding for multiyear grants in a single year, resulting in the appearance of "less funding" in other years, but that projects fulfilling the objectives may still have been ongoing in the years where the funding appears to be less. Thus, it is important to note the numbers of projects in looking across the chart, and to keep in mind that in a series, where, for example, most of the indicators are green, that the objective is likely to be largely "complete" according to the funding-based measure.

[2]Reasons why funding for certain projects may not have been captured in the portfolio analyses include projects that were supported by funding that was not specific for autism (i.e., projects that benefited autism but were supported by general neuroscience or developmental disorder funding) or projects supported by funders that did not participate in the portfolio analysis in a given year.

The far right column of the table lists the sum of the total funding aligned with each objective from 2008 to 2012. Highlighting of each total gives an indication of the progress toward fulfilling each objective.

- Green highlighting indicates that funding fully meets the recommend budget. Yellow highlighting denotes that funding for a particular objective partially meets the IACC recommended budget, while red highlighting indicates that there has been no funding towards the particular objective.
- Objectives whose overarching aim (e.g. the ultimate goal of the research as opposed to the number of projects called for in the objective) was achieved/partially achieved with funding that was not captured in the portfolio analyses, are colored pale green/pale yellow.

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