



2016-2017

INTERAGENCY AUTISM COORDINATING COMMITTEE
STRATEGIC PLAN
FOR AUTISM SPECTRUM DISORDER



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 Federal activities concerning autism spectrum disorder (ASD) and providing advice to the Secretary of Health and Human Services (HHS) on issues related to autism. The Committee was established by Congress under the *Children's Health Act of 2000*, reconstituted under the *Combating Autism Act (CAA) of 2006*, and renewed most recently under the *Autism Collaboration, Accountability, Research, Education, and Support (CARES) Act of 2014*.

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, family members of children and adults with ASD, advocates, service providers, and researchers, who represent a variety of perspectives from within the autism community. The IACC membership is composed to ensure that the Committee is equipped to address the wide range of issues and challenges faced by individuals and families affected by autism.

Under the CAA and subsequent authorizations, 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 other Federal departments, Federal agencies, research and advocacy organizations, and the broader autism community to accelerate research and enhance services with the goal of profoundly improving the lives of people with ASD and their families.

For more information about the IACC, see <http://www.iacc.hhs.gov>.

INTRODUCTION

The Interagency Autism Coordinating Committee (IACC) is a Federal advisory committee that advises the Secretary of Health and Human Services on issues related to autism spectrum disorder (ASD). It was established by the *Children's Health Act of 2000* (Public Law 106-310), reconstituted under the *Combating Autism Act of 2006* (CAA; Public Law 109-416), and was most recently renewed in 2014 under the *Autism Collaboration, Accountability, Research, Education, and Support Act (Autism CARES Act; Public Law 113-157)*. One of the statutory responsibilities of the IACC under the CAA and subsequent authorizations is the development of a strategic plan for ASD, to be updated annually. The *IACC Strategic Plan*, first issued in 2009, was developed by the IACC – including Federal officials and public stakeholder members – and each edition has been informed by extensive input from researchers, adults on the autism spectrum, parents, advocates, and the general public. This inclusive process has ensured that the *IACC Strategic Plan* reflects diverse perspectives from across the autism community. The *Autism CARES Act* requires that the IACC include in the *Strategic Plan* information concerning, “as practicable...services and supports, for individuals with an autism spectrum disorder and the families of such individuals,” along with information about ASD research. In this edition, which includes an entirely new set of strategic objectives, the *IACC Strategic Plan for Autism Spectrum Disorder* addresses this new requirement by taking a more comprehensive approach that not only addresses autism research, but also incorporates more information about gaps, opportunities, and implications related to autism services, supports, and policies.

This 2016-2017 revision of the *IACC Strategic Plan* is the work of the IACC membership appointed under the *CARES Act*. The *CARES Act* increased the required number of public

members on the Committee, which includes at least two members on the autism spectrum, at least two parents or legal guardians of individuals with autism, and at least two advocacy, services, or research organization representatives. Several of the members have dual roles as professionals in fields related to ASD as well as having personal experience with ASD. The slate of new and returning IACC members was announced in October 2015 and embodies a wide variety of views, perspectives, and expertise.

As in previous years, the *IACC Strategic Plan* is organized around seven general topic areas that are represented in the *Plan* as community-focused questions (e.g., Question 1, “How can I recognize the signs of ASD, and why is early detection so important?,” which covers the topic of screening and diagnosis). Each question is assigned a chapter in the *Strategic Plan* that provides an Aspirational Goal, or long-term vision for the question, and includes: a description of the state of the field; the needs and opportunities in research, services, and policy; and three to four broad objectives for each question topic. There is also one cross-cutting objective on the topic of ASD in females.

For the 2016-2017 *IACC Strategic Plan*, the Committee agreed that given the recent advances in the autism field, it was an appropriate time to re-evaluate the autism landscape and formulate new objectives for each question. With access to an extensive portfolio analysis conducted by the National Institutes of Health (NIH) Office of Autism Research Coordination (OARC), 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. The 23 new objectives in this *Plan* were created by the Committee to

address critical gaps and potential advances they perceived in the current research landscape. Because the objectives have been updated and broadened from the previous *Strategic Plan's* 78 research objectives, the IACC expects that multiple funder portfolios will play key roles in addressing different aspects of each objective in this *Plan*. Furthermore, in light of the wide range of needs in autism research and services, the IACC recommends doubling the 2015 overall autism research budget level of \$343 million to \$685 million by the year 2020. Although this funding would not be sufficient to accomplish all of the objectives described in this *Plan*, it would represent an aggressive step toward progress.

In formulating this new *Plan* for ASD activities, the IACC has moved toward a paradigm shift in how we approach autism. A few years ago, scientists saw autism as a disorder to be detected, treated, prevented, and cured. The majority of research was directed at understanding the genetic and biological foundations of autism, and toward early detection and intervention. Today, our understanding of autism is more nuanced. We realize that there are many different "autisms" – some severe, and some comparatively mild – and that ASD affects several distinct domains of functioning differently in each individual. We have come to understand that autism is far more common than previously suspected and there are most likely many undiagnosed children, adolescents, and adults in the population, as well as under-identified and underserved individuals and groups, such as girls/women with ASD, people in poorly resourced settings, members of underserved minority communities, and individuals on the autism spectrum with language and/or intellectual disabilities. Most importantly, individuals on the autism spectrum have become leading voices in the conversation about autism, spurring acknowledgment of the unique qualities that people on the autism spectrum contribute to society and promoting self-direction, awareness, acceptance, and inclusion as important societal goals.

Research on genetic risk and the underlying basic biology of ASD remains a primary focus of the research portfolio and does play an important long-term role in the potential to develop new and broadly beneficial therapies and interventions. These advances may one day mitigate or even eliminate some of the most disabling aspects of autism, especially for those on the spectrum who are most severely impacted. However, balanced with the potential for long-term efforts to lead to significant future advances and opportunities is the importance of efforts that can have a more immediate impact. Individuals on the autism spectrum today will remain autistic for the foreseeable future; most of them have significant unmet needs. To help those people – who range in age from infants to senior citizens – we must in the short-term translate existing research to develop effective tools and strategies to maximize quality of life, and minimize disability, while also ensuring that individuals on the autism spectrum are accepted, included, and integrated in all aspects of community life.

The community has been very clear in its calls for more research into adult issues and better services and supports for the millions of Americans living with autism today. Recent studies of adult mortality have indicated that people with ASD are at higher risk of premature death than people in the general population, painting a very disturbing picture that bears investigation. In light of data and insights from the community, the IACC proposes a comprehensive research agenda that addresses the needs of autistic people across the spectrum and across the lifespan, including improvements to services, supports, and policies. The IACC also believes that, as many in the autism community have indicated, efforts to address the many co-occurring conditions that accompany autism should be made a greater priority.

Though this *2016-2017 IACC Strategic Plan for Autism Spectrum Disorder* cannot possibly capture all the changes in the ASD field since 2008, the IACC has endeavored to deliver an updated picture of the evolving landscape of

autism, as well as a new, broad vision of the current and future challenges and opportunities in autism research, services, and policy. To provide a more complete and detailed view of autism research progress, this update accompanies two other annual IACC publications. 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*

describes specific scientific findings that members of the IACC identify as having significantly advanced the field and as having the potential to impact public health and quality of life in the ASD community. Together, with this *2016-2017 IACC Strategic Plan for ASD*, the Committee hopes that these documents will provide an insightful overview of the state of autism in 2017, as well as outline a strategic agenda for future progress.

VISION STATEMENT

The *IACC Strategic Plan for ASD* will accelerate and inspire research, and enhance service provision and access, that will profoundly improve the health and quality of life of every person on the autism spectrum across the lifespan. The *Plan* will provide a blueprint for ASD research and services efforts, engaging the participation and input of government agencies, private organizations, and the broader autism community.

MISSION STATEMENT

The purpose of the *Strategic Plan* is to focus, coordinate, and accelerate innovative research and foster development of high-quality services in partnership with stakeholders to address the urgent questions and needs of people on the autism spectrum and their families.

CORE VALUES

The IACC adopted the below core values and emphasized their significance to the *2016-2017 Strategic Plan* development and implementation:

Sense of Urgency: We will focus on responding rapidly and efficiently to the needs and challenges of people on the autism spectrum and their families.

Excellence: We will pursue innovative scientific research of the highest quality and development and dissemination of evidence-based services and practices to maximize the quality of life for people on the autism spectrum.

Spirit of Collaboration: We will treat others with respect, listen with open minds to the diverse views of people on the autism spectrum and their families, thoughtfully consider community input, and foster discussions where participants can comfortably offer opposing opinions.

Community Focus: We will focus on making a difference in the lives of people affected by ASD, including people with ASD, their families, medical practitioners, educators, and scientists. It is important to consider the impact of research on the quality of life, human rights, and dignity of people with ASD, from prenatal development forward.

Partnerships in Action: We will value cross-disciplinary approaches, data sharing, teamwork, and partnerships to advance ASD research and service activities.

Equity: We will prioritize improved access to detection, intervention, and other services and supports for individuals with ASD, and commit to the goal of reducing disparities across the lifespan, spectrum of ability and disability, sex and gender, racial and cultural boundaries, socioeconomic status, and geographic location to improve the health and quality of life of all individuals with ASD.

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

OVERVIEW OF PROGRESS ON STRATEGIC PLAN OBJECTIVES

The Interagency Autism Coordinating Committee (IACC) launched its first *Strategic Plan for Autism Spectrum Disorder Research* in 2009, providing a framework to guide the autism research efforts of Federal and private funders. The *IACC Strategic Plan* organizes research priorities around seven general topic areas represented as community-focused “questions.” The questions are divided further into research objectives that address key research needs, gaps, and opportunities identified by the Committee. Prior to the *2016-2017 IACC Strategic Plan*, the most recent update to the *IACC Strategic Plan’s* objectives occurred in 2011, leading to a total of 78 objectives for autism research.

The **2014-2015 IACC ASD Research Portfolio Analysis Report** provides the most recent progress on the previous *IACC Strategic Plan* objectives. In 2015, significant progress was made toward completing the objectives in the *2011 Strategic Plan*, with 97% (76 objectives) of the 78 objectives either partially or fully completed – meaning objectives had all or some of the required funded projects. Considering the period from 2008-2015, only 3% (2 objectives) of the *2011 Strategic Plan* objectives were not active at any point across this eight-year window. This indicates that the vast majority of priority areas identified by the IACC were deemed by Federal and private research funders to be worthy of investment and were implemented either partially or fully. However, many areas of partial funding in autism research initiatives left significant gaps over this period.

In 2015, ASD research funding supported projects relevant to all seven questions in the *IACC Strategic Plan for ASD Research*. However, some questions received greater

proportions of funding than others due to the activities of the funders included in the analysis. As in previous years, Question 2 (Biology) received the largest portion of funding (32%) in 2015, encompassing projects supported by nine funders. Research in this field focuses on identifying the biological differences and mechanisms in early development and throughout life that contribute to ASD, as well as the characterization of the behavioral and cognitive aspects of ASD. Projects ranged from basic neuroscience using cellular and animal models to clinical studies. Question 3, research which aimed at identifying potential causes and risk factors for the disorder, had the second largest portion of funding (18%). Question 3 research projects addressed topics such as identifying genetic mutations that increase the risk of autism, developing improved approaches to studying environmental exposures and gene-environment interactions, and exploring the potential roles of the microbiome and epigenetics on etiology. Treatments and interventions (Question 4) followed closely with 17% of total funding, which included research on behavioral therapies, pharmacological treatments, and technology-based interventions. Research projects in Question 4 encompass the development of new treatments using model systems and small-scale experiments as well as full-scale clinical trials. Investment in research infrastructure and surveillance (Question 7) had a significant proportion of funding at 16%. Projects in Question 7 covered data sharing, workforce development, ASD surveillance, and communication/dissemination of research findings and evidence-based practices. Research to improve screening and diagnosis (Question 1) of ASD was 9% of funding in 2015. Question 1 objectives focused on research to develop biomarkers, screening tools, and diagnostic instruments

to aid in early identification. Research focused on services (Question 5) and lifespan issues (Question 6) remained the smallest areas of funding (6% and 2%, respectively). Question 5 objectives addressed issues surrounding access to services, coordination of community-based supports, assessment of health and safety, and improving efficacy, cost-effectiveness, and dissemination of evidence-based practices. Research projects within Question 6 attempted to identify and address gaps in transition to adulthood and long-term outcomes in quality of life for people on the autism spectrum.

While each question's funding amount varied throughout the eight-year span, the overall ASD funding proportions remained relatively the same from 2008-2015. The underlying biology (Question 2) of ASD, the detection of risk factors (Question 3), and the development of treatments and interventions (Question 4) consistently received the greatest investments in research. Research focused on services (Question 5) and lifespan issues (Question 6) remained relatively low in funding throughout the years. Question 2 (Biology) is the only research area that received significant increases in funding over most of the time period from 2008-2015.

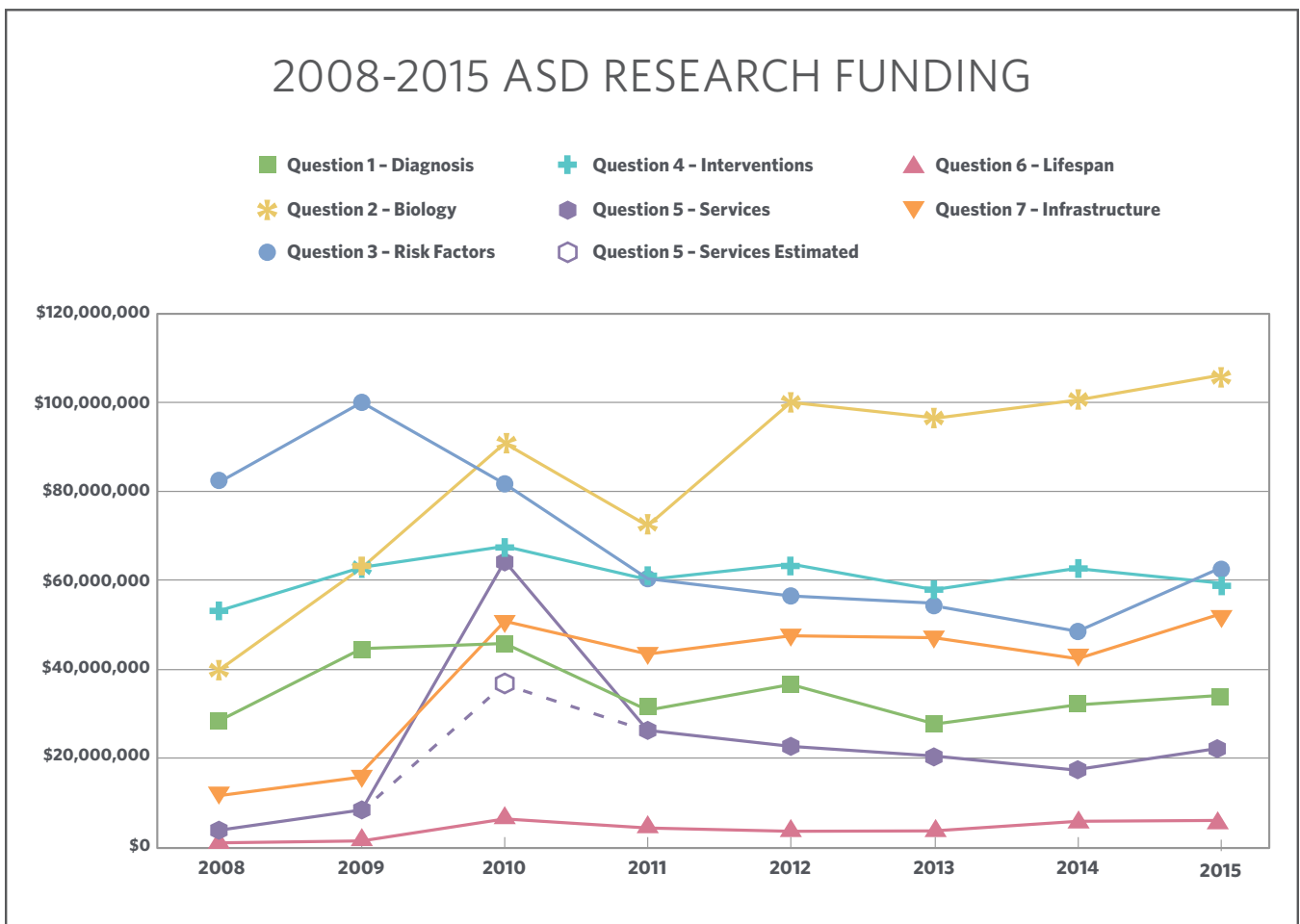


Figure 1. ASD research funding from 2008-2015 by Strategic Plan question area.

In 2008, the reported autism research funding for Federal agencies and private organizations was \$222.2 million and 745 projects. In 2015, funding for ASD research among both Federal and private funders totaled \$342.6 million and spanned 1,410 research projects. Over the eight years, autism research showed a general upward trend in funding, increasing by 35% since 2008. Looking over the last eight years, significant advances have been made in autism research in each of the question areas prioritized by the Committee. But, there are still some areas of research that lack the support needed to foster significant progress. Since the development of the last *IACC Strategic Plan*, autism researchers have made several important discoveries

and reached many milestones, but have also uncovered emerging areas in need of investments. While additional investment is particularly needed in these emerging areas of ASD research, an overall increase in funding to support the entire autism portfolio will be critical to move the field forward and capitalize on scientific opportunity, as is described in the *IACC Strategic Plan's* budget recommendation. This new edition of the *IACC Strategic Plan* builds on the priorities established in the previous editions of the *Strategic Plan*, identifies the gaps in research, and provides recommendations for future research and services endeavors so that we continue to make a difference in the lives of people with ASD and their families.

2016-2017 STRATEGIC PLAN OBJECTIVES



QUESTION 1 HOW CAN I RECOGNIZE THE SIGNS OF ASD, AND WHY IS EARLY DETECTION SO IMPORTANT?

- 1 Strengthen the evidence base for the benefits of early detection of ASD.
- 2 Reduce disparities in early detection and access to services.
- 3 Improve/validate existing, or develop new tools, methods, and service delivery models for detecting ASD in order to facilitate timely linkage of individuals with ASD to early, targeted interventions and supports.

CROSS-CUTTING

- 1 Support research to understand the underlying biology of sex differences in ASD, possible factors that may be contributing to underdiagnosis, unique challenges that may be faced by girls/women on the autism spectrum, and develop strategies for meeting the needs of this population.



QUESTION 2 WHAT IS THE BIOLOGY UNDERLYING ASD?

- 1 Foster research to better understand the processes of early development, molecular and neurodevelopmental mechanisms, and brain circuitry that contribute to the structural and functional basis of ASD.
- 2 Support research to understand the underlying biology of co-occurring conditions in ASD and to understand the relationship of these conditions to ASD.
- 3 Support large-scale longitudinal studies that can answer questions about the development of ASD from pregnancy through adulthood and the natural history of ASD across the lifespan.



QUESTION 3 WHAT CAUSES ASD, AND CAN DISABLING ASPECTS OF ASD BE PREVENTED OR PREEMPTED?

- 1 Strengthen understanding of genetic risk and resilience factors for ASD across the full diversity and heterogeneity of those with ASD, enabling development of strategies for reducing disability and co-occurring conditions in ASD.
- 2 Understand the effects on ASD risk and resilience of individual and multiple exposures in early development, enabling development of strategies for reducing disability and co-occurring conditions in ASD.
- 3 Expand knowledge about how multiple environmental and genetic risk and resilience factors interact through specific biological mechanisms to manifest in ASD phenotypes.



QUESTION 4 WHICH TREATMENTS AND INTERVENTIONS WILL HELP?

- 1 Develop and improve pharmacological and medical interventions to address both core symptoms and co-occurring conditions in ASD.
- 2 Create and improve psychosocial, developmental, and naturalistic interventions for the core symptoms and co-occurring conditions in ASD.
- 3 Maximize the potential for technologies and development of technology-based interventions to improve the lives of people on the autism spectrum.



QUESTION 5 WHAT KINDS OF SERVICES AND SUPPORTS ARE NEEDED TO MAXIMIZE QUALITY OF LIFE FOR PEOPLE ON THE AUTISM SPECTRUM?

- 1 Scale up and implement evidence-based interventions in community settings.
- 2 Reduce disparities in access and in outcomes for underserved populations.
- 3 Improve service models to ensure consistency of care across many domains with the goal of maximizing outcomes and improving the value that individuals get from services.



QUESTION 6 HOW CAN WE MEET THE NEEDS OF PEOPLE WITH ASD AS THEY PROGRESS INTO AND THROUGH ADULTHOOD?

- 1 Support development and coordination of integrated services to help youth make a successful transition to adulthood and provide supports throughout the lifespan.
- 2 Support research and implement approaches to reduce disabling co-occurring physical and mental health conditions in adults with ASD, with the goal of improving safety, reducing premature mortality, and enhancing quality of life.
- 3 Support research, services activities, and outreach efforts that facilitate and incorporate acceptance, accommodation, inclusion, independence, and integration of people on the autism spectrum into society.



QUESTION 7 HOW DO WE CONTINUE TO BUILD, EXPAND, AND ENHANCE THE INFRASTRUCTURE SYSTEM TO MEET THE NEEDS OF THE ASD COMMUNITY?

- 1 Promote growth, integration, and coordination of biorepository infrastructure.
- 2 Develop, enhance, and link data repositories.
- 3 Expand and enhance the research and services workforce, and accelerate the pipeline from research to practice.
- 4 Strengthen ASD surveillance systems to further understanding of the population of individuals with ASD, while allowing comparisons and linkages across systems as much as possible.



QUESTION

1

HOW CAN I RECOGNIZE THE SIGNS OF ASD, AND WHY IS EARLY DETECTION SO IMPORTANT?

Aspirational Goal: Provide the earliest possible diagnosis for people on the autism spectrum, so they can be linked to appropriate interventions, services, and supports in as timely a manner as possible to maximize positive outcomes.

INTRODUCTION

Observational studies of infants at risk for ASD reveal that, although timing of the emergence of ASD features is variable, subtle signs can be detected within the first few years of life. Experienced clinicians who are trained to use validated diagnostic tools can diagnose ASD by 18-24 months of age. Still, most children are not diagnosed in the U.S. until four years of age, with disparities in diagnosis related to socioeconomic factors, geographic location, and race/ethnicity.¹ Given the unprecedented growth and organization of the brain during the first three years of life,²

behavioral interventions initiated in ASD toddlers within this time period result in a range of positive changes including increases in social attention, language ability, and overall IQ.^{3,4,5} However, due to the lag in diagnosis, many children miss the opportunity to receive treatment during this critical period of neuroplasticity. This chapter reviews the state of knowledge about screening and diagnostic tools, as well as the current state of service delivery and challenges families face when trying to access screening and diagnostic services.

IMPLEMENTATION OF ASD SCREENING AND DIAGNOSTIC TOOLS

Although studies consistently report that screening using validated autism-specific parent-report tools can result in ASD detection as young as 12-18 months,⁶ these tools are only used systematically within about 50% of primary care settings.⁷ Reliance on using a standardized screening tool has even been shown to be more effective than pediatrician clinical judgment alone.⁸ Thus, the American Academy of Pediatrics (AAP)⁹ has embraced using universal ASD screening¹⁰ standardized tools as the gold standard for detecting ASD and recognizes screening as a critical service need to improve early access to care. Barriers that prevent widespread uptake of parent-report and other screening tools within primary care settings include: lack of education and understanding of ASD,^{11,12} lack of familiarity with screeners,^{11,13} uncertainty about where to send a toddler with a test-positive screen,¹⁴ lack of effective and timely means of connecting families of individuals with ASD to available resources,^{12,15} and the extra time and resources required to utilize standardized screening tools.^{14,11}

Given that many parents take their child for well-baby visits within a primary care setting, recent research has utilized this context to improve screening. To accommodate the dynamic and busy environment of a primary care setting, parent-report screening tools are designed to be very brief. A new revision to the *Modified Checklist for Autism in Toddlers, Revised*, (**M-CHAT-R**), the most commonly used parent-report screening tool, shows that with the administration of follow-up questions (M-CHAT-R/F), 50% of children who test positive are later diagnosed with ASD, and if all developmental delays are also considered, then over 95% of children who test positive are diagnosed with either autism or some other type of developmental

delay or disability.¹⁶ However, administering follow-up questions in the M-CHAT-R/F procedure can take anywhere from 5 to 30 minutes and as such does not overcome the barrier of time limits in primary care settings.¹⁴ Leveraging technology, recent studies have shown that a full administration of the M-CHAT-R/F on a computer tablet not only resulted in greater and more accurate documentation of the screening results within electronic medical record systems, but also eliminated the time barrier because parents answered the follow-up questions directly on the tablet, thus bypassing the need to engage medical personnel.¹⁷

Large-scale studies examining the M-CHAT^{1,18} and its revisions^{16,19,20} compared to the estimated prevalence rates suggest that many cases of ASD may be missed using the screening tool, especially in 18-month olds. This may be due to many factors, including: the accuracy of the screening tool, ability of parents to notice and report early signs of autism, readiness of parents to act on a positive autism screen, and the heterogeneity in symptom presentation at this young age, suggesting that screening efforts may need to go beyond simple parent-report tools. One such approach is a two-stage screening model that combines a general developmental screening tool based on parent report, **the Infant Toddler Checklist (ITC)**,²¹ with subsequent observational ratings to screen for ASD. Using this approach, detection rates have been reported as 15.1 per 1,000 children at a mean age of 20.8 months,²² which is very close to the expected prevalence rates for ASD.¹ Children identified through the M-CHAT-R/F alone display a lower developmental level than children ascertained with the ITC and follow-up observational rating,^{22,23} and a lower developmental level than those evaluated in a prospective

sample of younger siblings at familial risk for ASD,²⁴ suggesting that this tool may be better at detecting children at a lower developmental level and may sometimes miss less severely affected children. Continued improvement in screening approaches may be achieved by better understanding the psychometric features of parent-report screening tools in relation to observational measures,^{23,25} and by examining the effectiveness of different screening thresholds in relation to diagnostic accuracy and cost-effectiveness.²⁶ Additional new innovations in parent-report screening approaches include the incorporation of photographs into the questionnaire to illustrate items in a culturally unbiased manner,²⁷ combining multiple screening tools to improve sensitivity and specificity,²⁸ and free mobile applications (apps), such as **ASDetect** that augment descriptions of ASD characteristics with video examples and provide a video-led assessment of child behaviors. Studies are needed to validate the usability and accuracy of these apps, although there is empirical support demonstrating that the markers highlighted within the apps (e.g., pointing and showing) are predictive of an ASD diagnosis.^{29,30}

A growing appreciation of ASD as a condition marked by unique behavioral, neural, and genetic signatures that may precede noticeable clinical symptoms has resulted in a surge of prodromal and biomarker-seeking research which broadens the scope of future screening efforts. Of particular interest are potential biomarkers likely to facilitate gene-brain-behavior studies, diagnosis, or those that may act as prognostic markers. Observational studies continue to reveal that signs of ASD are subtle, but may emerge within the first year of life, particularly in the areas of social communication, attention, and motor development.^{24,31,32} Preliminary studies deploying eye-tracking technology to measure social visual engagement have demonstrated utility and accuracy in detecting markers of ASD in the first year of life.^{33,34} For the first time, structural and functional magnetic resonance imaging

(fMRI) studies of infants are beginning to predict later ASD diagnosis and core characteristics such as language outcome.^{35,36,37,38} Additionally, RNA expression profiles can classify toddlers with ASD at levels exceeding 80% accuracy.³⁹ While these findings suggest a future of exciting new tools for screening and diagnosis, they must be validated in other high-risk groups and in the general population, and they must be adjusted for broader use in order to be beneficial to the wider community.

Although engagement in early treatment has been associated with a range of positive changes including increases in social orienting, language ability, and overall IQ,^{3-5,40} no study has directly examined if children with ASD detected by early screening have better outcomes than those detected by other means, (e.g., parent or provider concern) an issue highlighted by the recent US Preventive Services Task Force (USPSTF) report¹⁰ on universal early screening. However, as noted by Dawson (2016),⁴¹ such a study would require large representative samples from across the country to be randomly assigned to either a screening or non-screening condition, and then followed to determine long-term outcomes and societal costs. Given that early treatment for children under age 3 years has been shown to result in positive gains,⁴² and has even been associated with an increased potential to lose an ASD diagnosis altogether,⁴³ such a study can be controversial.

While a considerable investment of time and resources would be required to conduct new randomized controlled trial (RCT) studies to specifically address concerns raised by the USPSTF, there are opportunities and study designs that could be leveraged using existing resources in the short term. First, data could be examined from within sample cohorts that include clinical longitudinal data from toddlers detected via screening as well as toddlers detected via other means (e.g., parent or clinician concern). Second, exclusively within cohorts of screen-detected toddlers, researchers could examine outcomes of children detected

at identical early ages via screening but that contained a subgroup of toddlers who started treatment well beyond the screen-detected age. In this way, the impact of very early treatment engagement as afforded by screening could be more directly examined. In terms of new, future studies, in instances where a traditional RCT design (intervention versus no intervention) may not be feasible and the health impact is high, other complex forms of RCT models could be used as well as utilizing administrative data. Several states collect state-level data on youth who receive ASD screening and subsequent developmental outcomes. This may afford an opportunity to compare children with and without early screening in terms of variations in developmental outcomes.

While early detection, whether achieved through universal screening or by other mechanisms such as parent or clinician concern, is an essential step in the health care process for ASD and deserves more research attention, it is just one step on the path to identification and eventual treatment. Screening in and of itself does not determine if and when parents actually follow through with subsequent diagnostic evaluation and treatment engagement, nor does it determine the quality and benefits of such treatment. Another key gap in the field is the lack of studies examining the many important factors that follow *after* screening has occurred.⁴⁴

There is indeed a growing appreciation of the importance of implementation science methods to examine contextual factors (e.g., mode of screening delivery) that may impact successful screening uptake. Some studies are currently underway, performed by researchers funded through the National Institute of Mental Health **ASD Prevention, Early Detection, Engagement and Services (ASD-PEDS) Network**. Another important factor is comprehensive tracking of treatment participation, which is essential to determine the long-term outcomes of children detected early by screening. To date, most studies do not report treatment engagement, and if it is reported, it is often at a very coarse level (e.g., number of hours).

In order for screening to be effective, ample evaluation centers must be available with appropriate ASD diagnostic expertise. Indeed, uncertainty regarding where to send a toddler for an evaluation is a barrier to screening noted by over 75% of pediatricians.¹⁴ Therefore, an increase in the number and accessibility of evaluation centers is necessary, based on population and expected rates of ASD. Likewise, significant enhancement of the screening and evaluation system is meaningful only if high-quality treatment providers are available and affordable. Some efforts have been made, such as **"Birth to Five: Watch Me Thrive!"**, which is a coordinated Federal effort to raise awareness about the importance of universal early behavioral and developmental screening. This resource offers a collection of research-based screening tools for children under the age of 5. However, there is still a need to investigate more cost-effective modes of treatment delivery, such as those that are either partially or fully deployed by parents.³

An increase in the number of toddlers screened and identified as possible ASD²⁰ also calls for the need to standardize policies regarding eligibility for *IDEA Part C* services, the Federal program that funds intervention services for children showing delays, including autism, from birth through 2 years of age. Generally, toddlers must first qualify for basic Part C services by exhibiting a particular state-mandated level of delay (usually a 25% delay in two or more areas), which often provides for just a few hours of speech or occupational therapy. Although autism is an automatic eligibility category, a child must be identified as either ASD or showing signs of ASD in a separate evaluation visit in order to be eligible to receive ASD-specific treatment. Currently, there are no guidelines mandating that all toddlers receiving Part C services should be examined for possible ASD. Even once a child is referred for an in-depth ASD evaluation, there are no policies regarding specific diagnostic and other evaluation tools that should be used to determine if a child is eligible for ASD-specific services. Unsurprisingly, many toddlers already receiving Part C

services for a developmental delay have not been properly evaluated for ASD. Even more concerning, the vast majority of toddlers with ASD (at least 75%)⁴⁵ who will go on to qualify for special education at school-age are still not

identified in time to receive early intervention. Providing clear guidelines regarding ASD detection and subsequent treatment eligibility through Part C will help to eliminate these deficiencies.

DISPARITIES IN ASD SCREENING AND DIAGNOSIS

DISPARITIES IN ASD SCREENING

The barriers that limit screening during well-child visits have immediate service access implications for children from diverse backgrounds. Overall, ASD screening rates during primary care visits range from 1-60%;^{7,13,46} some of the variability in use of standardized screening is based on children's sociodemographic characteristics. For example, screening may occur less frequently among Spanish-speaking families compared to English-speaking families.⁴⁷ Families with low levels of maternal education exhibit higher screen positive rates on the M-CHAT(-R);^{48,49} but are less likely to follow up with diagnostic evaluation, suggesting that these families are at risk for being underserved.⁵⁰ Additionally, consistent use of screening tools may depend on insurance reimbursement; children from low-income families may be more likely to be screened during check-ups since it is often reimbursed by Medicaid,⁵¹ but may not be covered by private insurance.

Research has shown that children from minority backgrounds are diagnosed on average more than a year later than their White peers.⁵² However, it has been demonstrated that when physicians follow a standardized screening protocol, including immediate referral for screen-positive cases, disparities in age of diagnosis are reduced to approximately 1 month.⁵³ Therefore, access to screening for all children, regardless of sociodemographic characteristics, language spoken at home, and geographic locale, is crucial to reduce existing disparities that impact life-long outcomes.

In addition to dedicating more resources to early screening in underserved communities, a corresponding increase in funding adequate evidence-based diagnostic evaluations will avoid lengthening waitlists.⁵⁴

VALIDITY OF SCREENING INSTRUMENTS IN DIVERSE GROUPS

A number of studies have examined ASD screening tools in different languages and cultural settings within the US and across the world.^{50,55,56,57,58} The variability of results from these studies indicate that there is a need for additional research to adapt tools that will be valid (i.e., demonstrate adequate sensitivity and specificity) in diverse populations. Factors including low educational attainment, language/literacy, rural versus urban locale, race, and ethnicity also impact screening reliability and validity⁵⁷ as well as screen-positive rates.^{50,58} Studies examining medical or state records for specific mention of ASD screening and diagnosis would be helpful in documenting disparities and also in tracking improvements based on policy changes or improved access to care.

The recent USPSTF report on universal ASD screening¹⁰ specifically highlighted the gaps in research on health outcomes of children detected through screening, particularly in those from minority and low-income families. It will be critical to evaluate the quality of screening instruments and programs in diverse samples of children, including

long-term outcomes. Implementation studies examining the translation from research settings to community settings with diverse populations, including examining fidelity of adhering to screening protocols, also is a critical gap in the existing literature.^{58,59,60,61}

DISPARITIES IN ACCESS TO DIAGNOSTIC SERVICES AND AGE OF DIAGNOSIS

Differences both in prevalence rates and age of diagnosis by sociodemographic characteristics likely relate to disparities in access to expert services. According to the most recent surveillance study by the Centers for Disease Control and Prevention's (CDC) Autism and Developmental Disorders Monitoring (ADDM) Network study,¹ White children were 20% more likely to have indicators of ASD in their school and health records than Black children, 40% more likely than Asian and Pacific Islander children, and 50% more likely than Latino children. A variety of factors, including economic challenges,⁵⁰ geographic distance between families and service providers,⁶² reduced professional resources and capacity,⁶³ and characteristics impacted by cultural knowledge, such as stigma⁶⁴ often contribute to diminished service availability and utilization in rural, minority, or other disadvantaged communities. A primary barrier to ASD early diagnosis is the limited availability of diagnostic clinics with providers trained in ASD diagnosis, leading to long waiting lists and poor reimbursement for comprehensive diagnosis.⁵⁴ This limited availability is especially pronounced in resource-poor and rural areas, with many children not diagnosed until entry into the school system.

In addition, family level variables such as insufficient financial resources, lack of insurance coverage, language barriers, geographic isolation, and limited knowledge of or experience with complex healthcare systems, may be barriers to the timely diagnostic evaluation of an at-risk child.⁶⁵ Overall, there is limited research that documents these systemic- and individual-level barriers that exist

from early ASD screening to appropriate diagnosis to early intervention.⁶⁶ Finally, and perhaps most importantly, there is a need for prospective studies that demonstrate that equal access to high-quality screening, with immediate referral for screen-positive cases to diagnostic evaluation and early intervention services, will reduce disparities in prevalence, as well as any disparities in long-term outcomes for children with ASD.

Practitioner efforts that can help to reduce disparities in diagnosis include increasing psychoeducation to raise awareness and reduce stigma, building external professional networks, promoting continuing education programs, using alternative service delivery models (e.g., telehealth, web-based, community health workers) or settings (e.g., schools, child care centers, mobile clinics) for screening/diagnosis, and providing wraparound services that address additional stresses (e.g., chronic illness, unemployment, lack of insurance) often faced by individuals in underserved communities. Finally, it is clear that children are not often well-tracked from the time of ASD screening to receipt of services.⁵² It is imperative to have a system in place that can assure children and families adequate, timely, and appropriate services as they move through the identification, referral, and treatment process.

VALIDITY OF DIAGNOSTIC INSTRUMENTS ACROSS SPECIAL POPULATIONS

There is general agreement that the best approach to ASD diagnosis includes both parent interview and an observational assessment of the child,⁶⁷ such as the Autism Diagnostic Interview-Revised (ADI-R) and the Autism Diagnostic Observation Schedule (ADOS-2). The ADI-R has been translated into 17 languages, and a small number of studies have examined the validity of the ADI-R in different countries with varying results.^{68,69,70,71} With respect to validation studies with diverse populations in the US, researchers found that the sensitivity and specificity of the ADI-R with a US-based Spanish-speaking population

of parents of children with ASD were lower⁷² than values previously reported for mostly White, middle-class respondents.⁷³ The communication domains were found to be especially problematic for parents whose primary language was Spanish when reporting on children who spoke mainly English.⁷² Little is known about the validity of the ADI-R among low-income families in the US. The ADOS-2 has been translated into 19 different languages; however, cross-cultural validation studies of the ADOS-2 have not been identified.

The development of screening and diagnostic tools has largely been accomplished using data from boys, which might put other underserved populations of ASD at a disproportionate risk of not receiving a clinical diagnosis. Based on recent literature, there appears to be a diagnostic gender bias, which means that girls are less likely than boys to meet diagnostic criteria for ASD at comparatively high levels of autistic-like traits.^{74,75} Girls may also exhibit different symptoms from boys, which may make current screening and diagnostic tools more likely to miss ASD in girls.^{76,77,78} It is important that future research addresses

the gender differences in ASD, both biological and behavioral, in the development of diagnostic tools. Also at risk of being underdiagnosed are individuals with ASD that have other co-occurring developmental conditions. A third of children with ASD also have an intellectual disability,¹ and many individuals with ASD have a dual diagnosis of attention-deficit/hyperactivity disorder (ADHD); having multiple conditions often leads to a misdiagnosis or a delayed ASD diagnosis.⁷⁹ While research is necessary to develop tools that account for the overlap in symptomology, health providers must consider multiple diagnoses during evaluation.

In addition, increasing numbers of adults are presenting to clinics for first-time diagnoses of ASD, and recent studies suggest that many adults with ASD may be unidentified and living in the community without appropriate supports.^{80,81} There is a need to improve diagnostic tools that are specific for adults; this will be discussed in more detail in Chapter 6: How can we meet the needs of people with ASD as they progress into and through adulthood?

WORKFORCE

The increased prevalence of diagnosed ASD cases over the past two decades has led to a need for a larger workforce trained in the identification and diagnosis of these disorders, including psychologists, psychiatrists, developmental pediatricians, neurologists, and speech and language pathologists. Early detection of ASD will require training those professionals who come in regular contact with young children, including primary care providers and child care providers, to incorporate effective screening and referrals in their daily practice patterns. In response to

this need, CDC, in collaboration with the Health Resources and Services Administration (HRSA), developed a web-based education program, the **Autism Case Training**, to inform healthcare providers on fundamental components of identifying, diagnosing, and managing ASD through real-life scenarios. Promoting, refining, and delivering similar education programs is a critical factor in building a workforce that can effectively serve individuals with ASD and their families.

Evidence demonstrates that healthcare professionals are less likely to detect ASD using developmental surveillance without the use of screening tools. Even experienced professionals may miss or misjudge symptoms during a brief observation.¹⁸ However, primary care providers face barriers to implementing screening that include the time necessary to identify ASD, the cost of conducting screening and the reimbursement for this work, and having appropriately trained personnel in their offices or referral networks. Also, practitioners may lack the technical training to review and compare complex psychometric information on the quality of developmental screening tools. Training for this workforce is needed to improve their ability to screen effectively, recognize ASD symptoms, communicate clearly with parents, and refer appropriately for evaluation and intervention services.

Parents may not recognize signs of developmental delay, or may have concerns about their child's development but do not know how or when to act on those concerns. There is a need to raise public awareness of the early signs of ASD, to encourage parents to observe and track their child's development, and to encourage them to discuss their concerns with their child's doctor, teachers, and other care providers. The "**Learn the Signs. Act Early.**" campaign developed by CDC, and the "**16 Gestures by 16 Months**" series developed by the **First Words Project** are examples of strategies that can be utilized to raise awareness and facilitate parent-provider collaborations. However, there is still a critical research gap on understanding how parent concerns can impact parent engagement in acting on referral for diagnosis and early intervention.

Addressing gaps in our understanding of how healthcare professionals can best reach families from underserved communities continues to be a challenge. There is an

opportunity to improve the identification of ASD through materials prepared in languages spoken by target groups within these communities, but even more important are efforts to implement culturally competent practices and engage a workforce with greater cultural diversity in order to better address the needs of culturally diverse populations. For example, outreach activities held in places of worship and other community gatherings where families feel more comfortable may improve parent-provider partnerships and lead to increased identification of ASD.

Some important service initiatives to address screening and diagnosis training are ongoing, but there is a need for additional efforts. The AAP supports universal screening for ASD and provides training to pediatric providers through several formats (publications, webinars, and face-to-face conferences). Leadership Education in Neurodevelopmental and Related Disabilities (LEND) and the University Centers of Excellence in Developmental Disabilities (UCEDDs) also provide training to practitioners from over a dozen healthcare disciplines. Despite the recommended guidelines for utilizing these resources, the professional community is not reaching most of the families and children in need of early intervention. Therefore, service-relevant policies need to make professional development and training more available as well as dedicate more resources in order to expand the workforce to address unmet needs for early screening and diagnostic services, including access to care. Furthermore, there is a need for improved policies to facilitate the collaboration of community-based programs and social supports with professional services.

LINKAGE TO INTERVENTION SERVICES AND OTHER SUPPORTS

It is critically important that children with ASD are identified early so they can be referred to intervention programs that address their individual needs. Eligibility criteria and the lead agency for early intervention vary by state (health agencies in some states, and child welfare or education agencies in other states). Similarly, some states or regions have more comprehensive insurance coverage and/or more coordinated systems of healthcare than others. Even in better-resourced areas, families are often faced with many complex steps from screening to diagnosis to treatment. Most infants and toddlers with a diagnosis of ASD miss the opportunity to receive early intervention services.⁴⁵ This service need is unmet to an even greater degree in children from minority backgrounds.⁵² There is a need to improve access to early screening and to increase the accuracy of screening tools because these are the gateway to early intervention services. Coordination of a care team that includes healthcare and childcare providers is critical to address gaps in screening, begin to break down barriers for families to act on screening results, and support family engagement in intervention services.

Nearly half of children with ASD have private insurance; the other half have insurance provided by Medicaid or the state-based **Children's Health Insurance Program (CHIP)**, or dual private and public coverage.⁸² However, about half of families of children with ASD report that their insurance coverage is inadequate to meet their myriad of complex needs and costs. As noted earlier, reimbursement for ASD screening may improve screening rates and more readily become a standard procedure in practices. A systemic

issue is that some insurance plans do not cover quality treatments, such as applied behavior analysis (ABA), or may place limits on essential behavioral, medical, or other healthcare. Additionally, family social service supports, which contribute greatly to meeting the needs of the child, are not covered. These limitations often leave families struggling in many ways, which results in significant financial and familial burdens. In fact, nearly half of families of children with ASD say their child's health condition has caused major problems for the family and in some cases bankruptcy and other family disruptions, such as divorce or job loss.^{83,84}

Currently, families must navigate different sectors of service in terms of information, provision, and funding (e.g., medical providers, local government, education) all within a very short period of time (from noted concern to early intervention age eligibility cut-offs). The different service sectors are not coordinated and often do not communicate with each other, particularly across health and social service agencies. Systematic barriers for families include considerable differences in the type and amount of services supported by insurance plans, geographic differences in type and amount of services available, and inequities and disparities existing across counties and states. Lastly, systems do not take into account families' concerns about stigma, the reluctance of professionals to make a diagnosis or share concerns about red flags of ASD in very young children, missed or false positive diagnoses, and the need for earlier evaluations and re-evaluations of very early assessments as symptoms are unfolding.

SUMMARY

Significant advances have been made toward early identification of individuals with ASD, so they can be linked to appropriate interventions, services, and supports in as timely a manner as possible. However, gaps still remain. There is a need to validate tools in diverse settings and populations. There is a need to evaluate the effectiveness of universal screening for improving outcomes in ASD. There is a great need to understand the disparities in access and/or utilization of screening and diagnostic tools, and entry into intervention services. In addition, research is needed to develop, adapt, and validate tools that will enable detection of autism in children with intellectual disabilities, girls, and adults. The challenges and barriers include gaps in the evidence base for the benefits of early detection in

diverse populations and settings; an insufficient workforce with expertise in ASD diagnosis and intervention; lack of medical home for families of children with ASD; the need for continued insurance reform; disparate and uncoordinated service sectors; and the lack of an infrastructure to track children and families in order to evaluate the efficacy of service systems. There have been important strides in the area of early detection of ASD features and in demonstrating the impact of early intervention. Yet, there are significant challenges and barriers to implementing screening, diagnostic, and treatment services broadly and reducing disparities in access and utilization. The way forward is reflected in the three objectives proposed for Question 1.

OBJECTIVES

OBJECTIVE 1: Strengthen the evidence base for the benefits of early detection of ASD.

Examples:

- Implement innovative designs to evaluate the benefit of universal screening for ASD, including research that addresses the specific research gaps noted by the USPSTF report.
- Conduct studies focusing on the differences and needs of special populations such as girls and individuals with intellectual disabilities.

OBJECTIVE 2: Reduce disparities in early detection and access to services.

Examples:

- Improve family engagement and help build an awareness of healthy developmental milestones and warning signs of concern.
- Demonstrate the validity of different screening and diagnostic tools for culturally diverse communities.
- Increase services in high-poverty and underserved regions; improve inclusion of these populations in research.
- Address differences in state policy requirements for Medicaid and the requirement of a diagnosis to receive services.
- Develop a culturally competent and more culturally diverse workforce.

OBJECTIVE 3: Improve/validate existing, or develop new tools, methods, and service delivery models for detecting ASD in order to facilitate timely linkage of individuals with ASD to early, targeted interventions and supports.

Examples:

- Continue research on the potential translation of biomarker findings into feasible and valid screening or diagnostic tools.
- Increase coordination and personalization of screening, diagnosis, and early intervention services through use of the medical home model, person-centered planning, or other service models.
- Conduct research to better understand and develop strategies to address reasons for lack of compliance with screening recommendations; address barriers to universal screening.
- Analyze the impact of insurance reform and national policy on coverage for screening, diagnosis, and intervention for children with ASD and their families.
- Evaluate innovative service delivery methods (e.g., use of technology) to improve detection methods and increase access.

CROSS-CUTTING OBJECTIVE

The topic of girls and women with ASD is mentioned in several chapters of the *Strategic Plan*, indicating the Committee's strong interest in this area. To combine the priorities for research and services to understand and better serve the needs of girls on the autism spectrum, this "cross-cutting" objective was developed. Individual projects assigned to this objective will be coded to different questions of the *Strategic Plan* depending on which aspect of ASD in girls and women is being studied. This will ensure the funding associated with those projects will be counted toward the totals of their respective questions, but also allows the projects to be added together into a single objective. The goal of a single "cross-cutting" objective on girls and women with ASD is to encompass the numerous research and services priorities identified by the Committee throughout the *Strategic Plan* and allow for this area to be identified as a priority for funders.

CC1. Support research to understand the underlying biology of sex differences in ASD, possible factors that may be contributing to underdiagnosis, unique challenges that may be faced by girls/women on the autism spectrum, and develop strategies for meeting the needs of this population.

Examples:

- Conduct research on the underlying biology of ASD in girls/women (differences in brain structure, function, physiology) and how this may create differences in phenotype.
- Identify risk and resilience factors that contribute to sex differences.
- Develop, adapt, or validate screening and diagnostic tools to detect ASD in girls.
- Develop strategies to meet the intervention, service, and support needs of girls/women with ASD.



QUESTION

2

WHAT IS THE BIOLOGY
UNDERLYING ASD?

Aspirational Goal: Discover how alterations in brain development and the function of physiological systems lead to ASD in order to enable the development of effective, targeted interventions and societal accommodations that improve quality of life for people on the autism spectrum.

INTRODUCTION

Current scientific evidence suggests that ASD results from subtle alterations during brain development that affect brain structure, function, and connectivity. However, our knowledge about its causes remains incomplete and significant gaps in science have hindered attempts to develop therapies to improve quality of life for individuals with ASD. Over the course of the last decades, several studies have revealed the role of prenatal or perinatal stressors and genetic contributors to the risk of developing ASD, possibly acting through changes in early brain development. The biological mechanisms by which known gene mutations cause syndromic ASD (i.e., the subtypes of ASD that are usually caused by a single genetic abnormality) by altering the underlying neural circuitry of the brain are under intense study. These genetic variants are associated

with remodeling of genetic material, changes to ion channels (which are the basis for cellular function and communication), and proteins that regulate cell-to-cell communication. Taken together, this research suggests there may be shared features of the underlying biology across the spectrum of autism. However, we currently know very little about the precise pathways that cause the circuit changes driving the core behavioral features in ASD, but new tools promise to accelerate this area of investigation. In addition, while there have been recent gains in understanding ASD developmental trajectories and the nature and prevalence of co-occurring conditions in persons with ASD, more work is needed to understand these aspects of ASD and develop strategies to target them successfully.

MOLECULAR MECHANISMS AFFECTED BY GENES IMPLICATED IN ASD

Genetic studies of ASD have identified more than 100 high-risk genes and estimate that several hundred additional genes of this type will be identified in the future.¹ It seems likely that over 1,000 genes conferring lower degrees of autism susceptibility will also be identified in the future.^{2,3,4,5,6,7} At present, the known functions of these genes converge on biological processes important for neuronal communication and regulation of the expression of genes and proteins.

The discoveries of gene mutations that cause syndromic ASD (e.g., tuberous sclerosis complex (TSC), Rett syndrome, Fragile X syndrome, Phelan McDermid syndrome), and the dozens of rare *de novo* (spontaneous) mutations that disrupt gene function in ASD⁸ have enabled scientists to explore the biological effects of the various involved genes in cellular and animal experiments. This has led to an explosion of research examining how these mutations alter the biology of cells and investigating their effects on neural circuitry and behavior. On the horizon are genetic tools that will enable the introduction of mutations into non-human primates,^{9,10} which possess a much greater behavioral repertoire and a more human-like brain than rodents or other animal models. However, these experiments will need to be designed carefully because the numbers of matched control and mutant animals need to be very small as compared to rodent studies.

A major advance over the last few years is the ability to take skin or blood cells from persons with ASD, create induced pluripotent stem cells (iPSCs), and differentiate these cells into neurons, which can enable the study of neural function at the cellular level. This new technology

allows scientists to study the effects of ASD mutations in human brain cells in addition to commonly used transgenic animal models. Furthermore, iPSCs are attractive models for identifying molecular phenotypes linked to syndromic ASD, but a more high-throughput means of identifying and validating their relevance to ASD is needed. A strategy for identifying relevant molecular phenotypes in iPSCs from the much more common idiopathic ASD (ASD of unknown cause) remains a daunting task. In addition, new research may make it possible to grow “brain organoids,” which are clumps of brain tissue partially organized to have some features of the human brain, from iPSCs. These partially matured “mini-brains” can be grown in a culture dish and can be used to enable the study of the early development of brain structures that occurs *in utero*, as well as the cellular and circuit abnormalities related to ASD-linked mutations.^{11,12} However, these *in vitro* studies will introduce a number of variables related to culture conditions, and deliberate actions will be required to evaluate reproducibility.

Though new iPSC and brain organoid technologies allow for the study of human cells and circuits derived from persons with ASD, there is no substitute for careful structural and transcriptomic studies in postmortem tissue which remains exceptionally rare. Efforts need to be redoubled to increase the accessibility of brain tissue from well-characterized ASD cases. The establishment of collaborations like the National Institutes of Health (NIH) **NeuroBioBank** and **Autism BrainNet** facilitates the distribution of high-quality, well-characterized human postmortem brain tissue for the research community.

Enhancing efforts to increase public awareness about the value of tissue donation for understanding brain disorders like autism will most effectively advance the science.

Studies of postmortem brain tissue from persons with ASD have demonstrated decreased expression of sets of genes related to synaptic function, including many of the known ASD risk genes. Surprisingly, despite the 4:1 male to female ratio in ASD, these changes in synaptic gene expression were not more evident in males than females. However, there was an observed upregulation of genes related to microglial and astrocytic function (brain cells that provide support for neurons) that was more pronounced in males.¹³ These gene expression differences may help explain why ASD occurs more frequently in males. Moving forward, new gene expression mapping technologies have the potential to better characterize altered patterns of gene expression in specific brain cell types, offering the opportunity to precisely associate gene expression differences at a cellular level. In these studies, it will be critical to include an examination of gender-related differences in gene expression.

The impact of sex chromosomes on differences in gene expression between males and females – and how this may contribute to ASD – is also an area of research needing additional attention. The role of genes on the Y (male) and X

(female) chromosomes extends beyond reproduction-related functions. Studies have suggested that genes on the sex chromosomes may act as broad regulators of gene expression. Therefore, differences in gene regulation by X-X gene pairs in females versus X-Y gene pairs in males may have different effects on the dosage-dependent expression of other genes, including those implicated in ASD-relevant molecular pathways.^{14,15,16}

Another remaining challenge is to understand how the effects of hundreds of implicated genes converge to cause ASD's common features. And conversely, more work is needed to determine how individual genes and their interactions with early life events explain the biological basis of the heterogeneity of ASD symptoms, which range from severe intellectual disability and absence of verbal language, to mild social deficits with normal cognitive function. With regard to the 4:1 male to female ratio in ASD mentioned above, further work is also needed to understand the phenotypic differences between girls and boys with ASD, and how these differences should inform development of screening and diagnostic tools, interventions, and services that meet the needs of both girls and boys on the autism spectrum.

STRUCTURE AND FUNCTION OF BRAIN CIRCUITS IN ASD

STRUCTURE AND FUNCTION

Autism is characterized by atypical patterns in physical brain connections (structure) and in how regions communicate with each other (function). Brain structure in individuals with ASD can be compared to typically developing children using advanced magnetic resonance imaging (MRI) techniques to measure size and shape of brain regions over time, as well as diffusion tensor imaging (DTI) to examine the structures of the major connections between brain regions. Brain circuit function can be investigated using non-invasive markers, such as functional magnetic resonance imaging (fMRI), magnetoencephalography (MEG), electroencephalography (EEG), and functional near-infrared spectroscopy (fNIRS). These studies have shown differences in activation patterns in individuals with ASD in response to sensory processing of visual, tactile, auditory, and verbal stimuli.^{17,18,19,20}

Although non-invasive measures of brain connectivity have demonstrated differences between brain regions in persons with ASD compared to controls, it is unclear how these differences account for the heterogeneity in ASD symptoms. Earlier findings from fMRI, DTI, and pathological studies highlighted a pattern of reduced long-distance connectivity and increased local connectivity.²¹ While these principles still largely hold, newer research has revealed greater nuance and specificity.^{22,23}

On the gross anatomical level, the brains of autistic individuals appear normal. Microscopic studies have reported disordered cell organization with smaller, more densely packed neurons in many regions of the limbic

system, a part of the brain which is known to play an important role in learning, memory, and emotions. One of the more reproducible findings is a reduction in the number of Purkinje cells in the cerebellum.

Current evidence suggests that early brain overgrowth is present in approximately 15% of 2-year-old boys with ASD, but is much less common in girls.^{24,25} Brain enlargement relative to body size in this subset of boys persists at least through 5 years of age²⁶ and is associated with lower language ability at age 3 and reduced intellectual ability at age 5.²⁷ Currently, the prevailing theory is that early brain overgrowth normalizes during adolescence and adulthood,²⁸ although this is based on cross-sectional studies. A truly longitudinal analysis, where the same individuals are imaged throughout life, is needed to clearly establish this. Studies at the cellular level have begun to describe differences in neuronal growth and organization in ASD brains.

Interestingly, recent studies have identified significant inter- and intra-individual variability in neural functioning in ASD. Heterogeneity in the ASD phenotype also contributes to greater functional variability within ASD groups. To address this heterogeneity, a greater number of studies are examining dimensional traits in large samples of ASD and neurotypical groups.

Ongoing work is linking these functional and structural differences to core features of ASD including studies on social communication, language, and restricted and repetitive behaviors. Recent work has identified neurobiological correlates of sensory processing in autism,^{29,30,31} including

findings of reduced modulation of connectivity between the thalamus (a brain structure responsible for relaying sensory and motor signals to the cerebral cortex as well as regulating consciousness, sleep, and alertness) and cortical regions in response to sound or touch. The extent of this reduced connectivity was related to parent reports of sensory over-reactivity.³⁰ In the domain of touch, reduced response was seen in ASD children in social-emotional brain regions to a soft caress compared to typically developing children, while increased activation was seen in response to non-caress-like touch in the brain's primary sensory cortex. This over-activation may be related to the hyper-sensitivity to touch seen in some ASD individuals.

There is a need for a greater understanding of the relationship between intrinsic functional brain organization during rest and functional connectivity dynamics during task states. Additionally, there is a need for a better understanding of brain function and connectivity during tasks that better capture the complexity of real-world interactions for individuals with ASD.^{32,33}

CIRCUIT ACTIVITY IN ASD

As is true of almost all brain disorders, the symptoms experienced by individuals with ASD are linked to alterations in brain circuit function. Alterations in the formation of brain circuits that occur *in utero*, during infancy, and in childhood can have long-lasting impacts on circuit function in adulthood. During these early critical time periods, connections between brain regions are dramatically molded by brain activity and may be altered by injury or inflammation.

Identification of genes involved in syndromic autism enable the study of the human phenotypes associated with those genetic syndromes as well as phenotypes of genetic animal models carrying the same mutations. The study of several forms of syndromic ASD have revealed nervous system differences such as differences in abundance of certain cell types, in neural circuits, and in brain activity.³⁴ Environmental

insults, for example those due to infection *in utero*, premature delivery, or perinatal cerebellar hemorrhage also alter the construction of brain circuits leading to ASD.

There are continuing challenges in applying animal models to understand the biology of autism. Because, in many cases, autism impacts uniquely human aspects of social-communicative behavior (e.g., spoken language), developing and measuring analogous phenotypes in animals has proven difficult. Because autism impacts brain regions not developed in some animal species, some neural circuitry is not readily amenable to study in these models. Moving forward, increased use of species more comparable to humans in both biology and behavior will be necessary. Notably, genetic tools previously limited in application to mice can now be applied in rats and even non-human primates, such as macaques and marmosets. Furthermore, the circuit alterations that have been described in ASD models vary considerably. Variability due to methodological differences among labs may diminish the value of the research findings. Incorporation of a more standardized and systematized approach to studying the altered circuits in ASD models could be valuable to the field.

Fortunately, new powerful technologies for interrogating and modulating brain circuits are revolutionizing neuroscience. The BRAIN Initiative is a multi-Federal agency, public-private partnership in the US to advance brain circuit neurotechnologies and also engage multiple international efforts. These technologies promise to expand the ability to understand brain circuit differences due to genetic and environmental influences that contribute to many diseases, including autism. The brain circuit alterations implicated in ASD in animal models can now be explored in detail using these new technologies to map neural connections over large expanses of brain,³⁵ record from a large number of neurons during a behavioral task, and turn on or off specific types of neurons to understand the nature of brain circuit alterations caused by biological mechanisms tied to ASD.

ROLE OF IMMUNE SYSTEM IN BRAIN DEVELOPMENT AND ASD

Increasing evidence suggests immune dysregulation and neuroinflammation may be implicated in the severity and pathogenesis of the autism phenotype.^{36,37,38} One recent meta-analysis of 17 studies identified significantly altered concentrations of immune regulators known as cytokines in ASD patients compared to healthy controls, adding to the evidence of increased inflammatory signals in ASD.³⁹ Despite many studies demonstrating altered levels of immune biomarkers and abnormal immune function in both the peripheral and central nervous system in ASD, it is not clear whether the immune system plays a direct role in the development of the disorder via an impairment of neurodevelopmental processes. Several recent studies suggest that maternal immunological factors may play a role in the pathogenesis of ASD during prenatal development.^{40,41,42,43,44,45,46}

Microglia are innate immune cells that reside in the central nervous system and are activated in response to infection or inflammation. Even in their so-called resting state, they perform critical functions, including regulating the number of neural precursor cells,⁴⁷ maintaining synaptic organization,

and synaptic pruning (removing excess or underutilized synapses during development).^{48,49} Analyses of autism brain tissue reveal alterations in genes that control microglial activation states and an association between microglia dysregulation and neuronal activity.⁵⁰ Evidence from human postmortem studies have found increased microglia activation, density, or size in various brain regions.^{51,52,53} Animal studies have also shown that microglia-mediated synaptic remodeling is abnormal in a mouse model of autism.⁵⁴ In addition, an increase in activated microglia in the amygdala, which plays a primary role in the processing of emotional reactions, was observed in a subset of human cases (two out of eight).⁵⁵

Further investigation of the role of microglia in animal models of ASD are warranted based on our emerging understanding of their role in normal development and potential contribution to ASD phenotypes. In addition, more studies are needed to identify the roles of molecules secreted by immune cells on brain development and function.

DEVELOPMENT, NATURAL HISTORY, AND VARIABILITY IN ASD

BRAIN DEVELOPMENT, DEVELOPMENTAL TRAJECTORIES, AND NATURAL HISTORY OF ASD

ASD is a developmental disorder, yet most studies of brain structure and function have focused on data collected from a discrete ASD population at a specific point in time or from postmortem brains. More studies are needed that will enhance our understanding of brain development, through longitudinal studies that gather imaging data (using methods such as structural and functional MRI and electroencephalography) from the same set of subjects repeatedly over an extended study period. Furthermore, advances in human imaging technology and longitudinal study designs may provide an opportunity to better distinguish true causes from consequences of specific pathological findings by making it possible to image brain tissue in live subjects throughout the lifespan. These kinds of studies will require standardized acquisition parameters to enable comparability across studies, and robust data sharing policies should be in place to enable expert analysis of the data by a variety of computational scientists.^{56,57}

Although defined behaviorally, the identification of causative genetic variants has begun to suggest the neurobiological basis of ASD. Many of these variants have been found to converge on basic processes in early brain development, such as cortical organization, synapse formation and function, the balance between neuronal excitation and inhibition, and the development of robust, functional neuronal networks that may impact early perceptual and cognitive processes.^{34,58} These processes may be measured through functional and structural neuroimaging methods well

before behavioral signs of atypical development emerge. Historically, research on early markers has focused on infant siblings of children with ASD, not only because they are at heightened risk for ASD and other developmental delays (prevalence estimates of ASD up to 20%), but also because they are identified prenatally and can be followed from birth.^{59,60,61,62,63,64} This body of research has led to the identification of atypical behaviors – particularly in the social domain – within the first years of life,⁶⁵ with some evidence of motor delays⁶⁶ and altered patterns of social attention⁶⁷ within the first year.

The brain connectivity changes that underlie autism are not static; their manifestations appear during the dramatically dynamic period of brain development and continue to change over the lifespan of the individual. Therefore, understanding the biology of autism requires large longitudinal studies to chart the trajectory of neural circuits over time, including how they adapt to inborn wiring errors and environmental exposures. Studies are needed that include pregnancy and follow maternal exposures and response, fetal development, and brain response to events that occur *in utero* and perinatally. Fortunately, new imaging techniques may enable safe study of the developing brain during prenatal development. The genetic and phenotypic heterogeneity of ASD are daunting, making generalization of findings dependent upon large numbers of subjects. Furthermore, the measures in these studies are often complex and subject to variability in their acquisition or analysis. This makes them difficult to reproduce and diminishes their value. To compare among individuals requires standardization; variability needs to be minimized and then measured for inclusion in the analysis.

The Lifespan Connectome Project is one example of a sophisticated brain imaging study of a large sample of typically developing individuals across the lifespan.

Methods to examine brain development are now more powerful, and normative data in typical development are needed to inform the studies in atypical development. One such collaborative effort includes the **Baby Connectome Project (BCP)**, which is a longitudinal study intended to provide a better understanding of how the brain develops from infancy through early childhood and the factors that contribute to healthy brain development. Variables of interest include patterns of structural and functional connectivity and their relationship to core behavioral skills from infancy to early childhood. Additional biological (e.g., genetic markers) and environmental measures (e.g., family demographics) are being collected and examined to provide a more comprehensive picture of the factors that affect brain development. Study data will be made available to the scientific community as it is measured. This knowledge will be tremendously useful in understanding brain function and how early interventions may shape our brain throughout our lifespan. Such coordinated efforts, with standardization of data acquisition and analysis, are needed in other imaging methods, such as EEG or MEG, and in the integration of multiple modes of imaging (structural and functional), particularly as they relate to later behavior. Ultimately, these studies will lead to the development of more scalable imaging tools that can be applied to large, more representative cohorts of infants and children. Additionally, as ASD manifests during development, it will be important to understand the critical windows during which circuit abnormalities may be reversible.

Research has suggested the prenatal period and first years of life are the critical time period for the onset and development of autism. Promising results have emerged from the **Infant Brain Imaging Study (IBIS)**, in which low- and high-risk (sibling) infants are being examined longitudinally with

structural MRI at ages 6, 12, and 24 months. Differences in white matter tract development from 6 to 24 months, particularly a slower change in a measure of fiber density, have been reported in infants who develop ASD.⁶⁸ More recently, the IBIS Network has identified hyperexpansion of the cortical surface area between ages 6 and 12 months in those infants who developed ASD, with brain volume overgrowth related to autism severity.⁶⁹ Another recent study found that infants who went on to develop ASD exhibited a significant excess of cerebrospinal fluid surrounding the brain at 6 to 24 months.⁷⁰ These studies have shown that brain changes can be observed as early as 6 months of life, even in children that show a regressive onset of autism at 18-24 months. At the present time, there have been virtually no studies in which high-risk children are studied earlier than 6 months, but this is a challenge worthy of future research efforts.

Going forward, large, organized longitudinal studies across the lifespan are needed to better understand developmental trajectories and natural history of ASD. Early results underscore the need to track and better understand longitudinal changes in brain development before autism symptoms emerge.^{68,69} Such measures can help us to understand the underlying mechanisms of atypical development and to elucidate the ideal timing and targets for early interventions. These measures can also link back to genetic mechanisms implicated in neurodevelopmental disorders more directly than behavioral assays. However, new mobile technologies are becoming available to monitor and quantify behavior over long time periods which should aid autism research in its integration of behavior with genetics, neuropsychological tests, neuroimaging, and other measures of biological function. The earliest behavioral and biological markers of risk, the unfolding of ASD in early infancy, and the comparison of these developmental processes in defined genetic syndromes with those found in familial risk groups remain relatively unexplored and offer promising avenues for new research. Other key

questions that can be answered through longitudinal studies of brain development include how features of ASD change over time,^{71,72} identification of adaptive brain changes in response to a developmental disturbance, changes that may be either beneficial or harmful, adaptive changes in brain function and structure that predict response to interventions, and developmental changes that inform core developmental features, such as language or nonverbal cognition.

PHENOTYPES AND SUBTYPES

Even within genetically determined syndromic ASD, there is considerable variability in the range and severity of symptoms. ASD most likely occurs due to a complex genetic architecture composed of multiple interacting biological pathways which combine to cause the phenotypic richness that can be observed even between siblings.⁷³ In preliminary studies that require replication, genetic associations have been found to segregate to some extent with specific phenotypes such as ASD with and without intellectual impairment,³ ASD with motor speech disorder,^{74,75} and other subphenotypes.^{76,7} Certain functional and structural changes in brain circuits are associated with specific phenotypes. The basic biology of circuits underlying aggression, anxiety, theory of mind (ability to understand and reason about the thoughts of others), language development, attention, and social cognition is still not completely understood, but fundamental advances would enable the search for disturbances in persons with ASD to eventually understand phenotypic variability. To accomplish this, it is necessary to standardize the classification criteria and include greater sample size in linking phenotypes to genetics, brain imaging, and brain tissue examination. In addition, MRI studies have traditionally been difficult in ASD individuals with intellectual impairment because of the requirement to remain still and understand directions in the MRI scanner; more of these studies have been done on high-functioning individuals. However, new methodologies have been developed that capitalize on the large body

of behavioral intervention knowledge that may enable high-quality imaging in ASD children with intellectual impairment, thus allowing for imaging studies on cohorts that are more representative of the heterogeneous ASD population.⁷⁷

Characterizing relevant aspects of heterogeneity is complex. Some factors, such as biological sex and genetic contributions, are developmentally stable and represent viable starting points for constraining and characterizing heterogeneity. However, within these categories, there is nested heterogeneity that has not yet been characterized in a consistent, reliable, or universal fashion. For example, distinct biological processes may be associated with cognition, language, social motivation, repetitive behaviors, or other factors that are challenging to quantify and are variable across development. Great progress has been made in developing nuanced and reliable measures of these constructs, and their integration into large studies of biology is necessary to elucidate distinct contributors to varying manifestations of autism. A notable challenge to autism research is the poor understanding of many of these factors in typical development; rigorous and longitudinal approaches to characterization and biological measurement in control samples are essential steps to developing a meaningful frame of reference for understanding atypical development in autism.

A broad challenge to clinical studies is heterogeneity in the diagnostic entity of autism itself. Rather than a singular diagnostic construct, autism represents a common behaviorally defined developmental pathway reflecting numerous etiologies and an unknown number of involved mechanisms. Previous studies with small sample sizes provide limited information and make it difficult to differentiate between what is true heterogeneity in the disease mechanism and what is simply variability due to underpowered statistics, inconsistent approaches, and diverse methodologies for measuring biological processes.

It will be important to conduct large studies involving thousands of individuals with autism with structured and consistent measurement according to rigorous methodological standards. For example, the **Autism Biomarkers Consortium for Clinical Trials (ABC-CT)** project is focused on developing biomarkers for ASD subgroups based on evaluations of brain function, visual attention, as well as behavior and speech in children aged 6-11. Such studies will enable investigators to determine the presence of mechanistically meaningful subgroups and, in the absence of true subgroups, to understand continuous relationships among biological processes and quantifiable aspects of the phenotype. It is critical that studies are designed with longitudinal components that can offer insight into changes associated with human development across the lifespan. The National Database for Autism Research (NDAR) provides a medium for making datasets publicly available to benefit from the universe of analytic resources beyond those maintained at individual laboratories carrying out the research.

BIOMARKERS AND PREDICTION OF ASD

The past few years have seen an increase in large-scale and longitudinal datasets. This, combined with increasingly sophisticated analytical techniques, has allowed for a more refined search for potential biomarkers of ASD. Pre-diagnosis fMRI response to speech combined with clinical behavioral measures in toddlers and young children predicted ASD prognosis.⁷⁸ Brain response to social stimuli (biological motion) accurately predicts whether boys have autism, but not girls⁷⁹ – again highlighting the need for a greater understanding of the neurobiology of females with ASD. Potential biomarkers are also being developed to predict treatment outcome success.^{80,81} There have also been advances in the identification of biomarkers that can predict autism risk in infants. Utilizing an infant sibling design, two promising biomarkers have been identified in infants as young as 6 months of age, including surface area expansion in specific cortical regions from 6-12 months of age⁶⁹ and the presence of excess cerebrospinal fluid surrounding the brain at 6-24 months.^{70,82} Ongoing work is using data-driven classification and prediction methods, which if combined with validation and replication efforts should further refine and develop these biomarkers.

CO-OCCURRING CONDITIONS IN ASD

ASD is associated with a wide range of co-occurring conditions that can cause an increased financial and psychological burden on families and caregivers as well as decreased quality of life for persons with ASD. Since 2013, much progress has been made in understanding the prevalence and underlying biology of conditions that commonly co-occur with ASD, including gastrointestinal (GI) disturbances, epilepsy, sleep disorders, psychiatric disorders, and immune/metabolic co-occurring conditions.

Additionally, more research is needed to investigate the potential role of these conditions in the underlying causes of ASD.

GASTROINTESTINAL CONDITIONS

GI symptoms and an inflammatory mucosal pathology have been demonstrated in several studies of ASD, and it has been estimated that up to 50% of ASD patients have feeding and GI conditions.^{83,84,85,86} A recent rigorous meta-analysis

of 15 studies in 2,215 children with ASD indicated a greater than two-fold elevated risk of GI symptoms among children with ASD than in those without ASD, and that children with ASD are more prone to specific symptoms of abdominal pain, constipation, and diarrhea.⁸⁷ Importantly, many of the genes implicated in autism are also expressed in the neurons outside of the central nervous system, including those that innervate the GI system. However, relatively little is known about autism risk gene functions in the digestive tract, as well as in sensory perception and motor function.⁸⁸ Genetic changes implicated in ASD may impact function of both the brain and GI system.

Additionally, alterations in the composition of the gut microbiome have been implicated as playing a causal role in ASD pathophysiology. Studies of fecal DNA have found certain bacterial clusters are overrepresented in children with ASD and GI complaints compared to neurotypical children with similar GI complaints, and demonstrate an altered microbial community with respect to both bacteria and fungi in ASD.^{89,90,91} Current research suggests that disturbances within the microbiota-gut-brain axis may contribute to the occurrence and development of ASD and that the application of modulators such as probiotics, helminths, and certain special diets may prove useful for the treatment of ASD.⁹²

EPILEPSY

Studies have shown that many of the risk genes for epilepsy and autism overlap.⁹³ Several studies demonstrate an increased prevalence of epilepsy in individuals with ASD, well above the general population risk, and some suggest that there is an increased risk of epilepsy in females with ASD when compared to males with ASD.^{94,95,96} The largest study to date comparing the autism phenotype in children with ASD with and without epilepsy found that children with ASD and epilepsy had significantly more autism symptoms and maladaptive behaviors than children without epilepsy.⁹⁷ Research in animal models suggests

that early life seizures may result in altered function of neurotransmitter systems and intrinsic neuronal properties during neurodevelopment that lead to the disrupted cortical connectivity that is characteristic of ASD.⁹⁸ The PREVeNT trial (Preventing Epilepsy Using Vigabatrin in Infants with Tuberous Sclerosis Complex) is an NIH-funded Phase II clinical trial that began in 2017 and will assess whether anti-epileptic treatment can prevent development of epilepsy in infants with TSC who display EEG biomarkers of abnormal brain activity prior to onset of seizures ([NCT02849457](#)).

SLEEP AND SENSORY DISORDERS

ASD is frequently accompanied by a variety of sleep problems that worsen daytime behaviors and core symptoms such as stereotypic, self-injurious, and repetitive behaviors. Studies indicate the prevalence of sleep problems in ASD are as high as 50-80% and that children with ASD have higher prevalence of sleep disorders than children with other neurodevelopmental disorders.⁹⁹ The most common sleep problems reported in ASD are sleep-onset insomnia, or difficulty initiating sleep, and sleep-maintenance insomnia, or decreased sleep duration. Several neurotransmitters, including serotonin, melatonin, and gamma-aminobutyric acid (GABA) play a vital role in the maintenance of sleep-wake cycles, and abnormal levels of these neurotransmitters have been described in ASD.¹⁰⁰

Hyper- and hypo-sensory abnormalities are frequently observed in individuals with autism and may have negative impacts on cognitive performance, social interactions, and stress. Recent work in animal models suggests that peripheral disorders have widespread impact on behavior in experimental animals.⁸⁸ A question for future research is whether hard-wired abnormalities that disturb sensory processing secondarily contribute to alterations in brain circuits involved in behavioral and social functions. This may lead to novel ways to therapeutically alter the developing child's sensory environment in order to

improve later-developing social skills. Further, it will be important to explore whether and how impairments in sensory processing during infancy may alter early brain development and contribute to the development of social and cognitive impairments later in life.

PSYCHIATRIC DISORDERS

It has been estimated that 69% of patients with ASD suffer from co-occurring psychiatric disorders and symptoms.¹⁰¹ As with the general population, age appears to be a relevant factor for psychopathology in patients with ASD. One study of adults with Asperger's Syndrome showed that the most

frequent co-occurring conditions were depression and anxiety disorder, and that obsessive-compulsive disorder and alcohol abuse/dependence were also observed.¹⁰² Recent studies reveal that consistently high levels of psychological symptoms and distress occur across the adult lifespan in ASD, where individuals with more severe depression and anxiety disorders demonstrated more severe ASD symptoms.^{103,104} At the molecular level, one study suggests that a variation in the serotonin 2A receptor gene may modulate the severity of depression symptoms in children with ASD.¹⁰⁵

RESEARCH POLICY ISSUES

A major challenge for the biological sciences is to utilize the most sophisticated technologies that produce ever-enlarging data sets while still ensuring the rigor and quality of research.¹⁰⁶ Moving forward, the field should embrace policies that enhance the replicability of findings and promote transparent reporting of experimental methods, use of common data elements, and sharing of data and analysis tools. Follow-up validation studies are a necessary part of this process, and data sharing should be integrated into the design of studies from the beginning. The National Institute of Mental Health NDAR platform is a valuable repository for high-quality ASD data, tools, and methodologies that researchers should leverage to enable re-analysis of data and facilitate collaboration to accelerate research progress.

Larger longitudinal studies require coordination among research centers and a shift in focus toward team science across multiple disciplines. The coordinated collection and analysis of valuable imaging, behavioral, genetic, phenotypic, and iPSC data can be enhanced by the recruitment of a more diverse workforce that includes not only neuroscientists, immunologists, and psychiatrists, but also experts in bioinformatics, machine learning, and behavior monitoring device engineers.

The inclusion of persons on the autism spectrum in research plans and messaging is crucial to identifying practical applications for improving the quality of life for ASD patients and their families. Standard methods for behavioral measurements and tracking quality of life across the lifespan are essential for addressing prescient issues supporting individuals with ASD in their daily lives.

SUMMARY

Significant progress in understanding the biological basis of autism has been made, but considerable challenges remain. Though there is a desire to demonstrate the impact of treatment on brain function, fundamental research that will allow us to fully understand the importance of alterations in brain function on development is needed. Basic science on the underlying biology of ASD continues to be critical to provide the foundation for translational advances that will lead to effective treatments.

OBJECTIVES

OBJECTIVE 1: Foster research to better understand the processes of early development, molecular and neurodevelopmental mechanisms, and brain circuitry that contribute to the structural and functional basis of ASD.

Examples:

- Identify neural circuit abnormalities that occur in significant groups of ASD individuals.
- Understand the role of the immune system and metabolic processes in ASD, including aspects such as the fever effect (behavioral improvement coincident with fever).
- Identify quantitative and reproducible biomarkers or behavioral monitors for ASD of utility in assessing effectiveness of future therapeutic or behavioral intervention trials.

OBJECTIVE 2: Support research to understand the underlying biology of co-occurring conditions in ASD and to understand the relationship of these conditions to ASD.

Examples:

- Determine the molecular basis of epilepsy in ASD.
- Determine the impact of GI dysfunction on ASD related behaviors and cognitive performance.
- Determine the impact of sleep disorders on ASD related behaviors and cognitive performance.
- Determine the relationship of co-occurring psychiatric disorders to ASD and their impact on the health and well-being of people with ASD.

OBJECTIVE 3: Support large-scale longitudinal studies that can answer questions about the development of ASD from pregnancy through adulthood and the natural history of ASD across the lifespan.

Example:

- Support the creation of large cohorts, characterized both phenotypically and genetically through the collection of autism-relevant exposure data and medical data on the parents and child from the prenatal period to adulthood.



QUESTION

3

**WHAT CAUSES ASD, AND CAN
DISABLING ASPECTS OF ASD BE
PREVENTED OR PREEMPTED?**

Aspirational Goal: Causes of ASD will be discovered that inform diagnosis, prognosis, and interventions and lead to prevention or preemption of the challenges and disabilities of ASD.

INTRODUCTION

Since the last *Strategic Plan* update published in 2013, there have been substantial advances in the understanding of factors that contribute to a diagnosis of autism spectrum disorder. Few would dispute that the causes of ASD are many and include both genetic and environmental factors. There has been an increased appreciation in the last five years of the incredible complexity and interplay of these factors in the development of autism. Indeed, modifications in more than 100 genes are now known to increase the probability of an autism diagnosis^{1,2} and very reasonable predictions are that 1,000 or more autism risk genes may ultimately be identified.¹ A plethora of potential environmental challenges have also been associated with autism, although studies in this area have not undergone the same exponential progress as genomics research. There has also been increasing emphasis on events during pregnancy, such as influenza infection, as potential causes of neurodevelopmental disorders. But, these studies have raised the interesting issue that environmental risks affect different people differently. This is the so-called “genes by environment” interaction. More and more modern medical problems are linked to the combination of a particular

genome and a particular life history of environmental exposure (the exposome).

The title of this chapter, which has been modified from the *2013 Strategic Plan Update*, emphasizes the desire to understand the causes of the disabling aspects of autism spectrum disorder. These go beyond the core symptoms of deficits in social communication and the occurrence of restricted patterns of behavior or interests to include what are typically referred to as co-occurring symptoms. In many cases, progress on the causes of these co-occurring symptoms is ahead of that for the core symptoms of autism. There is a growing appreciation that the causes of these medical problems urgently need to be addressed. They may be due to biological factors that are also causal of autism, manifestations of autistic behavioral problems such as poor diet that may lead to medical issues, or medical access issues which lead to poorer medical care. Regardless of the causes, this is a clear gap in autism research and intervention and urgently needs additional research attention and efforts at resolution.

The title to this chapter has changed (from “What caused this to happen and can it be prevented?”) because the neurodiversity movement has had a great impact on the IACC and on the premises of the *Strategic Plan* enterprise. It is fully appreciated now that some features of autism should not necessarily be targets for prevention. As discussed above, it is the most disabling features of autism that are now the major targets of prevention or preemption. Discussions of the causes of ASD always ultimately touch

on efforts at prevention. In the hypothetical situation that a known cause of autism is identified, the question arises whether the cause should be eliminated thus preventing some cases of autism. If the discussion were related to cancer, the answer would be clear. But, in autism it is not. There is clearly an increased sensitivity to any procedure or practice that would be directed at preventing the totality of autism, and this is reflected in the emphasis of this chapter.

GENETIC RISK FACTORS

The application of genomic studies has significantly advanced the understanding of genetic risk factors for ASD. Dozens of new ASD susceptibility genes have been identified over the past 5 years and genome-wide technologies have facilitated a molecular diagnosis in ~5-40% of ASD cases. This range in the rate of detection depends on the group of subjects examined and the technology used. Studies comparing individuals with ASD to typically developing individuals have indicated that as much as 7-8% of people with ASD carry either a large pathological DNA deletion or duplication.^{3,4,5,6} Earlier results from DNA sequencing studies have further confirmed the role of gene-disruptive mutations in ASD,^{7,8,9,10} and more recent data also support and add to these findings.^{11,12,13} The rates of *de novo* (new, spontaneous, non-inherited) likely gene-disruptive (LGD) and missense mutations (which result in amino acid changes) are significantly higher in individuals with ASD compared to their unaffected siblings (while the rate of mutations which do not alter amino acid sequence or biology does not differ).¹² As much as 21% of autism diagnoses may be accounted for by *de novo* single-nucleotide variant (SNV) and insertion/deletion mutations.¹⁴ Additionally, inherited LGD mutations have been found to show a preferential transmission from mothers to sons, indicating another potential risk factor contributing to an

estimated 8% of autism diagnoses.¹⁵ Recent whole genome sequencing studies of a large diverse ASD collection revealed a molecular basis in 11.2% of participants, including the finding that 7.2% carried copy number variations (CNVs; repeated sequences in the genome that vary between individuals) or chromosomal abnormalities,¹⁶ which further emphasize the need to use comprehensive genomic technologies.¹⁷ Overall, a consistent observation emerging from genomic studies is the vast genetic heterogeneity involved in ASD.^{18,19,20}

Follow-up evaluation of individuals with ASD who have disruptive mutations to the same gene or genomic region has further illuminated features and patterns of behaviors (sub-phenotypes) linked to these genetically defined subgroups. Clinical characterization of cohorts with disruptive gene mutations has revealed real, but subtle, phenotypic patterns tied to particular genes. Patterns of behavior linked to sub-phenotypes can prove helpful for establishing guidelines of care for clinicians. While major advances have been made through the application of genomic technologies, gaps exist in our understanding of the contribution of regulatory and other genomic regions to ASD risk. Whole genome sequencing will begin to illuminate the role of non-gene coding regions of the genome.

HERITABILITY

ASD is highly familial, so that siblings of children with autism are 10-20 times more likely to receive an ASD diagnosis themselves than non-siblings.^{21,22,23} Twin studies beginning in 1977²⁴ have provided significant evidence that ASD is strongly associated with genetic factors. All 13 twin studies on autism to date have found genetic and environmental contributions to autism, although the proportions of the two factors and interpretations have varied substantially. One research team,²⁵ for example, concluded that over 50% of the risk for autism in identical twins could be explained by shared environmental factors, whereas genetic heritability accounted for 37%. This somewhat surprising finding—that environmental factors contribute more substantially than genetics—has been challenged by a more recent, large-scale twin study,²⁶ which found that the largest contribution to autism liability comes from additive genetic effects. A recent meta-analysis concludes that the causes of autism are due to strong genetic effects, and that shared environmental influences are seen only if the most severe forms of autism are included.²⁷ A recent survey of autism twin studies finds that concordance for monozygotic twins is roughly 45%, versus 16% for dizygotic twins.²⁸ Thus, twin and family data suggest that genetic variation between people accounts for a very substantial portion of the liability to ASD at a population level. But, if autism had a completely genetic etiology, we would expect a much higher concordance (or shared ASD) rate in monozygotic twins; the lower rate may reflect, in part, that even monozygotic twins do not share an identical environment prenatally.

GENOMIC ARCHITECTURE

The recent successes in ASD genetic studies have confirmed the importance of genetic risk factors. Similar to other common psychiatric disorders, the genomic architecture of ASD is complex, involving both common and rare forms of genetic variation,²⁹ including common polygenic (multi-gene)

variation, *de novo* variation, copy number variation, and inherited rare variation.^{11,12,15,19,30,31,32,33} Common polygenic variation may account for the greatest fraction of genetic influence, and approximately 20-50% of population liability. *De novo* variation accounts for less liability at a population level, but can have a very strong impact on the individuals who carry such variants.^{12,32} These data represent population risk; a crucial next step is integrating our understanding of rare variants of large effect with more common polygenic risk factors to more accurately predict ASD on an individual level.

SEX DIFFERENCES

The overrepresentation of males among those diagnosed with ASD has been observed for decades.^{34,35,36} Overall, the male to female (m:f) ratio is approximately 4:1, but that ratio varies substantially based on IQ and other features of ascertainment.^{34,37,38} Specifically, in individuals with ASD and very low IQ, the male:female ratio is commonly estimated at 2:1 or 3:1; in individuals with ASD and high IQ, the m:f ratio becomes very large, often 7:1 or greater. This pattern has been consistently observed during the period of otherwise rapid changes in the epidemiology of ASD.

There are several theories as to why males and females might differ in their observed ASD liability.³⁶ Among biological theories, the extreme male brain hypothesis posits that the male brain is predisposed to many features that are on the ASD spectrum.^{39,40} The 'female protective effect' (FPE) hypothesis in ASD is amongst the most commonly investigated in recent genomics studies.⁴¹ The FPE hypothesis suggests that females are 'protected' from ASD (for unspecified reasons) such that, on average, a greater number of risk factors (or genetic "hits") is necessary for a girl to gain a diagnosis of ASD. In the context of *de novo* and gene-disruptive inherited variation, that suggestion has been supported by the recent genetics literature.^{6,12,15,42} Deleterious CNVs are three times more likely to be identified in autistic females when compared to males,⁴²

and loss-of-function mutations show a maternal transmission disequilibrium suggesting mothers are more likely to be carriers of such mutations than fathers.¹⁵ Similarly, classes of *de novo* variation that are strongly associated with ASD risk are approximately twice as likely to be observed in female cases, as compared to male cases. Recent gene expression analysis demonstrates that autism risk genes, rather than being sexually dimorphic themselves, interact with pathways and cell types that themselves are sexually dimorphic.⁴³

OVERLAP WITH OTHER DISORDERS

Neuropsychiatric and developmental disorders share many genetic risk factors, and this varies depending on the specific disorders being compared.^{30,44,45} ASD shares common risk genes with other neuropsychiatric disorders such as schizophrenia,^{46,47} and autism is sometimes a feature of other neurodevelopmental syndromes such as Fragile X syndrome, Rett syndrome, tuberous sclerosis, and Phelan McDermid syndrome.^{48,49,50,51} The common, polygenic influences on ASD risk are similarly associated with multiple phenotypic outcomes (different combinations of risk genes can lead to different neuropsychiatric and developmental conditions). In recent studies, and in contrast to the *de novo* findings, common polygenic risk for ASD has been positively associated with general cognitive ability, logical memory, and verbal intelligence.⁵² On average, ASD shares most risk with schizophrenia in the population, followed by bipolar disorder, but very little with substance abuse or major depression. It does not appear that this overlap involves the majority of common genetic risk for each disorder, and the extent to which overlap occurs, and what biological factors it represents, remain under investigation.

Rare familial mutations that cause syndromic ASD and *de novo* (spontaneous) genetic influences on ASD risk are also strongly associated with intellectual disability, epilepsy, and global developmental delay;^{12,53} neurological co-occurring conditions are identified in the majority of

children with ASD.^{54,55} Some of the ASD-associated *de novo* events that result in problems in protein production are more likely to be seen in cases of intellectual disability than in ASD itself.⁵⁶ Similarly, several CNVs that increase risk for schizophrenia also increase risk for ASD.^{57,58,59,60,61} This is consistent with these mutations having major effects on brain development, which subsequently can manifest as different clinical outcomes. However, there are many intellectual disability genes that do not appear to increase risk for ASD.⁶² So, understanding why some large-effect mutations that cause intellectual disability substantially increase risk for ASD, while others may not, remains an area of future investigation.⁶³

GENETIC TESTING AND COMMUNICATION OF RISK

Genetic testing is recommended by the Accreditation Council for Graduate Medical Education for those at increased risk for ASD.^{64,65} This includes chromosomal microarray (CMA) followed by Fragile X testing and other specific tests depending on the symptoms that are observed. Several studies review the current recommendations for genetic testing in ASD.⁵⁵ In addition to its usage in research studies, whole exome sequencing (WES) has been shown to have a high yield in clinical populations with developmental disorders including ASD. Thus, we expect that WES will gradually supplant CMA.^{66,67}

Given the incomplete penetrance of many large effect or familial genetic risk factors, care must be taken in pre-symptomatic or prospective risk counseling. Further understanding of the causal relationship between identified ASD risk genes and clinical outcomes is needed before guidelines for genetic counseling can be illuminated. Understanding parental concerns and attitudes when communicating complex genetic information that has an impact on family planning is also important.^{68,69}

NEW LARGE-SCALE GENETICS STUDIES LAUNCHED IN THE LAST 5 YEARS

Studies of the genetic architecture of ASD have resulted in the appreciation that much larger groups of subjects are needed to fully understand its complexity. In the last 5 years, several large-scale projects have been initiated. Recent large-scale efforts include **MSSNG** (funded by Autism Speaks), which seeks to sequence the genomes of 10,000 individuals affected by ASD, and the **SPARK study** (funded by the Simons Foundation), which seeks to sequence exomes of 50,000 families affected by autism. These studies are expected to not only identify additional autism risk genes but to also contribute to an understanding of the common variant patterns that enable expression of the mutations.

POLICY IMPLICATIONS OF ADVANCES IN GENOMIC SCIENCE

New technology and testing can also lead to increases in healthcare disparities; we must be vigilant to avoid this and support policies that enable access to all. Because of differences in population histories, understanding of genetic risk in one population may not be informative in others. This imparts an imperative to study diverse populations. Further, given the role of rare variants that will have very distinct frequencies in different populations, having information from diverse populations will be critical for the interpretation of genetic studies. When predictive testing is performed, care must be taken to ensure accurate prospective/predictive testing and that information about accurate probabilities of particular outcomes are communicated effectively and not mistakenly understood as absolutes. This requires genetic counselors or other professionals trained specifically in the communication of genetic risk to patients. This will be an increasingly important manpower issue as genetic information expands over the next decade.

ENVIRONMENTAL RISK FACTORS, INDIVIDUALLY AND IN COMBINATIONS OVER TIME

The growing number of studies that are exploring environmental risk factors reflect an emerging consensus that non-genetic avenues of research are also likely to bear fruit. In this *Strategic Plan*, it is advantageous for the IACC to adopt a broad definition of studies on “environment” as encompassing research on all potentially non-heritable etiologic influences. This includes studies of exogenous exposures such as pesticides, endocrine disrupting and other industrial chemicals, pharmaceuticals, heavy metals, infectious agents, dietary factors, as well as other factors, such as parental age, maternal medical conditions, birth complications, and time between pregnancies. Some of these “environmental” factors might themselves be genetically influenced, while others might be mediating the effects of exogenous exposure.

PREVENTION OR AMELIORATION OF DISABLING ASPECTS OF ASD

Research on environmental contributors to ASD should routinely collect and make use of data on specific ASD symptoms, the levels of symptoms and impairment, as well as co-occurring conditions. As linkages between exposures and specific impairing aspects of ASD are revealed, public health strategies can be tailored to prevent or mitigate these features by reducing harmful exposures and/or increasing factors that confer protection or resilience. Additionally, improved understanding of what role environmental factors play in ASD severity (including risk for co-occurring conditions) might eventually inform strategies for identifying children in need of specific types of early intervention services.

SUSCEPTIBLE PERIODS DURING DEVELOPMENT

The concept of windows of susceptibility, a central principle in environmental health sciences, is relevant to studies of environmental risks in ASD. Many lines of evidence point to prenatal origins of ASD.^{70,71,72,73,74,75} In addition, very large epidemiological studies link maternal bacterial or viral infection during specific times of pregnancy to increased risk for ASD in the offspring.⁷⁶

The periods of prenatal development that are most relevant to environmental risks for ASD are incompletely understood, however, and may be dosage- and/or exposure-dependent.⁷⁷ When considered together, many existing ASD studies suggest that preconception and early gestation are vulnerable periods for environmental exposures. This has been supported by previous reports linking autism symptoms to maternal ingestion of drugs such as thalidomide^{78,79} and valproic acid.^{79,80} Other factors associated with ASD risk include preterm birth,^{81,82,83,84} advanced maternal and paternal age at conception^{85,86,87,88} and short inter-pregnancy interval.^{89,90} In addition, the preconception/periconception period may be critical for the observed association of decreased ASD risk with maternal folate intake.^{91,92}

A few of the studies on air pollution exposure suggest an enhanced risk in the later part of pregnancy.^{93,94} Evidence from the broader neurotoxicology literature⁹⁵ also indicates that exposures in the late prenatal and early postnatal periods can exert significant effects on a wide range of brain and behavior phenotypes during the first years of life. All of these time windows cover critical stages

of rapid brain development and are also characterized by immaturity of both the immune system and metabolic detoxification mechanisms. These features combine to offer vulnerability and provide biological plausibility for environmental impact on ASD risk extending from preconception into the early postnatal period. Additional attention to the timing of exposures relative to the cascade of events that unfold during brain development is needed to identify and understand the molecular basis of exposure-associated ASD risk. With this in mind, study designs and biomarkers of exposure should be chosen to capture prenatal and early life exposures.

STUDIES IN LARGE AND DIVERSE POPULATIONS

While the number of ASD epidemiology studies and the resulting data are growing through efforts such as the **Early Autism Risk Longitudinal Investigation (EARLI)** and **Markers of Autism Risk in Babies-Learning Early Signs (MARBLES)**, most potential environmental risk factors have not been investigated sufficiently to draw firm conclusions.⁹⁶ The limitations inherent to observational studies mean that multiple studies in different populations and settings, with high-quality measures of exposure and adequate controls, are needed to reconcile disparate findings and establish robust linkages of an environmental exposure to ASD risk. The likelihood that many different factors, each with modest effect, will contribute to ASD means that large sample sizes may be needed to detect associations with exposure, especially for those exposures with low prevalence.

Under-represented minority communities and low-income communities often face disproportionate exposure to harmful environmental chemicals;^{97,98,99} additional attention is needed to ensure that these populations

are represented in ASD research and that disparities in environmental risk factor exposure are addressed. Inclusion of these vulnerable population subgroups in ASD studies may, in some regions, be particularly challenging when studies recruit from young children with a past ASD diagnosis. Data from the Autism and Developmental Disabilities Monitoring (ADDM) Network indicate that non-Hispanic black (NHB) children are significantly less likely than non-Hispanic white (NHW) children to receive an early comprehensive developmental evaluation,¹⁰⁰ and Hispanic children are less likely to receive an ASD identification by age 8 in comparison to NHW and NHB children. These findings underscore the need to carefully consider case ascertainment strategies that do not rely solely on previous ASD diagnosis in designing studies of ASD risk factors.

Given the clear differential in ASD risk in males and females, studies which examine risk and protective factors within sex-specific subgroups are especially important. However, given the lower ASD prevalence in females, nearly all studies to date have not had a sufficient sample of females to conduct such analyses. Thus, additional efforts are needed to increase representation of females in ASD studies to enable meaningful analyses of sex-specific differences and the role of both genetic and environmental factors in affecting those differences. The **Environmental Influences on Children's Health Outcomes (ECHO)** initiative of the National Institutes of Health is combining data from more than 78 cohorts comprising approximately 50,000 children and 40,000 women. Although the extent of ASD-related measures that are, or will be, included in ECHO has not yet been established, this initiative represents an exceptional opportunity to study ASD-related traits in large and diverse populations.

EXPOSURE SCIENCE

One of the most significant obstacles facing epidemiologic studies of environmental risks for ASD is exposure assessment. In many studies, exposure measures are not readily available for very early developmental periods and rely on indirect methods (e.g., participant recall of prior exposures), or utilize one or two biologic measurements of compounds with very short half-lives. Direct exposure assessment, such as through personal monitoring or use of an adequate time-course of exposure biomarkers, is expensive and burdensome for participants. Consequently, deep characterization of exposure during etiologically relevant time periods is typically limited to studies with small numbers of participants, yielding low power.

The recent development and application of the concept of the “exposome”^{101,102} represents a key advance that could accelerate progress in identifying environmental risks for ASD. The concept of the exposome calls attention to the totality of exposures across an individual’s lifespan.^{103,104} In addition to the universe of external environmental factors, the exposome concept can be extended to include endogenous biomarkers of exposure response – internal exposures that originate from metabolism and other cellular processes – as well as more general external factors that constitute social determinants of health. Measuring the exposome comes with challenges in capturing and integrating many individual measures over time. Recognizing that no single approach or tool likely will suffice, the field is embracing a multifaceted strategy, using multiple

tools to help characterize the exposome. For example, use of personal sensors and mobile devices can be harnessed to capture many aspects of the exposome in real time. Refinement of more targeted, conventional exposure assessment tools also has a place in characterizing the exposome.

General “omics” approaches such as transcriptomics, proteomics, metabolomics, and epigenomics show promise in identifying molecular response profiles that can be linked to exposures,^{105,106,107} and in some cases, these profiles persist over time. These downstream biomarkers may suggest groupings of exposures that operate by similar pathways. Linking direct measures of either individual or classes of exposures or the broad exposome with early “omic” markers of biological response in both targeted and non-targeted data analyses can provide complementary information of potential etiologic relevance.

Because exposomic approaches have the potential to generate high-dimensional exposure data, discovery-based analytic methods analogous to those being used in genomics can potentially be applied to uncover novel environmental risk factors – ones that would be missed by approaches that focus on a small number of established or suspected neurotoxicants. An exposomic approach also is well-suited to the simultaneous consideration of multiple exposures and risk factors; although, as the genomics field has learned, very large samples are needed to achieve significance in these kinds of analyses.

LINKAGES BETWEEN GENES AND ENVIRONMENT

GENE AND ENVIRONMENTAL STUDIES

Despite general agreement that both environment and genetics contribute to ASD risk, only modest progress has been made in identifying gene-environment interactions. A few epidemiology studies, such as the **Childhood Autism Risk from Genes and Environment (CHARGE)** study, have reported an interaction of exposures with common or rare structural genetic variation.^{92,108,109,110,111} However, each study focused on different combinations of exposures and genes, they lack independent replication, and two of these studies addressed severity of symptoms rather than impacts on incidence.^{108,111} Many large ASD genetic collections have been assembled but most include minimal or no exposure information. On the other hand, studies focused on environmental risks often feature deep exposure assessment and have incorporated some genetic information, but smaller sample sizes constrain the power of gene-environment interaction analyses.

A major gap has been identified and a concerted effort is needed to enrich existing, ongoing ASD studies by adding genetic data collection to environmental studies and exposure measures to genetic studies. Identifying and accounting for genetically driven effects on exposure levels is critical for interpretation of ASD-exposure associations. In the autism literature, it is notable that the genes implicated in the folic acid association with decreased ASD risk have not emerged in any of the genetic studies using genome-wide screening. Only in mothers who had low folic acid intake do those one-carbon metabolizing genes appear to play an etiologic role.¹⁰⁹ At this stage, it appears that the presence of a 'main effect' (a risk factor not dependent on another factor) is not always detectable and that investigation of interacting factors should not require that a main effect of a specific environmental factor or gene/SNP be known.

Availability of low-burden exposure measures that can be incorporated in large-scale genetic studies, perhaps leveraging innovations in exposomics or epigenomics, is a high priority. Once these data exist in concert in large sample sets, new statistical and analytic approaches for gene-environment discovery in human population research can be applied.¹¹² Polygenic risk scores have seen increasing use in complex disease studies and can yield improved efficiency for detecting interaction of genetic risk with candidate environmental exposures. The construction of a "polyenvironment" score, analogous to a polygenic risk score, could be explored to summarize information from several exposures thought to be acting through common mechanisms for use in genetic/genomic studies. Other approaches might include measures of genomic instability such as global copy number burden, used in two different gene-environment interaction studies.^{111,113}

MECHANISMS OF ENVIRONMENTAL RISK AND GENE-ENVIRONMENT INTERACTION

Increasing knowledge of genetics has led scientists to understand gene pathways that affect neural circuits rather than single genes acting in isolation. Early studies have demonstrated the convergence of genetic influences and environmental factors in the activity of these different gene pathways,¹¹⁴ providing evidence that genes and the environment might work synergistically, rather than additively. Studies that move beyond identification of genetic and environmental risk factors to reveal functional biological consequences associated with these risk factors are a priority. Epigenomics, metabolomics, transcriptomics, and proteomics can provide useful functional readouts for this purpose.

Model systems provide an attractive means for supporting causality and understanding biological mechanisms that underlie associations observed in human studies. Human induced pluripotent stem cells (hiPSCs) generated from individuals affected by ASD with a known genetic background are being used increasingly to study ASD.¹¹⁵ These provide a unique opportunity to assess susceptibility of early developmental processes to environmental chemicals in the context of defined genetic risk.¹¹⁶ There are a few reports of screening or computational approaches used to identify possible environmental exposures that could be priorities for pursuit in human studies.^{114,117} The Collaborative Cross and Diversity Outbred mouse populations¹¹⁸ represent important mouse resources that could be harnessed to dissect the contribution of environment to complex disorders such as ASD. Additional efforts that bring together interdisciplinary teams to facilitate integrative analyses and bidirectional flow of clues from human observational studies to laboratory-based experiments in model systems are warranted.

In addition to the utility of epigenomics (the study of the complete set of epigenetic modifications – such as methylation – on the genetic material of a cell) as easily attainable exposure biomarkers, many researchers recognize the potential for mechanistic roles in ASD. Epigenomics is a leading candidate for mediating effects of exposures on regulation of transcription (the first step in gene expression)^{119,120,121} and could provide a point of convergence for genes and environment in autism risk. Multiple lines of evidence implicate altered epigenetic marks in ASD etiology. Several known genetic disorders with ASD-related presentation, such as Fragile X and Angelman syndrome, have established epigenetic mechanisms. Further, results from rare-variant ASD genetic discoveries point to remodeling of genetic material as a shared pathway in ASD genetic risk. Few studies have directly examined chromatin marks or DNA methylation for association with ASD, but some small studies have observed associations.^{105,122,123}

A significant body of work demonstrates that environmental chemicals can alter DNA methylation, and these alterations have been linked to changes in gene expression and a range of behavioral phenotypes.^{124,125,126} ASD studies that integrate methylation, exposure, and phenotype data in the same population are a priority. Research to establish whether epigenetic marks measured in peripheral tissues are predictive of changes in target tissues is especially important for interpretation of human studies.¹²⁷ Also needed are studies that identify exposure-induced impacts on a full range of epigenomic mechanisms and that determine their relevance to ASD. Finally, research to understand how exposure-induced epigenomic changes may transmit autism risk across generations is warranted.

MULTIVARIATE RISK ACROSS COMPLEX SYSTEMS

There is a need to capitalize on findings emerging from existing studies to examine how genetic and environmental factors interact to contribute to phenotype, not only at the molecular and cellular level, but also in the broader physiological context. For example, a substantial body of work implicates immune dysregulation in ASD, including the association of ASD with maternal infections and autoantibodies, cytokine and other immune biomarker signatures, functional alterations in immune cell subsets,¹²⁸ and differential expression of innate immune and inflammatory genes.¹²⁹ These findings together have motivated studies exploring how a range of environmental exposures may contribute to the immune alterations observed in ASD, some of which have been detectable at birth.¹³⁰

The endocrine system is another promising area of inquiry. The established role of hormonal systems in brain development, the marked male bias in ASD, and a growing recognition that many environmental chemicals act as endocrine disrupting chemicals (EDCs) sets the stage for investigations exploring possible links between ASD and EDCs.¹³¹ Some research studies have suggested that

factors that protect females from autism risk may be found on hormone-sensitive genes,¹³² and these could be targets for EDCs. Further work elucidating connections across metabolic, hormonal, and central nervous systems in the context of EDCs is needed.

The microbiome (the combined genetic material of the microorganisms in the body) represents a third priority area of inquiry. There is increasing evidence for links between the gut microbiome, brain, and behavioral phenotypes relevant to ASD.^{133,134} The microbiome is also emerging as an important component of response to environmental exposure. Studies have demonstrated persistent changes in the function of the microbiome after exposure to immune

activation and environmental chemicals,^{135,136} particularly during early life when the microbiome is being colonized. A role for the microbiome in metabolism of environmental chemicals is now established.^{137,138} This means that differences among individuals in microbiome composition can affect the internal dose and biotransformation of toxicants and act as susceptibility factors. Small clinical studies using antibiotics or microbiome transplant support a potential role for microbial imbalance in contributing to the cause of core ASD behaviors. Taken together, these data suggest possible linkages among exposures, microbiome function, and ASD phenotypes. This is an area that has only begun to receive research attention which should be expanded in the foreseeable future.

RESOURCES TO ACCELERATE ENVIRONMENTAL RISK AND GENE-ENVIRONMENT RESEARCH

BROAD DATA AND RESOURCE SHARING

As the number of studies focusing on environmental risks for ASD increases, attention to broad data access and sharing becomes critical for enabling reuse and extracting the maximal value from the data that have been collected. Consideration of privacy and consent issues in environmental health data is needed to ensure the development and implementation of policies that protect privacy while ensuring the value of shared data. Combining data across observational studies can yield increased power and strengthen generalizability, yet heterogeneity of the types of exposure measures used creates challenges for both meta-analyses and pooled analyses of primary data. On the other hand, when different types of measures of exposure in different studies all lead to consistent findings, that consistency alone increases confidence in the conclusions.

The development of consensus data standards will make it possible for investigators to consider, at the outset of a study, inclusion of common environmental measures/standards.¹³⁹ Use of low burden exposure measures, such as those available through **PhenX¹⁴⁰** or the **Early Life Exposure Assessment Tool (ELEAT)**, enable genetics researchers to enrich their analyses to account for environmental contributions to risk. Increased sharing of study-specific exposure instruments and methods is another area of need. The **National Database for Autism Research (NDAR)** currently provides a robust platform for making data – particularly data in standard formats – easy-to-find and accessible. Implementing common data standards for exposures could facilitate the incorporation of these type of data in NDAR.

In addition, genetic databases including MSSNG and the **Autism Sequencing Consortium (ASC)** are anticipated to provide mechanisms for expanded data libraries to include key environmental variables, allowing for assessment of gene-environment interactions. Recent findings^{108,111} illustrate the benefits of incorporating environmental information in large data resources. With regards to mechanistic tools, new models of ASD, especially those with distinguishing genetic mutations of interest, should be made widely accessible to researchers. This can include, but is not limited to, sharing breeding pairs of animal models with commercial vendors for their widespread distribution. Finally, to realize the potential impact of data sharing, efforts must be put into the analytic approaches needed to make gene-environment discoveries from the aggregation or collective analysis of large heterogeneous data sources. Efforts that encourage methodological development as well as bioinformatics implementation and secondary data analysis funding will be necessary.

INTERDISCIPLINARY TRAINING AND CAREER DEVELOPMENT

The workforce needs related to environmental research in ASD align with an increasing recognition that solving complex questions will require team science approaches. Programs and opportunities that train scientists and support research and networking programs in ways that encourage crosstalk and coordination of efforts spanning cellular and molecular neurobiology, toxicology, genetics, epidemiology, and exposure science are needed. Training opportunities should be created around novel statistical and big data approaches geared toward complex exposure data, with the goal of accelerating analyses that address multivariate risk.

PUBLIC HEALTH IMPLICATIONS

COMMUNICATION AND DISSEMINATION ACTIVITIES FOR ENVIRONMENTAL RISK FINDINGS

The multivariate risk structure of ASD, with many factors contributing modest risks, and different combinations of risks likely to operate in different individuals with ASD, presents challenges for communicating findings to affected families and the broader public. Epidemiologic studies that report associations of specific exposures with ASD at the population level can lead to serious misinterpretation if extrapolated to individual cases, and a focus on individual risks can mask the importance of exposures whose modification could have substantive impact when measured across the population. Moreover, the limitations inherent

to observational studies means that results of a single study require additional independent studies for replication and assessment of generalizability. Conflicting findings among studies are common, and may reflect spurious results or an unappreciated dependency of the association on other factors. Additionally, it is particularly difficult to separate the effects of some exposures from other factors, due to inherent collinearity – for example, distinguishing true medication effects from effects due to the underlying health condition for which medication was required. For these reasons, communicating environmental and genetic findings in ASD requires careful attention to context, including providing information about the strength of any newly reported finding on the scale most appropriate for the audience, the difference between cause and association,

the specific potential limitations of any individual study including the possibility of unmeasured confounding, the population attributable risk, and the need for additional studies to confirm the association.

SUMMARY

In many cases, risk factors for ASD are shared by other disorders, and additional research is needed to ensure that corresponding public health efforts will have broad utility for protecting health beyond the implications for autism. The hope of identifying and understanding ASD risk factors is that they can be mitigated to reduce ASD-related disability.

OBJECTIVES

OBJECTIVE 1: Strengthen understanding of genetic risk and resilience factors for ASD across the full diversity and heterogeneity of those with ASD, enabling development of strategies for reducing disability and co-occurring conditions in ASD.

Examples:

- Understand the contribution of regulatory and other genomic regions to ASD risk. Whole genome sequencing will begin to illuminate the role of non-gene coding regions of the genome.
- Identify additional autism risk genes but also contribute to an understanding of the common variant patterns that enable expression of the mutations.
- Understand the causal relationship between identified ASD risk genes and clinical outcomes so that guidelines for genetic counseling can be illuminated. Understand parental concerns and attitudes when communicating complex genetic information.

OBJECTIVE 2: Understand the effects on ASD risk and resilience of individual and multiple exposures in early development, enabling development of strategies for reducing disability and co-occurring conditions in ASD.

Examples:

- Understand the timing of exposures relative to the cascade of events that unfold during brain development to identify and understand the molecular basis of exposure-associated ASD risk.
- Conduct multiple studies in different populations and settings, with high-quality measures of exposure and adequate controls, to reconcile disparate findings and establish robust linkages of environmental exposure to ASD risk.
- Refine more targeted, conventional exposure assessment tools to characterize the exposome.

OBJECTIVE 3: Expand knowledge about how multiple environmental and genetic risk and resilience factors interact through specific biological mechanisms to manifest in ASD phenotypes.

Examples:

- Develop low-burden exposure measures that can be incorporated in large-scale genetic studies, perhaps leveraging innovations in exposomics or epigenomics.
- Move beyond identification of genetic and environmental risk factors to reveal functional biological consequences associated with these risk factors.
- Integrate methylation, exposure, and phenotype data in the same population.



QUESTION

4

WHICH TREATMENTS AND INTERVENTIONS WILL HELP?





Aspirational Goal: Develop a range of targeted treatments and interventions that optimize function and abilities across the lifespan to achieve meaningful outcomes and maximize quality of life for people on the autism spectrum.

INTRODUCTION

The evolution of this Aspirational Goal reflects the progression of priorities in the autism community. Over the past several years, the IACC's focus has shifted from "preventing disabilities" (2009 IACC Strategic Plan), to encouraging "building adaptive skills" (2013 IACC Strategic Plan Update), and now emphasizes the construction of lifespan approaches and utilization of more meaningful treatment outcomes for individuals living with ASD and their families. This change also underscores the shifting landscape of treatment opportunities driven by exciting discoveries from cognitive neuroscience, which reveal breathtaking developmental reorganizations of brain function in adolescence and young adulthood,^{1,2,3} adding new possibilities for intervention and learning across the lifespan.

Since the 2013 IACC Strategic Plan Update, there has been an explosion of behavioral intervention studies and advancements in intervention science, including continued progress in the development and evaluation of multiple intervention types. Key advances include improvements in community implementation of effective interventions, greater numbers of fully powered randomized trials,

comparative efficacy studies, and implementation science studies that consider child outcomes as well as best implementation practices. Additionally, the diversity of study participants has improved, as researchers more often strive to include underserved families as well as populations previously excluded or overlooked in ASD research, such as girls and minimally verbal children.

There has also been much progress in brain-behavior measures as predictors of outcomes of interventions, as well as the development of adaptive interventions, recognizing that sequential and multiple interventions are often required to improve child outcomes. Finally, technology has been used more frequently, as a tool within an intervention (such as iPads for communication and storyboarding), to deliver interventions using telehealth methods, and to collect data in real time that can be used to guide intervention and gauge treatment response.

The next generation of more precise, personalized treatments and interventions will be developed with the benefit of the knowledge gained from neuroscience and

genetics research on the systems biology of ASD. Researchers are now utilizing the latest discoveries and tools from these fields to develop and evaluate genetically targeted pharmacology, neuroimaging-guided direct brain stimulation, combination drug (or brain stimulation) and behavioral

treatments, and intervention approaches that match the needs of individuals with ASD. Great progress has been made, and will continue to be made, by prioritizing the understanding of the brain basis of ASD and biological mechanism(s) underlying a given therapeutic approach.

INTERVENTION AND TREATMENT TYPES

The autism community continues to emphasize the importance of establishing evidence-based practices in interventions.⁴ Evidence-based practice is grounded on the premise that there are interventions that have evidence of their positive and strong effects for individuals with ASD, and that practitioners (e.g., psychologists, psychiatrists, speech pathologists, teachers) should therefore prioritize their use while working with families. When strong evidence for an intervention or treatment to address a specific goal or outcome does not exist, the practitioner should try the intervention with the most evidence, although the empirical efficacy may fall below an established standard. Clinical and/or professional expertise plays a major role in selecting an intervention or practice to address a specific goal or more generalized outcomes and is especially useful for adapting the intervention for the individual with ASD when needed.

Looking forward, advances in neuroscience and genetics that provide knowledge of the biobehavioral mechanisms of treatment efficacy (summarized in Chapter 2 of this report) support a new principle to guide evidence-based practice: *Preference should be given to those treatments and interventions for which there is a current or emerging understanding of the biobehavioral mechanism(s) of action.* This will facilitate highly innovative, randomized, experimental therapeutics trials in human participants. Such trials will improve our understanding of the developmental mechanisms underlying ASD risk and resiliency, thereby enabling the development of novel treatments and intervention strategies.

BEHAVIORAL INTERVENTIONS

Behavioral interventions fall into two broad classes: focused intervention practices and comprehensive treatment models (CTMs). Focused intervention practices are instructional or therapeutic approaches applied to an individual's goals (e.g., making social initiations to peers, reducing self-injury), designed to produce outcomes related specifically to the goal, and are implemented over a relatively short period of time until an individual meets his or her specific goal. Meanwhile, CTMs address broader outcomes (e.g., increases in cognitive abilities, adaptive behavior, social and communication skills). CTMs consist of many focused intervention practices organized around a conceptual framework, are documented through treatment protocols, and exist over a more extended time period. Examples include the Lovaas Model⁵ and the Early Start Denver Model (ESDM).⁶

Practitioners use these two classes of interventions/treatments in different ways. They may select multiple focused intervention practices to build individualized programs for children, youth, and adults with ASD, or they may fully adopt a comprehensive treatment program in which the focused interventions and their use are already prescribed.⁷ Although several CTMs have been shown to be efficacious, they may be implemented less often by practitioners than focused intervention practices.^{8,9} The National Standards Project and the National Professional

Development Center on ASD (NPDC) have conducted critical and rigorous reviews of the intervention research literature and identified sets of focused intervention practices that have evidence of efficacy.¹⁰

The NPDC work specifically focused on practices that could be implemented in school and/or community settings. Similarly, deBruin and colleagues conducted a meta-analysis of school-based interventions in high schools, finding evidence of efficacy for many of the same focused intervention practices (i.e., antecedent-, video-, and consequent-based interventions).¹¹ Other reviews have documented the efficacy of 1) school-based, focused interventions on challenging behavior, 2) the use of peer-networks to foster social engagement, 3) social skills training, and 4) academic interventions.^{12,13,14,15,16,17} Research on the efficacy of several behavioral interventions continues today, including the Lovaas Model, ESDM, JASPER (Joint Attention, Symbolic Play, Engagement, and Regulation), LEAP (Learning Experiences and Alternative Program for Preschoolers and Their Parents), PRT (Pivotal Response Treatment), First Words Project, DIR/Floortime (Developmental, Individual-Difference, Relationship-Based), EMT (Enhanced Milieu Teaching), and STAR (Strategies for Teaching based on Autism Research).^{5,6,18,19,20,21,22,23,24,25,26}

School-Based Interventions It can take over a decade and a half for evidence-based interventions to become widely implemented in the community when developed in the laboratory. Thus, researchers are increasingly developing and testing interventions in school-based settings, with the added goal of sustaining the intervention beyond the study period. Two recent studies demonstrate that similar outcomes can be obtained in the community and the lab.^{27,28} Both of these studies implemented JASPER aimed at improving core impairments in social communication, and noted sustainability of the intervention over a short-term follow-up. As a whole, these and other findings highlight the effectiveness of teacher-implemented interventions in school settings on improving one of the core features

of ASD and pave the way for more school-based intervention research.

Parent-Mediated Interventions As diagnostic advances have made it possible to identify children with ASD at earlier ages, researchers have tested a number of parent-mediated interventions in order to meet the need for interventions that can be implemented as early as possible. Most of these are labeled Naturalistic Developmental Behavioral Interventions (NDBIs), a newly vetted grouping of early interventions based on applied behavior analysis (ABA).²⁹ Several recent studies have yielded significant improvements over earlier studies by comparing the experimental treatment to an active control group involving parent education but no hands-on coaching, versus comparing an experimental treatment to treatment as usual.^{30,31,32}

One conclusion of these recently completed studies is that active hands-on parent coaching for social communication outcomes is more effective than parent education models where the same information is provided without active coaching. This conclusion is further supported by another recent study of toddlers at risk for ASD, finding that initial gains in parent responsiveness did not sustain to the follow-up, speaking to the need for longer-term, more intense, or more hands-on intervention.³³ A recent parent-mediated intervention study based on the DIR/Floortime intervention approach suggests efficacy of this model for improving parent and child outcomes.²² Researchers have also studied the benefits of parent group interventions, where groups of parents are coached to deploy interventions. In a recent study of the PRT approach, researchers found that parent group interventions yielded significant parent and child benefit.³⁴ While more cost effective than 1:1 therapy sessions, more research is needed to determine the generalizability and sustainability of parent group interventions to foster meaningful improvement in child behaviors, communication, and functioning.

Altogether, the foregoing studies add to the positive outcomes attained through parent-mediated interventions but raise issues about meaningful outcomes (i.e., spontaneous versus prompted outcomes) and the specific “active ingredients” – or essential components – of treatment (i.e., hands-on coaching, dose, approach). In the future, researchers will need to better understand for whom an intervention works best, and why an intervention provides benefit. Understanding the mechanisms behind effective behavioral interventions helps researchers to identify the essential components of an intervention, making it possible to develop a repertoire of components that can be combined in various ways to customize treatment. Two recent studies suggest that parent synchronization (attuning of the parent’s behavior to the child’s attention) and mirrored pacing (following the child’s lead) are important components or active ingredients of parent-mediated interventions.^{35,36}

Behavioral Interventions in Understudied Populations

Developing interventions for minimally verbal children has been very challenging. A recent study tested whether JASPER combined with a behavioral language intervention with or without an augmentative and alternative communication (AAC) device facilitated greater spoken language over 6 months.³² This study took an adaptive treatment approach, adjusting the treatment midway through the study based on an individual’s progress. The results of this study suggest important implications about the treatment approach and timing of providing an AAC device in treating minimally verbal children with ASD.

For instance, the approach focused on developmental pre-requisites to spoken language, including joint attention, joint engagement, and play along with systematic modeling and prompting for spoken language. The researchers utilized a developmental, child-directed approach with strong naturalistic reinforcement strategies. Adults were contingently responsive to child attempts at communication and provided expansion of language

through models that matched the child’s communicative intent. This may have provided the combination of supports needed for minimally verbal children with ASD to successfully increase their spoken communication. Earlier access to speech-generating devices along with naturalistic behavioral interventions at the start of treatment may be most beneficial to minimally verbal children. This is an area that demands much greater research attention.

Girls with ASD are another understudied and underserved group. Recent studies find subtle but important developmental differences between preschool-aged boys and girls with ASD.³⁷ Studies of older children find girls with ASD who have lower IQs also have more impairing symptoms of ASD than boys. Girls with higher IQs report better friendships and social skills and fewer repetitive behaviors than boys.³⁸ School playground observations of girls with ASD find they are overlooked and neglected by their classmates in more subtle ways, whereas boys with ASD are often overtly rejected.³⁹ In part, these differences between girls and boys with ASD are due to the ability of girls to camouflage their interaction difficulties.⁴⁰ These findings suggest that gender should be included as a tailoring variable when individualizing interventions for children with ASD.

Groundbreaking brain imaging and genetics studies have revealed important differences between males and females in the brain and genetic mechanisms underlying autism. For instance, genomic studies have provided tantalizing evidence for a “Female Protective Effect” (FPE) hypothesis in ASD,⁴¹ such that a greater amalgamation (more and/or more intense) of risk factors is necessary in females versus males to lead to autism. To illustrate, deleterious copy number variations (CNVs) are three times more likely in autistic females than in males.⁴² Furthermore, recent gene expression work from postmortem brain samples demonstrates that autism risk genes, rather than being sexually dimorphic themselves, interact with pathways and cell types that themselves are sexually dimorphic.⁴³

Looking ahead, as it is becoming increasingly clear that females and males with ASD differ in terms of causes, developmental profiles, and symptom profiles, we need to understand how they respond differently to treatment approaches. At present, there are no adequately powered studies that focus on sex differences in behavioral and/or neural-systems-level treatment response. Such studies should be a major priority for the research community.

Discoveries of neuroplasticity in the adult brain have opened new opportunities to consider autism interventions for use in adulthood. Very few studies of behavioral interventions have been performed in adolescents or adults with ASD, and most of these have focused on training adults to read social cues.⁴⁴ Executive and social brain networks exhibit the greatest rates of functional maturation during adolescence, establishing adolescence and young adulthood as a sensitive period for socio-emotional and self-control development.⁴⁵ These new findings suggest that the period from adolescence into young adulthood may offer an important new window of opportunity for individuals with ASD, their families, scientists, and clinicians to design novel approaches for improved outcomes and superior quality of life.

MEDICAL INTERVENTIONS

Pharmacological Treatments In contrast to the many behavioral intervention options available, only two drugs, risperidone and aripiprazole, currently have Food and Drug Administration (FDA) indication for use in ASD, specifically for the symptom of irritability. There are no approved treatments for the core symptoms of ASD, which include social communication difficulties and restricted, repetitive patterns of behavior, interests, or activities. Although clinical trials of pharmacological interventions for core symptoms of ASD are now underway, they will require several years for completion, analysis, and reporting; thus, there are few published findings to date. Advances in genetics and neurobiology have led to an increase in the number of clinical trials testing medical treatments for ASD.

While the majority of such trials are testing pharmacological treatments, neurostimulation (discussed separately below) is also gaining momentum as a modality to alter brain activity and neuronal connectivity, as is the development of approaches based on stem cell technologies.

There has been an abundance of open-label, single-center drug trials that report effectiveness in small samples. Unfortunately, many of these results were not replicated when tested in subsequent larger, randomized, placebo-controlled trials. Many of the drug trials in ASD exclude individuals with intellectual disability and very young children due to ethical and/or practical challenges. However, a mechanism-based intervention intended to improve core symptoms of ASD may be more effective if administered relatively early in life and may be most effective in those most severely affected. Thus, it is crucial that such individuals are included in upcoming trials. This will require researchers to carefully consider how interventions can be adapted to accommodate children or individuals with intellectual disability, and to identify age- and ability-appropriate outcomes and outcome measures. Additionally, researchers must ensure that parents and families are well-informed and actively engaged through all stages of the trial.

Many different genes may contribute to the susceptibility of developing ASD. This heterogeneity of underlying causal mechanisms makes it challenging to identify convergent molecular pathways and brain circuits involved in all individuals with ASD, although there has been recent progress. One promising target is oxytocin, a neuropeptide involved in social cognition that has been investigated in a number of ASD studies.^{46,47,48} However, its molecular properties pose challenges for potential therapeutic use; thus, further work is needed to determine the best doses and compare methods of delivery. Moreover, given the variation of oxytocin's effects based on behavioral context, studies aimed at understanding how oxytocin might enhance responses to evidence-based behavioral interventions are recommended.⁴⁹

Other randomized, placebo-controlled treatment trials have targeted additional mechanisms proposed to contribute to the pathophysiology of ASD, with varying successes.^{50,51,52,53,54} N-acetylcysteine (NAC), an antioxidant treatment, was well-tolerated and had the expected effect of modulating oxidative stress markers, but had no impact on social impairment in youth with ASD.⁵⁰ D-cycloserine, a partial agonist of the N-methyl-D-aspartate (NMDA) glutamate receptor, was tested in combination with social skills training. No difference was found in the drug treatment group compared with placebo.⁵¹ The serotonin partial agonist buspirone was used to target core symptoms during the developmental period of low serotonin synthesis capacity in young children with ASD. Low-, but not high-, dose buspirone showed significant improvement in a measure of restricted and repetitive behaviors.⁵² Finally, a double-blind clinical trial using the diuretic bumetanide that reduces intracellular chloride, thereby augmenting GABAergic inhibition, showed that bumetanide significantly reduced clinical symptoms of ASD in children 3-11 years old and was well-tolerated.⁵³ Furthermore, bumetanide combined with a behavioral intervention resulted in a better outcome in children with ASD than a behavioral intervention alone.⁵⁴ Larger trials are needed to validate these initial findings. Moreover, given the importance of context and a developmental perspective on ASD, it will be very important to conduct well-powered studies that combine pharmacological treatments with evidence-based practices including behavioral approaches, cognitive behavioral therapy, and social skills training. This issue is discussed in detail below.

A number of treatment trials are targeting the associated or co-occurring conditions of autism. One of the most prominent is anxiety, which affects at least 40% of individuals with ASD.⁵⁵ Treatments range from cognitive behavioral therapy (CBT)^{56,57} to medications.^{58,59,60,61} While there have been some notable successes, there is also substantial variation in outcome. The variation in success

may be due, in part, to the difficulty in assessing anxiety symptoms in autism and to the inappropriate stratification of appropriate subjects. When individuals with and without anxiety are grouped together as the "experimental" group, it is often difficult to attain a high enough level of response to consider the trial a success. This is an issue that relates to all treatment trials of the co-occurring conditions. And, additional research efforts must be directed to adequately subdividing individuals with autism into more homogeneous subgroups that have common symptom profiles.

Given that the rates of diagnosed ASD cases are rising and that there are no effective drugs to treat its core symptoms, it is imperative to further develop pharmacological treatments. Involvement of private industry will be crucial to help address this unmet need, including in industry-academic collaborations. Important private partners include the pharmaceutical industry, as well as those in software, electronics, and robotics development. As much as possible, multi-site, longer-duration, placebo-controlled studies should be prioritized in order to produce more reproducible results, such that private industry will take on the challenges of conducting large Phase III registration studies.

Direct Brain Stimulation Transcranial magnetic stimulation (TMS) is a potentially promising method for identifying neural mechanisms and treating aspects of altered brain function in ASD.⁶² TMS can offer a non-invasive tool to study aspects of the altered physiology underlying ASD. Treatment strategies involve using TMS to modulate brain plasticity and network activity.^{63,64,65} In particular, repetitive TMS (rTMS) can alter brain excitability and network activity beyond the duration of a stimulation session or treatment study, and is being examined as a treatment that could potentially reduce both core and associated ASD symptoms.⁶⁶

Recent studies have investigated whether neuromodulation via rTMS or transcranial direct current stimuli (tDCS) can induce neurophysiological and clinical benefits in individuals with ASD.^{67,68,69,70,71} Preliminary results suggest that TMS might be of therapeutic value for improving core and associated symptoms of ASD. However, work on brain stimulation as a therapeutic technique for ASD is still in the very earliest stages of development. There remain many unanswered questions and potential barriers for widespread application of these techniques. In particular, the mechanisms by which these techniques might improve brain and behavioral function in ASD are not yet known. Most studies to date have been based on small samples, employed open-label designs, and provided mixed results; some people with autism appear to benefit while others do not. There is a need for well-controlled, randomized trials with adequate sample sizes to better understand whether brain stimulation is efficacious and safe and whether there are subgroups of individuals with ASD that might benefit from treatments based on brain stimulation. In particular, one major barrier to the widespread application of brain stimulation in treating ASD is the potential to cause epileptic seizure activity, especially in people who are already at risk for developing seizures. Epilepsy is a potentially devastating condition that is much more common among individuals with ASD, especially those people with ASD and lower intellectual abilities.

Stem Cells Stem cell technology has greatly advanced our understanding of typical and atypical neurobiological processes, thereby offering new opportunities for treating neurodevelopmental disorders including autism. Increasing evidence suggests that the pathophysiology of autism may involve neuroinflammation, at least in a subgroup of cases.⁷² Immune pathology in individuals with ASD is evident in overexpression of immune-related gene networks in postmortem brain tissue,⁷³ presence of maternal antibodies to fetal brain tissue,⁷⁴ atypical levels of proinflammatory cytokines (IL-6, TNF- α) in the cerebral spinal fluid,⁷⁵ and

excessive microglial activation leading to aberrant neural connectivity pathways.^{76,77} Stem cell therapies have been shown to modulate immune activity and facilitate neural connectivity and are being tested in autism populations.

Preclinical models have shown that umbilical cord blood contains effector cells that, through paracrine signaling, can alter brain connectivity and suppress inflammation.^{78,79} Infusions of stem cells in mouse models of autism have resulted in improvements in autism-like symptoms.^{80,81} In humans, infusions of autologous cord blood cells have been shown to be safe and beneficial in patients with cerebral palsy and other acquired brain injuries.^{82,83,84} A Phase I, open-label trial assessed the safety and feasibility of a single intravenous infusion of autologous umbilical cord blood in 25 children with ASD, 2-6 years of age.⁸⁵ Assessment of adverse events across a 12-month period suggested that the treatment was safe and well-tolerated. Significant improvements in children's behavior were observed on parent-report measures of social communication skills and autism symptoms, clinician ratings of overall autism symptom severity and degree of improvement, standardized measures of expressive vocabulary, and objective eye-tracking measures of children's attention to social stimuli, indicating that these measures may be useful endpoints in future studies. Behavioral improvements were observed during the first 6 months after infusion and were greater in children with higher baseline nonverbal intellectual ability. Double-blind, placebo-controlled studies of the efficacy of umbilical cord blood for improving autism symptoms are currently underway.

As with brain stimulation, this research is only just beginning, and there are many hurdles to overcome and unanswered questions to address before the field will know whether stem cell techniques can provide safe and useful treatments for ASD. This will be an important area of investigation to monitor as researchers work to replicate and expand these initial, encouraging findings.

TARGETING SPECIFIC BIOLOGICAL MECHANISMS

The prospect of precision medicine in ASD, i.e., specific, targeted treatments developed after gaining a better understanding of specific disease pathophysiology, is a tantalizing one. Genetically defined disorders such as Rett syndrome (RTT), Fragile X syndrome (FXS) and tuberous sclerosis complex (TSC) provide a unique opportunity to develop mechanism-based treatments for ASD. Thanks to basic science discoveries describing the molecular pathogenesis of these disorders, researchers have begun efforts to evaluate treatments targeting specific proteins in the implicated biological pathways.⁸⁶ In future work, biomarkers should be incorporated in order to help detect objective improvements in response to treatment and to identify optimal developmental periods to apply the treatment trials.

The most common cause of classic RTT is a *de novo* mutation in the X-linked gene MECP2 (methyl-CpG-binding protein 2). MECP2 mutations are inherited in X-linked dominant fashion, and females are almost exclusively affected. In light of the basic science discoveries in the pathogenesis of RTT,⁸⁷ researchers have proposed multiple routes to treatment for the disorder based on knowledge of MECP2 function. These strategies are designed to address either the underlying gene defect or downstream pathways implicated in the disorder. Clinical trials are underway evaluating the use of two different NMDA receptor antagonists, dextromethorphan and ketamine, to improve outcomes like epilepsy in RTT.⁸⁸ Among neurotrophic factor effectors downstream of MECP2, IGF-1 has been studied.⁸⁹ Double-blind, placebo-controlled trials of rhIGF-1 and NNZ-2566 (a synthetic version of the terminal tripeptide fragment of IGF-1) have recently finished and are being prepared for publication. The cholesterol pathway has recently been identified as being involved in RTT,⁹⁰ and lovastatin is currently under investigation in an open-label trial for females with RTT. Finally, directly or indirectly

manipulating faulty copies of the MECP2 gene, transcript, or protein is an appealing approach for treating RTT. Read-through strategies as well as gene transfer approaches using adeno-associated viral vectors are being actively pursued.

FXS is an X-linked, trinucleotide repeat expansion disorder involving the FMR1 (fragile X mental retardation 1) gene. This is a leading single-gene cause of ASD. The FMRP protein encoded by this gene regulates protein synthesis in neurons. Advances in our understanding of the pathophysiology of FXS have led to the development of numerous targeted trials. The most prominent theory of FXS, the metabotropic glutamate receptor (mGluR) theory, posits that many symptoms of FXS are due to exaggerated responses to activation of mGluRs. The prediction of this model was that reduced activation of mGluR would remedy the symptoms of FXS. However, recent clinical trials (Phase II and III) with two different mGlu5 inhibitors (basimglurant and mavoglurant) showed no therapeutic benefit in FXS patients for reasons that are as yet unclear.⁹¹ Driven by lessons learned from previous trials of mGluR antagonists, investigators are planning a multicenter placebo-controlled trial of mavoglurant for children with FXS ages 2 ½ to 6 years of age. This trial will examine outcome measures, including language, for all participants with a parent-implemented language intervention provided to all participants and psychopharmacologic intervention provided only to some.⁹²

Approximately 50% of the patients affected with TSC also develop ASD, and 90% will have seizures sometime in their life. Importantly, many patients with TSC will be diagnosed with this disease very early in life, usually in the newborn period, due to the presence of heart tumors. This provides the unique opportunity to investigate the development of ASD in this high-risk group during the first year of life. A recent study shows that an abnormal electroencephalography (EEG) signature has 100% positive predictive value for clinical seizures, 2-3 months prior to

the onset of these seizures.⁹³ These data have led to the initiation of a “prevention” trial in the high-risk infants with TSC using the anti-seizure medication vigabatrin. TSC patients have hyperactivation of the mTOR pathway, which controls neuronal protein synthesis similar to FMRP. The hypothesis that overactive mTOR signaling in TSC may be amenable to mTOR inhibitors has led to trials involving the use of this class of medications in patients with TSC. A large Phase III trial demonstrated that adjunctive mTOR inhibitor treatment was effective for refractory focal epilepsy in TSC patients.⁹⁴ Whether mTOR inhibitors will also be effective in improving neurodevelopmental symptoms including ASD is not yet known. A Phase II trial was recently completed; results are pending.

Taken together, advances in the study and treatment of RTT, FXS, and TSC have laid the groundwork for similar mechanism-based treatment trials in genetic disorders associated with ASD. Translating successes from animal studies have not been straightforward to date. Intellectual disability commonly affecting individuals with these neurogenetic disorders is an additional obstacle in study design in this field. Next steps will need to include biomarkers to help detect objective improvements in response to treatment and to identify optimal developmental periods to apply the treatment trials.

TECHNOLOGY-BASED INTERVENTIONS

Digital-based technology interventions for individuals with ASD have continued to increase in accessibility, breadth, and depth of use. Scientific evidence for the effectiveness of technology-based or technology-enhanced interventions has increased, with a larger number of randomized controlled trials (RCTs) appearing in recent years that highlight the breadth of technology applications in ASD research as well as their increasing rigor.⁹⁵ In the field of robotics, recent work has highlighted potential advantages of robots over human agents for accelerating several aspects of intervention research. Yet a number of challenges and gaps have been highlighted, which are also shared by speech-generating devices, virtual reality, video games and computer-assisted instruction, mobile applications, and telemedicine.^{96,97,98} It will be essential for future studies to address these challenges, as the development of interventions using digital technologies offers new opportunities to accelerate research progress. Furthermore, the proliferation of technology-based platforms purporting to help individuals with ASD points to a need for new, efficient, and scalable methods and infrastructure for evaluating technology-based interventions. Technology-based interventions have tremendous potential to benefit individuals on the autism spectrum in many ways, including by helping them improve social and communication skills and gain greater independence, all of which can improve the overall quality of life.

OUTCOME MEASURES AND BIOMARKERS

Over the past few decades, significant progress has been made in the development of new behavioral interventions and identification of novel drug targets aimed at reducing core and associated ASD symptoms and improving quality of life across the lifespan. A major challenge in determining whether new treatment approaches are efficacious has been the measurement of treatment response. Measurement of treatment response is particularly complex in ASD due to the heterogeneity resulting from an individual's symptom profile, sex, cognitive and language abilities, and development level. Moreover, many existing assessment measures were developed for screening and diagnosis and are not sensitive to assessing change in symptoms over time.

Considerable effort has been directed toward evaluating which existing measures are suitable for clinical trials and for developing quantitative, objective, and sensitive measures of treatment response. Increasingly, the input of key stakeholders, including caregivers and persons on the autism spectrum, is solicited to ensure that outcome measures reflect the priorities and needs of persons for which the treatments are being developed. Several reviews and consensus statements have been published that have evaluated the appropriateness of existing parent report and observational measures for clinical trials, including measures of social communication, anxiety, and repetitive behaviors.^{99,100,101,102} Studies validating observational measures of ASD symptom severity based on the Autism Diagnostic Observation Schedule (ADOS) have also been published,¹⁰³ and a brief observational assessment of social communication change has also been recently developed.¹⁰⁴

Biomarkers of treatment success are needed, as are “stratification” biomarkers for matching people to the best treatment for them at the best time. For example, while oxytocin (OXT) has been a promising target for treating core social communication symptoms in ASD, trials have not produced consistently positive or negative results. This is widely thought to be due to genetic and phenotypic heterogeneity among trial participants who nonetheless all receive the same diagnostic label of ASD. A recent study demonstrated the potential for pretreatment blood levels of OXT to serve as a stratification biomarker. Individuals with the lowest pretreatment blood OXT concentrations benefited the most from intranasal OXT administration.¹⁰⁵ 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 definitively indicate the requisite dose or duration of treatment. Predictive biomarkers (those that help to match individuals to particular treatments) will help to create more precise treatments and help individuals with ASD and their families to avoid wasted time and resources.

BIOMARKER DISCOVERY

Initial efforts have focused on developing measures that are linked indirectly or directly to underlying neural circuitry, which can offer insight regarding whether the treatment is influencing specific aspects of neural circuitry, inform researchers of the neural mechanisms that might underlie the treatment effects, and predict treatment response. These measures include eye tracking, electrophysiological responses, and magnetic resonance imaging, among others. Such measures can also serve as an early efficacy signal that can detect response to treatment before changes in

more distal measures such as language and social abilities are evident. Early efficacy markers can be used to identify which individuals are most likely to benefit from a given treatment and/or in adaptive study designs to indicate early in the trial whether modifications in the treatment (e.g., dose) should be made.

Eye Tracking (ET) ET has great potential for acting as an early indicator of treatment efficacy by tracking changes in social attention.¹⁰⁶ While applications of ET to clinical trials and interventions are still relatively new, results have been encouraging and suggest that ET can be used as a method for measuring response across a wide range of treatments. Promising future directions for developing ET as a marker of change include: furthering data-driven, computational, and machine learning approaches towards subtyping and stratification within the autism spectrum and for improved discrimination between individuals with ASD and controls; the design of ET batteries with the express goal of treatment measurement; the adaptation and advancement of ET metrics in technology-driven/technology-interactive interventions, such as virtual reality, robotics, and simulators, as well as in novel adaptive paradigms designed to change gaze strategies; and advancement of methodological considerations including the promotion of big data studies, facilitation of replication, and increasing adherence to more rigorous and universal technical and methodological standards.

Electrophysiological Measures Recent studies suggest that EEG, a non-invasive measure that can record patterns of brain activity throughout the lifespan, offers promise as a metric of treatment response related to neural circuitry.¹⁰⁷ Children and adults with ASD have distinct electrophysiological signatures, offering the possibility of using such measures to detect treatment response. Furthermore, distinct EEG signatures have been found among genetic subtypes of individuals with ASD and related disorders, and these signatures could be used in future clinical trials to test drugs targeted to individuals

with ASD associated with specific genetic syndromes. In future work, prior to these measures being useful as potential biomarkers, it will be important to demonstrate their ability to reliably predict a signature of dysfunction at the individual subject level, as opposed to group averaged data.

Magnetic Resonance Imaging (MRI) MRI techniques, including functional MRI (fMRI) and Diffusion Tensor Imaging (DTI), have provided a wealth of information regarding the neurobiological underpinnings of ASD. Specifically, task-based fMRI studies have pointed to atypical social-brain functioning and activation in ASD, while resting-state functional MRI and DTI have pointed to deficiencies in integrative social information processing as indicated by white matter atypicalities and diminished long-range connectivity.^{108,109} Despite the potential for brain imaging techniques to elucidate mechanisms underlying behavioral treatment response, few studies have directly used it for treatment monitoring or prediction of treatment efficacy. However, this appears to be rapidly changing, with several recent studies expanding on earlier work.^{110,111} Considerable progress has also been made recently in regards to the use of brain imaging techniques for understanding *in vivo* pharmacological neural action in individuals with ASD. Altogether, these advancements are beginning to provide the context for expanding the scope and applicability of brain imaging techniques for monitoring treatment across the lifespan, including before the signs of ASD are overtly apparent. Given the many successes yielded from the application of MRI methods to the development of biomarkers in ASD and related fields, considerable opportunity exists for further research and development in this area.

Advances in Developing Measures of Treatment Response Digital technologies, such as mobile devices, provide another approach for developing quantitative, objective, and sensitive measures of treatment response.¹¹² These tools provide opportunities to study biomarkers in

combination with self-report data, often in more naturalistic contexts such as the home. The ability of technology-based systems, such as mobile applications, wearables, and internet resources, to automatically record and generate data will increasingly provide richer, denser, and more meaningful information to researchers. Novel analytic methods, such as machine learning and computer vision analysis, can provide new insights into patterns of behavior. Although early in their development and application to ASD populations, such measures have the advantages of being scalable, objective, and feasible. Thus, studies that explore their utility as a method of treatment monitoring should be pursued. Additional emphasis should also be placed on transforming these signals into useful forms to maximally aid and personalize ongoing, real-world treatment of issues faced by individuals with ASD. As the understanding of these data streams matures, new methods and systems will need to be created to harness the power of this data and to manage the massive flows of information reaching data consumers.

Recently, a number of substantial investments have been made to support large, collaborative efforts aimed at validating biomarkers and outcome measures for use in ASD clinical trials. These consortia involve public-private partnerships among academia, advocacy and other non-profit organizations, government, and industry, with a goal

of de-risking investments into pharmacological ASD trials and optimizing the success of such trials. These projects are examining a wide range of potential biomarkers and their relationships with observational and caregiver-report measures of behavior in large samples of individuals with ASD versus typical development over time. Furthermore, regular communication, data sharing agreements, and shared measures across the existing consortia will increase the scientific utility of these investments. One example is **ABC-CT (Autism Biomarkers Consortium for Clinical Trials)**, a National Institutes of Health (NIH)-, Foundation for the NIH-, and Simons Foundation-funded consortium of sites that aims to develop, validate, and disseminate objective measures of social function and communication for ASD with the ultimate goal of advancing these measures as markers and predictors of treatment response.

In sum, multiple laboratories are conducting studies to develop better ways of measuring treatment response. Continued investment in such studies will ensure that, as new behavioral and medical treatments are developed, we will have the capability of testing their efficacy. Such investments will also be essential for developing improved methods for identifying subgroups that are responsive to specific treatments and identifying neural mechanisms underlying treatment response.

INNOVATIVE COMBINATIONS OF THERAPEUTIC MODALITIES

There are now tremendous opportunities for combining therapeutic modalities in ways that allow for positive impacts from the amalgamation that are greater than the sum of the parts. One example would be the combination of psychopharmacology and behavioral treatments. The core impairments of ASD (e.g., social communication)

have not been responsive to drug therapies yet. But, the possibility of combining drugs with behavioral interventions still holds promise for improvement in these core areas. A few of these studies are in progress, but none have been reported during this review period.

Advancement of new or reconceptualization of existing treatments into modular therapies (where therapies are organized into therapeutic modules that can be combined and reused in flexible arrangements) can provide finer granularity and more tractable opportunities for understanding change in individuals. This is an area of great need and can especially help address co-occurring conditions, such as anxiety, aggression, and depression.

Similarly, adaptive interventions, which incorporate more flexible study designs, can make more efficient use of existing clinical, research, and participant resources, providing more information to researchers and potentially greater benefit to participants. To encourage adoption, investment in study design methodology research (including dissemination of methods and development of trial design resources) will be of significant value.

ACCELERATING RESEARCH AND INCREASING ACCESS TO EVIDENCE-BASED INTERVENTIONS

While research in interventions for individuals with autism has shown consistent growth and advancement, opportunities exist for accelerating the pace of research. First, high-quality intervention studies are expensive to conduct and require substantial specialized expertise to oversee. Additional investment in human and research infrastructure is likely to yield compounding gains in autism intervention research progress. Creating and sustaining networks of institutions, investigators, clinicians, and families committed to shared, large-scale implementation of interventions or experimental research will combat fundamental heterogeneity issues in ASD research, leading to more reproducible and robust scientific findings. These networks can be leveraged to promote testing of novel interventions, exploration of unique scientific perspectives, and commitment to a culture of non-exclusive innovation transcending traditional boundaries. Additional investment should focus on bridging gaps between scientific evidence and clinical and/or community applications of interventions.

Additional opportunities may emerge from standardization of reporting and protocols so as to facilitate aggregation or comparison of clinical trial data at meta-analytic levels. Examination of evidence at a higher analytical level may

provide more comprehensive information about treatment effectiveness when clinical uncertainty is matched with appropriate variation along key implementation parameters. Similarly, sharing data at finer level of detail may additionally facilitate data mining investigations that may help to identify more streamlined assessment or nuanced precursors and predictors of treatment response.

Further resources should be directed towards promoting the development of applied scientific tools, including more robust statistical methods, data mining techniques, basic science methods, laboratory techniques, and optimized pipelines for discovery. Additional resources could also be spent at the tail end of intervention science, on the wider dissemination of implementable discoveries. Examples would include encouraging Phase II transitions to Phase III trials, identifying appropriate industry partnerships to foster larger-scale intervention implementation, and *in vivo* studies of ongoing new intervention integration efforts. Incorporation of business and operations perspectives into autism research infrastructure development may help to optimize intervention deployment efficiency, enabling more studies to be conducted in a sustainable fashion. By focusing on practical barriers to ultimate treatment

deployment (including insurance, provider adoption willingness, and marginal expenses), a more robust, efficient, and complete pipeline from idea to effective individual treatment can be realized.

INCLUSION AND EMPOWERMENT OF STAKEHOLDERS IN INTERVENTION RESEARCH

Empowering individuals with ASD and their families to act as active directors in the research process can also accelerate scientific progress. Development of tools to help stakeholders manage and maintain research, educational, behavioral, and clinical records could help them better advocate for participation in studies most relevant to their needs or most aligned with their personal goals. With a focus on usability and controlled data sharing, such tools could become interfaces by which information could be bi-directionally shared with researchers and relevant providers, reducing redundancy in information requests, streamlining study deployments, and reducing participant burden.

Currently, several incarnations of such systems have been developed, including Microsoft HealthVault and Apple HealthKit. However, efforts towards tailoring interfaces, cross-platform interoperability, and common standards must be pursued so as to best meet the specific needs of the autism community, to prevent data from becoming unnecessarily locked to proprietary platforms or formats, and to better enable data exchange. Creation of user-friendly research registries that promote awareness of relevant ongoing intervention studies or technologies, that can be personalized by user preferences (including constraints on geography, participation characteristics, and study facets), that are updated regularly and managed in a sustainable fashion, and that facilitate connections between legitimate researchers and qualified research participants (with appropriate governance of privacy and participant

rights) would further enable stakeholders to direct their research agenda. Adaptation of stakeholder-held records, including genomic information, for the purposes of creating an interface that would facilitate recruitment of participants with extremely specific characteristics (e.g., pharmacological trials targeting specific gene mutations) may be critical for appropriately powering highly targeted studies and for providing stakeholders access to the most tailored and innovative science.¹¹³ Throughout the research process, the involvement and feedback from the autism community should be emphasized so as to provide continuous context for research endeavors.

Much more attention has recently been given to quality of life outcomes for addressing the needs of individuals with ASD, including: academic success, autonomy and self-sufficiency, financial stability, health and well-being, inclusion, independent living, meaningful employment with fair wages, pursuit of dreams, recreation and leisure, respect and dignity, safety, self-identity and acceptance, social connections, and subjective well-being. Using such outcomes allows professionals, parents, and individuals to develop intervention plans that will allow a person with ASD to advance daily in each of the quality of life indicators. Measuring such outcomes can occur both in the short- and long-term and can be developed based on the needs of the individual in terms of their level of skills, functioning, and ability. When such indicators are maximized, the individual will be able to fully live a life maximizing long-term success.

SUMMARY

While there have been multiple, important advances in the field of autism interventions and treatments, there is still much progress to be made. Researchers must continue to develop new treatments as well as adapt existing treatments for diverse settings and populations, including males and females, individuals with co-occurring conditions and varying levels of ability across multiple domains, individuals across the lifespan, and those in settings or communities that are under-resourced or underserved. Moving forward, there are several important issues to consider. First, it will be important to leverage advances in our understanding of the neuroscience and neurobiological mechanisms underlying all therapeutic approaches. Second, researchers need to consider designs and recruitment strategies that allow for testing ways to maximize effectiveness and precise matching of treatment plans to individual needs and neurobehavioral profiles by combining therapeutic

approaches. More robust, standardized outcome measures should be developed, including adaptive measures, predictive measures, biologically based metrics, measures that address heterogeneity, and measures of practical outcomes and quality of life that will help better target therapies to individual needs and goals. It will also be important to study combination therapies that mimic how therapies may be delivered in real-world settings, and that offer the opportunity to provide greater benefits than any individual therapy alone. To realize the goal of developing the next generation of ASD therapies, funders will need to devote significant investment to building and enhancing the research pipeline to train of the next generation of multidisciplinary intervention scientists. Finally, it will be essential to provide more tools to practitioners through translation of research to community-based practice and to deploy effective, novel dissemination strategies.

OBJECTIVES

OBJECTIVE 1: Develop and improve pharmacological and medical interventions to address both core symptoms and co-occurring conditions in ASD.

Examples:

- Advance the study and treatment of genetic syndromes related to ASD, including RTT, FXS, TSC, and utilize the groundwork provided by investigations of these disorders to develop similar mechanism-based, genetically targeted pharmacology treatment trials for ASD.
- Explore innovative treatment modalities and combination therapies.
- Develop therapies to address challenges across the spectrum and across the lifespan.
- Investigate treatment response, including how females with ASD respond differently to treatment approaches, with a focus on the use of cognitive neuroscience tools to examine alternative mechanisms of change underlying symptom change.
- Develop biomarkers that can help inform decisions about the most appropriate interventions for particular individuals from across the autism spectrum and provide objective, early assessments of treatment response, prior to overt symptom change.

OBJECTIVE 2: Create and improve psychosocial, developmental, and naturalistic interventions for the core symptoms and co-occurring conditions in ASD.

Examples:

- Support research to ensure that interventions include the whole autism spectrum and diverse populations, including females, minimally verbal individuals, intellectually disabled individuals, adults, and individuals in under-resourced and underserved communities.
- Leverage the neuroscience of neuroplasticity of the adolescent and adult brain to develop psychosocial interventions targeting these age groups, meeting their specific needs, offering a path toward continued development of life skills, and enhancing quality of life.
- Define the “active ingredients” of successful therapeutic approaches as a basis for future innovation and tailoring of interventions to particular populations or settings.
- Explore combination therapies.
- Develop outcome measures that include biomarkers of treatment success, measures of improvement across multiple domains, and improvements in quality of life.

OBJECTIVE 3: Maximize the potential for technologies and development of technology-based interventions to improve the lives of people on the autism spectrum.

Examples:

- Develop tools allowing individuals with ASD to track and direct their own treatment.
- Develop technology-based interventions that help people with ASD improve their social and communication skills, increase their independence, and in many other ways help improve the quality of their lives.
- Develop interventions for minimally verbal children and those with intellectual delay, with a focus on the use of technology to augment communication (for minimally verbal children) as well as adaptive, individualized treatment approaches for both groups of underserved children.
- Increase access to interventions by developing technology-based treatments that can be deployed outside of primary care or clinical settings.



QUESTION

5

WHAT KINDS OF SERVICES AND SUPPORTS ARE NEEDED TO MAXIMIZE QUALITY OF LIFE FOR PEOPLE ON THE AUTISM SPECTRUM?

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

INTRODUCTION

In previous editions of the *IACC Strategic Plan*, Question 5 (Services) addressed access and coordination of services for individuals with ASD and their families. Research on services and supports focuses on self-directed care, coordination of funding and services among state and local agencies, community-based supports, and the need to better measure the health, safety, and mortality of people with ASD. Previous Question 5 *Strategic Plan* objectives included support for research to develop and evaluate the training of service providers who work with individuals with ASD, and to improve the efficacy, cost-effectiveness, dissemination, and implementation of evidence-based practices. In 2015, 6% (\$21 million) of ASD-related research funding from Federal agencies and private organizations addressed issues related to services.¹ A lack of sufficient funding raises considerable barriers for researchers to develop, test, and implement service system delivery models that increase the supply of care and address the gaps between research and practice.²

There have been several notable positive changes over the last few years regarding services research and planning, particularly due to an increased focus on the needs of individuals with autism as they age out of childhood.

For example, the U.S. Government Accountability Office (GAO) released two reports, the first entitled ***Youth with Autism: Roundtable Views of Services Needed during the Transition into Adulthood*** in 2016³ and the second entitled ***Federal Agencies Should Take Additional Action to Support Transition-Age Youth***,⁴ that described the needs of youth with ASD transitioning to adulthood and ways in which Federal agencies might fill current service gaps. New research on the cost of ASD across the lifespan has contributed to the knowledge base around ASD services. Researchers estimate that the lifetime cost of supporting an individual with ASD without intellectual disability in the United States is approximately \$1.4 million.⁵ Contributors to total costs for children with ASD were direct nonmedical costs, such as special education (including early intervention services), and indirect nonmedical costs, such as parental productivity loss. For adults with ASD, contributors include accommodation (residential care or supportive living accommodation), direct medical costs, and individual productivity loss. Other studies show that caring for a child with ASD can cost over \$17,000 per year more than caring for a child without ASD, with 18% of these costs associated with increased use of healthcare services.⁶

While these studies highlighted some of the areas in which the needs of individuals with ASD are not being met, they have not defined solutions. Adequate, cost-effective services are still lacking, as are strategies to decrease financial stress for families.

In this chapter, we describe gains and opportunities in specific service-related areas. For all the recent successes in ASD services research, gaps in services remain for children and adults with autism and their families.

PROGRESS IN THE FIELD

EDUCATION SYSTEM

Most school-aged children with autism receive the majority of their ASD-related services through the public education system.⁷ The number of children receiving these services, as well as the cost of their education, is increasing. A growing body of research suggests a nationwide problem of ineffective educational programming and the need for stronger educational workforce development, support, training, and supervision. With relatively little research on developing specific guidance for addressing challenges within the education system, it is necessary for educators working with students on the autism spectrum to address the complex and growing set of challenges.

While Federal and state legislation has placed a greater focus on accountability and performance standards, there is little agreement or standardization of how performance should be measured. The *No Child Left Behind Act* and the *Individuals with Disabilities Education Improvement Act* (IDEA) both state that students with ASD must have access to high-quality, research-based interventions that help keep them in the least restrictive instructional environment that can meet their learning needs. National programs such as the **SWIFT (School-Wide Integrated Framework for Transformation) Center** have documented change strategies and instructional approaches that can be used to meet these legal requirements. Federally funded programs such as the **National Professional Development**

Center on ASD have demonstrated improved outcomes when students are the recipients of evidence-based practices, and they have begun to develop practices to assist with the scale-up of these interventions. Unfortunately, implementation of evidence-based practices remains the exception rather than the rule; implementation of innovative interventions is challenging due to limited fit with classroom needs and lack of professional support. New research in implementation science highlights the need for a systems approach that includes involving leadership in and across schools to develop a strong culture and climate for quality implementation.

Our definition of autism and our understanding of how autism co-occurs with other mental health challenges has expanded. Eighty percent of students with ASD have co-occurring physical or mental health challenges,⁸ requiring new education strategies and coordination across multiple service systems. Recent research has focused attention on co-occurring anxiety^{9,10,11} and depression,^{12,13} as well as suicide risk.^{14,15,16,17} Models for recognizing and addressing these challenges in schools have not yet been developed or disseminated.

Many schools have not fulfilled the promise of educating children with autism in the least restrictive and most integrated environment suited to their needs. While several models of inclusion have demonstrated efficacy,¹⁸ the type and quality of inclusion programming to which

children with ASD have access is highly reflective of local policies, resources, and expertise rather than reflective of evidence-based practices grounded in research. There is also a need for quality interventions to help keep children with ASD in an instructional environment that maximizes their potential; because of the range of learning styles of children with ASD, students often need options such as distance learning and smaller group instruction.

Currently, the public education system is not adequately preparing all children with autism for adulthood. Although there have been improvements in recent years, approximately half of students with ASD leave secondary school without employment or plans for further education.¹⁹ While much of school programming is focused on those who will attend college, this is not an option for many students with ASD, who will also leave school without the skills needed to enter the workforce. During the transition to adulthood it is important to teach youth with autism the social and vocational skills necessary to have successful outcomes after leaving the education system.

HEALTHCARE SYSTEM

There has been considerable progress in some areas of ASD services-related research within the healthcare system. One important funding stream for reimbursement of services provided to individuals with ASD is the Medicaid program. Jointly operated between the states and the Federal government, Medicaid provides healthcare coverage for individuals below certain income thresholds and encompasses a wide array of benefits, such as case management; physical, occupational, and speech therapies; and rehabilitative services that are often used by individuals with ASD. The **Early and Periodic Screening, Diagnostic and Treatment (EPSDT)**, the child health portion of Medicaid, mandates the provision of medically necessary services found at section 1905(a) of the Social Security Act to Medicaid beneficiaries under the age of 21. EPSDT ensures that children and adolescents receive

appropriate mental health, developmental, and specialty health services. In 2014, the Centers for Medicare and Medicaid Services (CMS) issued guidance affirming the applicability of EPSDT standards to the treatment of ASD. Outside of Medicaid, there are large disparities in insurance coverage and reimbursement rates based on differences in state health coverage mandates. The effects of the discrepancies in billing rates and reimbursement prevent implementation of evidence-based practices and interventions for individuals with ASD and their families.

There is a continued need for ASD insurance reform. Families of children with ASD who have a **medical home** – a partnership with their primary care doctor to provide personalized treatment plans – report fewer unmet needs and more shared decision making with healthcare providers.²⁰ The *Affordable Care Act (ACA) of 2010, Section 2703*, created an optional Medicaid State Plan benefit for states to establish Health Homes to coordinate care for people with Medicaid who have chronic conditions. While ASD is not a chronic condition listed in the statute, it is subject to state application, then review and approval. State ASD insurance mandates increase ASD diagnosis and treatment rates by 13%, after controlling for other variables.²¹ This effect increases the longer the insurance mandates are in place. However, the number of children receiving ASD services is still fewer than would be expected given current prevalence estimates, though this does not control for public versus private service utilization.

Mounting research shows that **Medicaid Home and Community Based Services (HCBS) waivers** can significantly meet the service needs of people with ASD and decrease their unmet healthcare needs, especially among those who would not otherwise qualify for Medicaid.²² Those with ASD who access services through waivers are also less likely to use inpatient and long-term services care.²³ Since 2010, CMS has undertaken several activities that have provided new information about ASD

services available in the community. Among these is a report published in 2014, *Autism Spectrum Disorders (ASD): State of the States of Services and Supports for People with ASD*, which assesses existing state programs and supports for families living with ASD in all 50 states and the District of Columbia.²⁴ This CMS study provides a comprehensive view of services that received support from various Federal sources and were made available through state programs across the country.

APPROPRIATE SERVICES TO ADDRESS HEALTH AND SAFETY CONCERNS

Recent studies have shown that people on the autism spectrum are at increased risk of many health challenges and premature mortality.^{17,25} Research is needed to both understand what causes poor health and safety outcomes and to develop strategies to improve outcomes. Among the most pressing health concerns for children and adults diagnosed with ASD is ensuring adequate support to address co-occurring conditions, which may include mental disorders, sleep problems, gastrointestinal disturbances, or other issues.²⁶ Unfortunately, there is a lack of understanding and awareness among service providers regarding the challenges these conditions pose to individuals with ASD and their families.²⁷ This often leads to a lack of appropriate services and multifaceted interventions. Parents of children with ASD and co-occurring psychiatric conditions are more likely than other parents of children with ASD to report that their child's needs are not being met.²⁶ A broad assessment of mental health, learning, and cognition problems associated with ASD is crucial to determine appropriate services and treatments for people with ASD throughout the lifespan.²⁸

There is mounting evidence that these co-occurring conditions contribute to premature death among individuals with ASD. A Swedish study showed that the average death for an adult with autism is 54 years, and that loss of life years is mostly attributable to suicide,

seizures, and metabolic disease, among other conditions.²⁹ To address these significant health disparities, it is necessary to increase implementation of services and evidence-based approaches in addition to research to improve services for co-occurring conditions.

Wandering behavior presents additional safety risks for some individuals with ASD. Recently, the National Autism Association (NAA) released a report stating a third of reported ASD wandering/elopement cases in the United States were either fatal or required some level of medical attention, while encounters with water, traffic, and other threats accounted for an additional 38% of cases.³⁰ Among emergency care visits, adolescents with ASD accessed emergency department services four times as often as adolescents without ASD.³¹ There are also disparities in emergency department visits among children with ASD living in rural areas compared to urban places.³² Ensuring broad access to services through more innovative strategies is necessary to close the gaps in health and safety for children and people with ASD. One strategy that has seen success is ECHO Autism, a University of Missouri telehealth program aimed at reducing wait times and improving primary care for children with autism living in remote areas.³³ The program has seen success in Missouri and plans to replicate and expand the model to isolated areas throughout the country and world.

The healthcare system needs to emphasize increasing access in underserved populations and increasing cultural competency among service providers. The literature suggests disparities in utilization and access to healthcare and educational services for those with ASD from minority populations and families from lower socioeconomic status (SES).^{34,35,36,37,38} Ethnic minority children with ASD tend to receive diagnoses almost one year later than White children and often receive fewer specialty services.³⁹ Despite initiatives to increase the quality of healthcare provider interactions with families of children with ASD

and developmental disabilities, the health service systems do not meet the needs of minority populations.⁴⁰ Disparities in access and utilization may be due to the lack of cultural competency of providers, perceived low quality of care, or the lack of family-centered care, among other factors.³⁵ While research has been funded to assess variations in and access to services in relation to health disparities, the research needs to be taken a step further to study how to address what we have learned. We need to better understand what portfolio of services will result in the best outcomes for diverse populations.

Overall, it is important to continue to support research to test quality services and supports as well as evidence-based interventions that can eventually be implemented in a community setting and be accessible through medical coverage. A systematic, evidence-based, collaborative approach can facilitate the scaling up of evidence-based practices in community settings.⁴¹ Factors identified to aid in scaling up evidence-based interventions in community settings are organizational support and readiness, program and implementer characteristics, and sustainability planning.⁴²

ENSURING INDIVIDUALIZATION, CHOICE, PERSON-CENTERED PLANNING, AND SELF-DIRECTION

Often, service systems approach the needs of individuals with autism as one-size-fits-all, yet the heterogeneity of autism requires different supports for different people. Individuals with ASD and their families want to be able to make choices about their lives and actively engage in the planning of their services and supports. According to a National Core Indicators survey, the number of adults with autism receiving services through developmental disability (DD) agencies increased from 10% to 15% between 2008/2009 and 2013/2014.⁴³ Further, of the adults who used DD services, those with ASD had significantly less input into all measured life choices

(e.g., choosing roommates, choosing day activities) compared with those without autism. Also, fewer adults with autism were legally independent adults without guardianship (37%) than were adults without autism (53%).

In recent years, there have been greater efforts to advocate for use of person-centered planning models, particularly in Federal service systems. Medicaid-funded HCBS waivers are required to be furnished according to a person-centered plan of care, reflecting the services and supports that are important for the individual to meet needs identified through a functional assessment, as well as what is important to the individual in terms of preferences for the delivery of those services and supports. However, there are many individuals with ASD who are not using HCBS waivers but still need the right tools and services to achieve person-centered care throughout their lifespan. While research has identified some of the barriers to person-centered planning, the services community has yet to develop successful strategies to ensure individualization and choice for individuals with ASD to lead independent and meaningful lives.

CAREGIVER SUPPORTS

Caregivers may experience significant levels of stress as they support an individual's needs and manage medical and therapy appointments, while also engaging in work and other responsibilities.^{44,45} The high cost of services also creates increased financial strain for families, who often are the main caregivers across the lifespan. Families often need respite services to be able to take care of themselves, have breaks from caregiving, and increase their own social and emotional well-being so they are in turn able to support and care for their family member with ASD.⁴⁶ Also, respite care has been shown to reduce hospitalizations among children with ASD.⁴⁷ Mindfulness-Based Stress Reduction interventions have been shown to be helpful for families of individuals with disabilities, but those studies have primarily focused on families of children.⁴⁸

Parent education about autism and parent training focused on teaching behavior management strategies are both effective in reducing disruptive behavior – with parent training having a slight advantage in one study.⁴⁹ More research is needed regarding the effectiveness of these services for different parent populations and across different types of parent educators.

Further, studies are needed to examine the transition of care from parents to other family members, once parents are no longer able to provide care. There is a rich history of caregiver transition research among adults with intellectual disability, but little is known about how this process occurs in families caring for a relative with ASD.

OUTCOMES, QUALITY OF SERVICES, AND SERVICE NEEDS

One size does not fit all when addressing unmet service needs. Even though parents from both low- and high-income homes have awareness of their child’s service needs, parents from lower-income homes report more barriers to accessing services. Specifically, they report needing more information about services and more in-home services, while higher-income parents report needing higher-quality services.⁵⁰

Despite public investment in special education, studies show high rates of disconnection from jobs and continued education after high school. Of young adults who were not working or attending school, 28% also received no ASD-related services.⁵¹ Overall, one-fourth (26%) of young adults with autism received no services between high school and their early twenties.⁵¹

A qualitative study of service receipt and unmet service needs during the last year of high school found that youth with ASD in this cohort were receiving fewer services than youth with ASD captured in earlier data from the Department of Education’s National Longitudinal Transition Study-2 (NLTLS2).⁵² Two-thirds of the sample from the

2015 study had unmet service needs during the last year of high school, with 30% having three or more unmet needs. Specific needs included career counseling/job skills training and life skills training. Youth with autism without ID were far less likely to receive these services. Barriers included cost, geographic access to services, and lack of providers who accepted their insurance.

Results from the Pennsylvania Autism Needs Assessment survey, which represented people with autism ages 2-59 years indicated that, compared to other age groups, adults received fewer services for their specific unmet needs in social skills training (43%), speech-language therapy (22%), individual supports (21%), and occupational therapy (21%).⁵³ Focus groups of Pennsylvania adults with ASD who use Medicaid-funded services and those who care for them identified a specific set of needs: training (co-occurring diagnosis, sexuality, long-term planning), community engagement (individualized community activities geared to interests of individuals), socialization, and employment.⁵⁴

The complex needs of the service system make it difficult to sustain implementation science. For example, organizations trying to implement evidence-based practices might not be able to maintain the cost to fund these services and supports long-term. Current and future research initiatives need to consider improving the service infrastructure.

HOUSING, SUPPORTS, AND OTHER SERVICES ACROSS A CONTINUUM OF SEVERITY AND NEED

Residential services, postsecondary education, employment supports, behavioral and communication supports, lifetime learning supports, and other services are discussed in more detail in Questions 4 and 6 of the *Strategic Plan*, but they are important to mention here in that these services must also be provided based on the continuum of severity and need, and they must be integrated with other services as part of a coordinated system of services and care for individuals with ASD.

WORKFORCE

Underlying many of the challenges described in the above sections is the lack of a well-trained, supervised, and motivated workforce. Several studies have documented practitioners' insufficient use of evidence-based practices in community settings, as well as the difficulties associated in implementing these practices because practitioners lack appropriate pre-service training and preparation, oversight in the field, or a sense that the use of these practices is expected, supported, and rewarded.^{55,56} The field of implementation science has begun to address how to impact practitioner behavior through organizational change and direct-to-practitioner support. However, these strategies do not address more fundamental issues related to attracting highly qualified individuals to relevant professions, creating pre-service training programs that prepare individuals to deliver evidence-based care, and keeping individuals in the field once they complete their education and/or training.

COORDINATION OF SERVICES

There is also a need for systematic analyses of the complexities of accessing the service systems. While there is a lack of research in this area, families face multifaceted challenges to access services that often delay the receipt of early intervention services for a child. Expansion of Section 2703 of the ACA to include ASD and other developmental disabilities may increase the number of families who have a medical provider and a medical home and improve access to and coordination of care. Coordination of service sectors is urgently needed. Also, families must deal with different sources of funding for services, frequently with different rules for who, what, and how many services can be provided, with no clear sources of information about what these sources are and how they interact. The different service sectors are not coordinated and often do not communicate with each other, particularly across health and social service agencies. In most instances,

there is not funding to support coordination or an assigned liaison. There are other systematic barriers for families such as differences in the type and amount of services supported by insurance plans and the inequities and disparities in type and amount of services available among geographic location.

Individuals with autism often require services provided through different agencies and paid for through different systems. Care delivered across these systems often is inefficiently and ineffectively coordinated. Some of the challenges are endemic to systems that are providing care concurrently (e.g., the education and healthcare systems); other challenges are endemic to hand-offs between systems as individuals age out of one set of programs into another.

Some service models have been shown to promote better integration of care. For example, health home models and medical home models provide conceptual frameworks to coordinate and integrate services, as well as build systems of care for persons with ASD and their families.⁵⁷ Use of these models is not widespread, however, nor do these models address a host of other coordination challenges. For example, analysis of the **National Longitudinal Transition Study-2** found that only 58% of youth with ASD reported having received a transition plan by the Federally required age.⁵¹ The transition plan is a critical document that offers a template for coordination between the school system and systems that serve adults. In a 2012 report, GAO found that youth and their families faced challenges in identifying, navigating, and establishing eligibility for services for adults with disabilities, including autism⁵⁸ (GAO-12-594). The same report found that adult service systems did not routinely provide a coordinated plan of services or objectives for youth making transition to adulthood. There is a particular gap in implementing and evaluating the coordination between policy and practice for the services needs of individuals with ASD.

SUMMARY

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 implementation of best practices across settings. The Committee continues to highlight the need for researchers 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. There also needs to be an understanding of what portfolio of services will result in the best outcomes for diverse populations. More innovative research approaches and the resulting data will be needed in the future to support progress toward the IACC Question 5 Aspirational Goal of creating an environment where "communities will develop, access, and implement high-quality, evidence-based services and supports that maximize quality of life and health across the lifespan for all people with ASD and their families."

OBJECTIVES

OBJECTIVE 1. Scale up and implement evidence-based interventions in community settings.

Examples:

- Identify best practices, including systematic evidence-based collaborative approaches, to scale up existing services and increase access to evidence-based interventions in communities.
- Test and implement cost-effective healthcare services that increase the supply of care.
- Develop approaches that scale up the use of evidence-based practices in the educational setting and address the gaps between research and practice.
- Funding for provider training is a part of Question 7 Objective 2, but is cross-referenced here because successfully growing the service workforce is necessary to achieve this objective to successfully scale up and deliver evidence-based ASD interventions.

OBJECTIVE 2. Reduce disparities in access and outcomes for underserved populations.

Examples:

- Support research to understand and develop strategies to address health disparities, health inequity, and disparities in services access and utilization for underserved populations. Underserved communities include families with low socioeconomic resources, youth and adults with severe intellectual impairment, those who are racial/ethnic minorities, and women.
- Develop culturally competent service provision strategies, improve the quality of care and perception of quality of care to encourage utilization, and increase family-centered care as well as other best practices to reduce disparities.

OBJECTIVE 3. Improve service models to ensure consistency of care across many domains with the goal of maximizing outcomes and improving the value that individuals get from services.

Examples:

- Develop better metrics and measurement tools for health outcomes of people with ASD across the lifespan.
- Develop, test, and implement metrics and measurements for ASD services, as well as Federal, state, and local programs.
- Quantify outcomes in order to inform effective service models.
- Continue research into determinants of service quality, including accessibility, continuity, and flexibility of services.



QUESTION

6

HOW CAN WE MEET THE NEEDS OF PEOPLE WITH ASD AS THEY PROGRESS INTO AND THROUGH ADULthood?



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, satisfying relationships, and meaningful access to services and supports.

INTRODUCTION

Each year in the United States, approximately 50,000 individuals with autism spectrum disorder (ASD) turn 18 years old.¹ According to 2016 Centers for Disease Control and Prevention (CDC) data, prevalence of ASD in 8-year-olds rose dramatically from 1 in 150 in 2002 to 1 in 68 in 2012.² The 2002 cohort is now 23 years of age. Thus, across the next decade, we can expect a 123% increase in the number of youth with an ASD diagnosis exiting secondary school. There are significant concerns about how this increase will affect the transition and adult disability service systems. Research to understand the unique needs of this growing population is urgently needed in order to develop services and programs that facilitate opportunities for people on the autism spectrum to lead fulfilling, self-determined lives.

Since the *2013 IACC Strategic Plan Update*, there has been continued progress in understanding adult life for those on the autism spectrum. Nearly every study finds that adults with ASD have difficulty accessing disability and medical services, experience high rates of unemployment and underemployment, face difficulties in daily living skills and achieving independence, and contend with elevated rates

of physical and mental health disabilities. However, we also know that *some* individuals with autism *do* experience positive outcomes. Little progress has been made in understanding how best to support these individuals and their families so that good outcomes are the norm rather than the exception. This leaves providers and policy makers with an absence of evidence-based knowledge to use when deciding which services, supports, and programs will be most beneficial to adults with ASD, and few resources to implement those programs.

The increasingly influential voice of the self-advocacy community has highlighted the vast heterogeneity in strengths, impairments, and functioning among adults with ASD. Thus, real progress toward achieving the Aspirational Goal is even more challenging than previously thought, as it is highly unlikely that any given service or program can effectively meet the needs of all adults with ASD. Yet, these same voices also highlight the many and varied ways that adults with ASD can make rich contributions to society, making it even more imperative to understand how to support them in achieving their highest potential.

It is important to note that nearly every study cited in the following sections focuses on early adulthood and the transition years, and utilizes samples with little racial/ethnic or socioeconomic diversity. It is unclear to what

extent these findings apply to individuals in mid- or later-adulthood, from racial/ethnic minority groups, or with fewer socioeconomic resources.

PROGRESS IN THE FIELD

TRANSITION TO ADULTHOOD

The years immediately prior to the *2013 IACC Strategic Plan Update* – from 2010 to 2013 – were instrumental to demonstrating the challenges faced by youth with ASD and their families during the transition out of secondary school and into adult life. Studies during this time demonstrated high rates of unemployment and underemployment,^{3,4} difficulties accessing services,⁵ disconnection from friendship and social activities,⁶ and the negative impacts of secondary school exit on behavioral development.⁷

Increasing access to vocational rehabilitation (VR) services for adults with ASD has not significantly improved employment outcomes across the last decade; only one-third of adults with ASD receiving VR services achieve successful employment.⁸ These adults earned lower wages and worked fewer hours than other young adults with disabilities receiving services. Thus, even when receiving services, employment outcomes are poor for young adults with ASD.

Pursuing postsecondary education can be important in fostering independence, self-determination, and employment success. Greater numbers of individuals with ASD are seeking higher education opportunities in vocational/technical skills, 2-year colleges, and 4-year colleges/universities.^{9,10} Yet, fewer than half of college students with ASD feel they are able to handle most of the challenges they encounter.¹ The types of needed supports identified by individuals with ASD in higher education settings are

not those typically provided by disability services, such as supports for living on campus or living independently, training to engage in self-advocacy, and interacting effectively with peers and instructors.¹¹ For students with ASD who have significant mental health concerns, intensive services addressing emotion regulation in addition to the organizational and social skills necessary for college success may be needed. For students with co-occurring intellectual disability, a college-like transition program with a focus on independent living skills may be appropriate.

Little has been published on issues related to community participation, such as housing, social participation, and community integration, since the *2013 IACC Strategic Plan Update*. There is some evidence to suggest that youth with ASD tend to become more isolated from structured social/recreational activities in the community after leaving secondary school.^{12,13} This may be problematic for many, as the presence of meaningful daytime activity is a key contributor to quality of life.¹⁴ While no new data has been published on housing for people with ASD since the *2013 IACC Strategic Plan Update*, the most recent study found 87% of young adults with ASD lived with their parents or guardian after high school and only 19% had lived independently.¹⁵

There is a growing number of small intervention trials, funded through the National Institutes of Health, aimed at smoothing the transition process and improving adult outcomes for people with ASD. Targeted initiatives

responsive to objectives in the previous *IACC Strategic Plan* are supporting many of these new interventions. Ongoing studies are testing programs to: improve transition planning in schools; train parents how to advocate more effectively for adult disability services;¹⁶ improve family climate through group psychoeducational intervention;¹⁷ target self-regulation and social competence among college students with ASD;¹⁸ improve employment supports;¹⁹ increase social skills,²⁰ and build job interviewing skills and customized employment supports.^{21,22,23} Those interventions that show promising initial results ideally will be tested in large-scale randomized controlled trials, with the ultimate goal of incorporating them into intervention options to improve adult outcomes.

Despite these promising new directions for research, important gaps in knowledge remain. First, much of our information about the transition to adulthood comes from large, population-based studies such as the National Longitudinal Transition Study-2 (NLTS-2). These studies have provided seminal information about the range and scope of needs of youth with ASD exiting secondary school in the United States. Yet, the measurement in these datasets does not have the detailed, personalized information needed to provide targeted recommendations to disability service workers on college campuses, parents who want their sons and daughters to succeed in college or employment, or adults themselves who are searching for the most appropriate services and supports based on their unique situations. Coupling high-level snapshots like the NLTS-2 with “deep-dive” data collection into the lives of adults with ASD of all ages will likely provide the best evidence about how to support these individuals. Furthermore, the ASD community could benefit from a close examination of research and services strategies that have been effective with other vulnerable youth (e.g., exiting foster care) and adult (e.g., those with severe mental illness) populations to identify policy and practice approaches that could be adapted for people on the autism spectrum.

Given the high level of need, many publicly and privately funded initiatives are in place to improve post-secondary educational and employment participation and retention. College support programs for students with ASD are developing across the country, and college and universities without these programs consistently express a need for greater ASD-related support services. Yet, the effectiveness of these post-secondary education and employment programs is almost never evaluated. It is important to determine which of these many initiatives are producing positive results and for whom, so that an evidence base can be developed to guide service providers and policy makers as they are deciding which programs to implement.

Many of the cohort studies that inform our knowledge base about transition and adult outcomes involve samples of individuals who were diagnosed with ASD 20, 30, or even 40 years ago.^{24,25,26} With the many fast-moving initiatives around transition services and supports, community employment, and access to post-secondary education, it is unclear whether the post-school activities of youth with ASD who left secondary school 10 or more years ago are representative of today’s youth. Thus, it will be important to follow existing cohorts in the future, as well as continue to develop and follow new cohorts of youth with ASD as they transition to adulthood. This combination of strategies will allow us to understand development throughout adulthood, and ensure that recommendations for transition-related interventions and services do not reflect outdated needs of individuals and families.

LIFE COURSE OUTCOMES BEYOND TRANSITION: EMPLOYMENT, VOCATIONAL SKILLS, AND COMMUNITY INTEGRATION

Although most studies on adult outcomes since the last *IACC Strategic Plan* update have focused on the transition years, a handful have examined outcomes beyond early adulthood. Discoveries in the employment realm have centered on understanding patterns over time.

For many people with ASD, maintaining work or post-secondary educational positions once they are obtained is a significant challenge.^{27,28} The few studies that have examined employment beyond young adulthood do not find patterns of improvement over time; most adults who are unemployed or underemployed in early adulthood tend to stay that way, and independence in vocational positions declines over time for some.^{25,29} Also, many adults with ASD are working in segregated work settings. In 2014, the **Workforce Innovation and Opportunity Act (WIOA)** was signed into law to help increase competitive employment opportunities for individuals with disabilities. However, there is limited research focused on adults with ASD transitioning from segregated work settings into integrated employment. It is important to note, however, that poor employment outcomes are not universal; some adults with ASD successfully obtain and maintain jobs. Little is known about the factors that distinguish those adults who have greater versus fewer struggles with employment; those factors that have been identified are difficult or impossible to change, such as IQ or early language. One notable exception is self-care skills, which consistently predict employment and are amenable to intervention.^{3,29} There is a limited body of research examining employment supports available to some adults with ASD and how they can be beneficial to maintaining employment, such as the use of low- and high-tech assistive technologies and communication aids, natural supports, and mentoring. A wide variety of employment service options are needed, including expanding current models of job finding and development services, long-term intensive services and supports, and long-term but minimal supports (e.g., a few hours/month).

There is almost no research on the community participation of adults with ASD in middle or later adulthood. The needs of individuals with ASD in terms of employment, housing, social participation, and community integration almost certainly change as they age. There is also a need for research on transportation access for adults with ASD, including for

commuting to work and traveling to school, healthcare services, and community life activities. Yet, evidence to support the development of targeted programs and support is woefully lacking. Families and corporations are leading the way in innovations to find and sustain meaningful employment and community housing for adults with ASD, but further research as well as state and Federal government programs are needed to address current and future needs.

The heterogeneity of ASD traits and severity for those on the spectrum necessitates a variety of housing options to fit the specific service needs of each individual. Perhaps by virtue of the required infrastructure, housing options have been slow to respond to changing needs, values, and research findings regarding adults with ASD. Lakin and colleagues (2008)³⁰ describe the national agenda to increase the number of community-based housing options for individuals with intellectual disabilities as a way of increasing community participation and self-determined choice making. The recent **final rule from CMS** gives clear preference to small, community-based homes over larger congregate care settings and intentional communities. Some advocates have hailed this ruling as a victory that will increase community participation; others, especially those who care for severely impaired and medically fragile individuals, have expressed grave concerns that appropriate care will not be available under this new financing arrangement. There are remarkably little data available to support which housing options work best for which individuals, with studies presenting contradictory findings regarding the level of community participation and choice making that individuals with ASD or ID have in different housing options.^{31,32} Research is desperately needed on the most appropriate housing arrangements and in-home supports, and perhaps more importantly, strategies to better observe what happens in these arrangements, to increase community engagement, and to maximize quality of life.

Longitudinal studies of adults with ASD remain rare, but those that have been conducted provide some suggestion that many adults move into and out of “successful outcomes” across adulthood.^{25,27,28,29} To make progress toward the Aspirational Goal, there needs to be more focus on understanding how outcomes and needs of adults with ASD change over time, and how these variations compare to the general population. A one-dimensional look at outcomes such as vocation, health, illness, or quality of life at a specific point in time will not capture the rich diversity of life course trajectories. Further, it is almost certainly the case that interventions and programs to improve outcomes are more or less effective depending on when during adulthood they are delivered (right out of secondary school, for example, versus later in adulthood). However, we lack the basic, large-sample, descriptive studies to understand which types of interventions and services might be most effective for which adults, and when in the life course they have the most influence.

Another barrier that slows progress in adult ASD research is the inadequacy of current measurement tools. Without valid, sensitive outcome measures, it becomes exponentially more difficult to detect whether an intervention or service is effective and should be pursued. Further, it may be necessary to reconsider indicators of outcome altogether. Studies have typically defined what constitutes a “good outcome” (e.g., community employment, spending time with friends) and thus should be the target of services and supports. However, it is unknown whether these outcomes are the most meaningful to individuals with ASD or their families. It may be that the fit of the activities to the individuals’ interests and abilities is most important, or it may be that subjective quality of life should be an equal or greater focus as objective indicators like employment or post-secondary education. To reach the Aspirational Goal, careful research is needed to understand how to define “good” outcomes in a systematic yet personalized way, and then measurement tools are needed that reliably capture those outcomes. Once outcomes can be assessed in a way

that takes into account the desires, skills, and abilities of adults with ASD and their families, then the Aspirational Goal of developing programs and supports that allow adults on the autism spectrum to reach those outcomes will be more feasible.

HEALTH AND HEALTHCARE

Current knowledge about mental health, physical health, and healthcare experiences among adults with ASD is also limited. Co-occurring psychiatric conditions (i.e., two or more mental health diagnoses co-occurring in an individual), known to be high among children and adolescents with ASD, remains challenging in adulthood. Most children with ASD who have other psychiatric disorders continue to have at least one co-occurring diagnosis in adolescence and early adulthood.³³ More than half of adults with ASD have at least one additional psychiatric disorder, a rate that is considerably higher than in the general population.³⁴ Difficulties with mood and anxiety appear to be most problematic,^{35,36,37} and failing to address these mental health symptoms adequately can lead to poor outcomes. For example, individuals with ASD with higher levels of anxiety and depressive symptoms are more likely to experience difficulties in adaptive functioning.³⁸ Even more sobering, recent research has indicated the rate of suicidality is estimated to be nine times higher among adults with ASD than in the general population.³⁹ Outside of person-level factors such as gender, verbal ability, and ASD severity,^{33,35} little is known about the full range of factors related to stability or emergence of co-occurring psychopathology among these adults.

Co-occurring physical conditions are also a concern. Compared to adults without ASD, those with ASD have increased rates of common physical health conditions (e.g., sleep disorders, gastrointestinal disorders, and diabetes), as well as rarer conditions (e.g., stroke, Parkinson’s disease, and genetic disorders).³⁴ Children and adults with ASD in the United States have a higher risk of

being overweight or obese than the general population, putting them at risk for cardiovascular disease, cancer, and other chronic conditions across the lifespan. More work must be done to develop and test interventions that prevent, control, and/or moderate the effects of physical and mental health disabilities.⁴⁰

While adults with ASD experience increased rates of co-occurring conditions, individuals with ASD are also at greater risk of injuries such as falls, suffocation, drowning, and self-harm.^{42,49} Unintentional injuries and wandering can often lead to premature mortality, indicating the critical need for prevention programs targeting these risks.⁴⁹ There is also a lack of research on understanding alcohol and substance abuse disorders among adults with ASD, but this will be necessary for developing and implementing prevention and treatment strategies.⁴¹ Other health concerns related to safety and risk, such as wandering and victimization, are discussed later in this chapter.

Studies on healthcare utilization indicate adults with ASD utilize a disproportionate amount of outpatient, inpatient, prescription, and emergency department services.^{31,42,43,44} Only one study has examined self-reported utilization of preventive services, finding that adults with ASD were significantly less likely to report tetanus vaccination and pap (Papanicolaou) smears than adults without ASD.⁴⁴ Further, adults with ASD experience more barriers to service use and participation in the medical visit, as well as lower satisfaction.^{40,44,45} Specific barriers include anxiety related to the medical visit, as well as unmet needs for additional time to process information and ask questions, additional modes of communication, and reduction of sensory stimulation. It is important to note that self-report is a substantial challenge for many adults with ASD when visiting medical settings. The physician-patient dynamic is highly dependent upon the patient describing specific details of acute and chronic conditions, including pain and injury; it is often difficult for adults with ASD to engage in the same manner of self-report of medical conditions.⁴⁵

Relatively little is known about the aging process in people with ASD and what types of interventions, services, and supports might foster health maintenance as individuals age. Several studies have suggested that people on the autism spectrum are vulnerable to premature death due to a number of causes, including epilepsy, late diagnosis of medical conditions, and accidents.^{39,46,47,48,49} More research is needed to understand causal and risk factors and develop strategies to prevent early death. In addition, research on how autism characteristics, co-occurring conditions, and physical and social functioning change during the aging process will be needed to develop evidence-based practices to support the needs of people with ASD as they age. We anticipate that the needs of those who are currently older adults, who may not have received interventions and services earlier in life, may also be different from the needs of current youth and young adults who received different types of interventions and services in the period before reaching adulthood.⁵⁰ Thus, research on current older adults with ASD and longitudinal research to follow the trajectories of youth and young adults will both be necessary to meet the needs of the population of adults with ASD.^{51,52}

Although there is a reasonably good understanding of the prevalence and disparities in various health states for adults with ASD, there are several gaps in this knowledge base, including how best to screen for and clinically assess secondary conditions and monitor progress, as well as treatment dissemination and provider training.^{25,53} There have been few attempts to establish the validity of instruments commonly used to assess other psychiatric conditions in individuals with ASD. There has also been limited consideration of differences in how the manifestations, course, or treatment of psychiatric disorders might differ for these adults. Further, the majority of studies on physical health needs of adults with ASD utilize retrospective point-in-time data and lack objective

health assessment measures. Better measurement tools and methods are necessary to understand the scope of physical and mental health needs and design appropriate services and supports.

Research involving adults with ASD clearly show that they desire and are often capable of more independent management of their health.^{44,54} To ensure these adults are able to participate in their care to their fullest abilities, the healthcare system must increase health professionals' knowledge about ASD in general and risk factors for co-occurring conditions. Similar to the general population, providers should examine the adult's general physical and mental health needs and provide guidance on how to ensure the person is living the healthiest and highest quality of life possible. Small adjustments to the clinic setting (e.g., preparatory written/verbal communication about visit procedures, private waiting rooms, use of alternative forms of communication, care coordination, and extended time) can greatly improve the healthcare experience, compliance, and involvement for adults with ASD. Previous initiatives to improve care for those with ASD in the United States have fallen short in allocating funding and provide little guidance regarding appropriate care for this population.

ADULT DIAGNOSIS

Longitudinal studies demonstrate clear evidence that ASD-related difficulties persist well into adulthood. In several cohorts of children diagnosed with ASD in early childhood, 80-90% of individuals continued to meet criteria for clinical diagnoses of ASD as adults.^{24,55} Simultaneously, increasing numbers of adults are presenting to clinics for first-time diagnoses, and recent epidemiological work suggests that many adults with ASD may be unidentified and living in the community without appropriate supports.⁵⁶ In addition, as development of screening and diagnostic tools, as well as other autism research, has largely been accomplished using data from boys and men, girls and

women on the autism spectrum may be underdiagnosed, and we know little about their ASD trajectories across the lifespan.^{34,57,58}

Research to improve adult diagnosis is very new and, as such, there are many important gaps and areas for future study. First, there is limited knowledge of the manifestations of ASD in adults. Longitudinal studies have found that some adults with ASD show "improvement" in autism severity compared to estimates obtained during earlier childhood or young adulthood.^{25,59,60} However, an extensive body of child research has shown that ASD characteristics differ depending on a child's developmental stage (i.e., language and cognitive abilities, as well as chronological age), and the types of behaviors that best differentiate children from neurotypical peers are somewhat different from behaviors that differentiate adults with ASD from neurotypical peers.^{61,62} Thus, apparent "decreases" in autistic characteristics may simply reflect that instruments designed for use with children do not adequately query the types of behaviors or deficits most relevant to adults with ASD. Currently, there is not a standard tool or measurement used for diagnosing ASD in adults. However, there is an ongoing study to adapt the Autism Diagnostic Observation Schedule-2 (ADOS-2) Module 4 for use in diagnosing adults.^{62,63} There is also hope that work being done to create biomarkers that predict ASD, such as perceptual computing measurements of quantitative traits, will be able to be adapted as tools for diagnosing adults as well.⁶⁴ Research is needed to understand how ASD characteristics change across development and how core deficits manifest in adults. Studies must include consideration of young, middle-aged, and older adults, including those diagnosed as children and those identified in later life.

Second, little is known about individuals who obtain first-time ASD diagnoses as adults. Many of these adults have other mental health concerns; in one study of young adults seeking a first-time ASD diagnosis, 46% had a previous psychiatric diagnosis, and 53% had contact with

mental health services.⁶⁵ These findings suggest that a population of individuals with high needs is being misdiagnosed or “missed” as children. Research is needed to understand profiles of strengths and challenges of this population, to inform development of screening and diagnostic tools and best diagnostic practices for adult ASD referrals. Such research will need to take into account that adult psychiatric assessment traditionally relies on self-report, whereas ASD diagnostic practices rely more on direct observation in structured clinical settings and/or caregiver report. Childhood caregivers may not be available or may have difficulty recalling specific behaviors occurring many decades ago. Exclusive reliance on self-report may also not be ideal, due to possible limitations in insight, communicative difficulties, or over-reporting of autism characteristics to achieve secondary gain (e.g., involvement in legal system, to obtain financial assistance).

Third, currently it is not known if and how later-life diagnosis affects mental health or well-being, or fosters identification of supports or interventions. Considering that state-funded support programs often require documentation of diagnosis prior to 18 or 22 years of age, it is unlikely that someone diagnosed in middle adulthood would be able to access ASD-related supports. Obtaining a diagnosis in the absence of appropriate services and supports may be detrimental to well-being for some individuals. On the other hand, they may benefit from private services, participation in online communities for individuals with ASD, etc. Research in this area is needed to educate adults self-referring for diagnosis about the possible benefits and risks of obtaining an ASD diagnosis, as well as to provide insights into the types of services that should be developed to support the adult’s integration of diagnosis into their self-perceptions.

SERVICE DELIVERY FOR ADULTS

As the research base continues to build, there are improvements in service delivery that can be made to reach the Aspirational Goal more quickly. First, it is critical that additional funding is provided for adult disability services. Currently, waiting lists for services in most states are very long, and adults with ASD rarely receive the range and extent of services that would allow them to reach their potential. Adults with ASD and their families who are more vulnerable to poor outcomes in adulthood – by virtue of having fewer socioeconomic resources or being of a racial/ethnic minority group – also have the greatest difficulty accessing needed services.^{3,5} It will be nearly impossible to reach the Aspirational Goal of self-determination, choice, and meaningful access to services – especially for those who are most vulnerable – without a significant investment in the quantity and quality of adult disability services and actively working to reduce barriers to access.

One way to increase quality is to invest more in the training of professionals, across disciplines, to work effectively with adults with ASD. Few adult care providers (healthcare, mental health, employment supports, etc.) have received training on how to support adults with ASD. The implications of this lack of training are far-reaching. Staff turnover is a significant issue in vocational and residential support services, and likely stems (at least in part) from inadequate training. Many adults with ASD receive their healthcare in pediatric settings, due to a dearth of adult providers who feel competent and comfortable treating them. This can pose a health risk, as pediatric providers are not trained to treat adult health issues. In terms of diagnostic issues, few validated screening and diagnostic instruments are available for use in identification of ASD in adults, and few clinicians specializing in adult screening and diagnosis are available to provide services. Neither Psychology nor Psychiatry educational programs (as well as other disciplines) are adequately preparing trainees to diagnose adults with ASD. The few programs that offer clinical rotations

through specialty clinics often focus on persons under the age of 18 or 22, due to their presence in pediatric departments. As such, there is a need for training grants and initiatives focused on training professionals who will be working with adults to detect, diagnose, and address mental and physical health-related needs in this population.

Progress will be achieved more quickly if greater focus is placed on the coordination of services between states, between agencies that provide adult services, and between school-based and adult services. Currently, Medicaid-funded services do not transfer between states, limiting people's mobility when relocation to another state would serve them well. Given that most adults with autism have complex needs that bring them into contact with multiple public service systems, there is an urgent need for research and initiatives focused on care coordination, interagency collaboration, strategies for integrating extant funding streams, and community-based collective impact strategies. WIOA specifies that state VR agencies must set aside 15% of their funding to provide pre-employment transition services (pre-ETS) to secondary school students who are eligible under either the *Individuals with Disabilities Education Act* or *Rehabilitation Act* Section 504. However, it remains to be seen if state agencies will be able to carry out the responsibilities associated with legislation such as WIOA. It will be important to monitor the effectiveness of these initiatives with careful data collection and analyses. Also, WIOA is designed to encourage state-level experimentation and variability in program design. This presents a unique opportunity to study emerging practices and capitalize on this variability to learn what works for whom.

SAFETY, VICTIMIZATION, AND INTERACTIONS WITH LAW ENFORCEMENT

In the past 5 years, safety issues have emerged as a key concern in the autism spectrum community, yet the research evidence on this topic has lagged far behind.

Elopement and peer victimization (social, verbal, and physical) are common in children and adolescents with ASD, but there is limited research on these topics as they relate to adults.^{66,67} A 2012 survey conducted by the National Autistic Society in the UK found over a third of adults with ASD experienced bullying or discrimination at work.⁶⁸ A recent report suggested that, relative to adults in the general population, adults with ASD were twice as likely to experience sexual coercion or rape.⁶⁹ Although there is some suggestion that adults on the autism spectrum might more often be involved in the criminal justice system, recent data from the NLTS-2 suggests that transition-aged youth with ASD were actually less likely than those with other disabilities to be stopped by police or arrested.⁷⁰ It might be that when they are engaged with police, impairments related to ASD make those interactions more difficult, leading to negative outcomes.

Careful research is needed to understand the experiences of victimization in adulthood – sexual victimization, physical victimization, and being taken advantage of – as well as the prevalence of other safety risks, such as wandering and the often adverse outcomes that unfold from wandering. While little is known about adults with ASD wandering behaviors, a recent report found 27% of adolescents engaged in wandering behavior within the past year.¹⁰ Wandering from safe places and situations can lead to individuals with ASD being lost, missing, or injured. Studies are needed to understand the characteristics of those adults whose safety is at risk, so that preventative efforts can be put into place. Research focused on adults in the criminal justice system is also important to understand precipitating factors for criminality or adverse interactions with law enforcement; Helverschou et al. (2015)⁷¹ found that among criminal offenders with ASD in Norway, 67% of crimes were related to obsessions or special interest. A recent study assessing the experiences of adults with ASD and police officers in England showed conflicting views on the quality of the interaction;⁷²

police officers expressed satisfaction with how they had worked with individuals with ASD, whereas the individuals with ASD were largely dissatisfied with their police interaction. Research strategies to develop a better understanding among law enforcement might lead to less adverse interactions and result in treatment rather than incarceration, which does not improve the situation for people with disabilities. Long-term studies should also examine the impact of childhood victimization or other threats to safety, as these might lead to mental health concerns among adults with ASD.⁷³ Intervention studies to improve awareness and safety are necessary.

There are currently a limited number of programs to improve safety for individuals with ASD. In some communities, policy officers and judges receive training on autism spectrum features, so that impairments associated with ASD are appropriately considered in interactions. Despite this, the current research is insufficient to understand the types and extent of need, or to inform evidence-based programs to ensure safety among adults on the autism spectrum.

LONG-TERM AND CAREGIVER SUPPORTS

One of the best understood predictors of outcomes in adulthood is level of cognitive functioning: relative to those with ASD without an intellectual disability, adults with ASD who have an intellectual disability are significantly less likely to be employed or living in the community (e.g., Howlin and Magiati, 2017).⁷⁴ However, little is known about how to support adults with ASD and co-occurring intellectual disability in reaching their maximum potential.

More work is needed to understand and evaluate the effectiveness of long-term supports for those with high support needs (such as those with significant cognitive impairments). As many of these adults will be receiving some sort of formal adult disability service, more rapid headway can be made in this area if service providers systematically collect outcome data. As with other areas, the results will not be one-size-fits-all: the most

appropriate supports will depend on the skills and desires of the adult, as well as the specific area being targeted (e.g., vocational skills versus mental health). Supports should also take a lifespan developmental perspective, encouraging the development of new skills and abilities throughout adulthood. For those adults with difficulty communicating, parents and other care providers can play a key role in relaying their sons' and daughters' preferences and interests. Person-Centered Planning tools such as PATHs⁷⁵ and MAPs⁷⁶ can be useful to incorporate the perspectives of adults with ASD with more significant impairments.

Further, the knowledge base about how to support individuals with ASD as they move into middle and later adulthood is almost non-existent. Small-sample studies have provided some suggestion that needed supports will likely intensify in old age; relative to typically developing controls, older adults with ASD experienced more severe cognitive declines in some domains and higher frequency of Parkinsonism.^{77,78} Housing needs will surely intensify when parents are no longer able to provide care.

Often families play a critical role in providing support to their adult sons and daughters on the autism spectrum. Once youth with ASD leave the school system, responsibility for finding and coordinating services tends to fall to parents and siblings. In many cases, adults with ASD continue to live with their parents until parents are no longer able to care for them. Even when adults live independently or semi-independently, parents often provide supports (e.g., financial, tangible) that facilitate the son or daughter remaining in that residential situation. For many adults who are better integrated into their communities, high support needs can greatly exceed available resources of family members for coordinating and organizing community-based life activities.^{12,79} Exceedingly high levels of stress among parents of adults with ASD have been found via self-report measures as well as biological indicators of stress (e.g., cortisol).⁸⁰ However, there are few interventions aimed at supporting families.

Most parent-focused interventions, when their children with ASD are adults, provide caregivers with skills or knowledge to better support their sons and daughters, and not necessarily to improve their own stress and well-being.^{16,17}

Despite the prominent role of families in the lives of their adult sons and daughters with ASD, their influence is often ignored in research. There is a significant research gap in understanding which families are most effective in

supporting their adult offspring with ASD, as well as in how to provide services and supports so that families can continue to provide care.⁸¹ These research questions become even more important in the face of an underfunded adult service system. Because housing and other adult services are limited in availability, it is even more critical for policy makers and providers to ensure that families are well-supported so that they can continue their caregiving role as long as possible.

SUMMARY

To understand how to support adults with ASD, it is first necessary to investigate the specific areas in which adults might need supports. This is, perhaps, where the greatest progress toward the Aspirational Goal has been made. We have reasonably strong evidence about the struggles faced by adults with ASD in acquiring needed disability services, accessing healthcare, finding appropriate employment or vocational activities, and achieving good mental health – at least during young adulthood.^{3,5,26,35,38,82} Yet beyond basic description, there are numerous gaps in knowledge that limit our ability to support these adults effectively. The vast majority of what is known about autism spectrum disorders in adulthood has come from samples of primarily white, middle-class, well-resourced families of males with ASD who are of average or above average intellectual functioning. It is unclear how much of our current knowledge about how to achieve the Aspirational Goal would translate to those adults and families who are under-represented in research. Thus, studies should focus on including more diverse participants, including families with low socioeconomic resources, youth and adults with severe intellectual impairment, those who are of racial/ethnic minorities, and women on the autism spectrum.

It is unlikely that we will make meaningful progress toward the Aspirational Goal without substantially increasing

funding for autism research and services focused on adults.

Research focused on adult issues has lagged far behind other types of ASD-related research, comprising only 2% of all autism research spending in 2015.⁸³

Many fundamental questions about the life course that are unanswered among adults with ASD – such as basic understandings of how core and related autism characteristics, functional outcomes (e.g., employment, education, independent living), and health change across adulthood, along with the variable factors that predict improving life course trajectories and quality of life – have been well-researched in other groups and conditions. These questions form the necessary building blocks for effective and efficient interventions and services; nevertheless, these questions can be seen as lacking significance or innovation for those outside the autism field (who assume the answers are known). This can be a significant barrier when attempting to obtain funding for adult autism research. We will make more rapid progress toward realizing the Aspiration Goal once it is clear that a range of studies – from understanding biological and cognitive processes underlying outcomes, to more “natural history” studies of the life course, to evaluating existing services, to intervention trials to improve outcomes – are critical to support adults with ASD in reaching their maximum potential.

OBJECTIVES

OBJECTIVE 1: Support development and coordination of integrated services to help youth make a successful transition to adulthood and provide supports throughout the lifespan.

Examples:

- Use population-level data to understand unmet needs, disparities in access and outcomes, emerging usage trends, cost issues and the effectiveness of services in achieving their desired outcomes.
- Conduct research to determine the prevalence of autism in adults and the scope and distribution of service needs among the population to inform policy and program planning.
- Develop strategies for reducing socioeconomic or racial/ethnic disparities in service access and related outcomes for adults with ASD.
- Investigate social capital, the network of supports, and community integration provided by families, service providers, and others to understand the range of formal and informal supports needed to achieve successful adult outcomes.
- Develop additional service coordination across agencies (e.g., educational and vocational rehabilitation; mental health and vocational rehabilitation).

OBJECTIVE 2: Support research and implement approaches to reduce disabling co-occurring physical and mental health conditions in adults with ASD, with the goal of improving safety, reducing premature mortality, and enhancing quality of life.

Examples:

- Conduct large-scale longitudinal studies across adulthood into older age to examine trajectories of physical and mental health conditions, and address the additive and interactive effects of biological, cognitive, behavioral, and environmental factors that lead to co-occurring conditions.
- Conduct studies to improve self-management of co-occurring mental health disabilities, including anxiety, depression, and/or suicidality.
- Engage adults on the autism spectrum and their families, through collaborative and participatory research, to be involved in the development of ecologically valid measures of quality of life, which can be used to understand the factors associated with positive quality of life throughout adulthood.
- Create programs to recruit and train more general physical and mental health providers to be knowledgeable about and willing to treat adults with ASD. This applies to primary care providers, community mental health providers, and specialists.

OBJECTIVE 3: Support research, services activities, and outreach efforts that facilitate and incorporate acceptance, accommodation, inclusion, independence, and integration of people on the autism spectrum into society.

Examples:

- Examine factors and support strategies that promote successful participation and retention in post-secondary education, employment, and/or community living activities across the spectrum of ASD and across the adult lifespan.
- Develop reliable outcome measures that take into account the desires of the individual and his/her family, as well as the match of the activity with the interests, skills, and abilities of the adult.
- Conduct long-term follow-up studies examining the effects of interventions and services delivered in childhood on later adult outcomes.
- Conduct large-scale studies of programs to improve the skills that may underlie many aspects of community integration (e.g., adaptive behavior, executive function)
- Better understand the needs of adult service providers, as well as the characteristics of effective providers.
- Encourage more skilled workers to enter and remain in the adult disability service provider field, which is critical to improving self-determination of adults with ASD.



QUESTION

7

HOW DO WE CONTINUE TO BUILD, EXPAND, AND ENHANCE THE INFRASTRUCTURE SYSTEM TO MEET THE NEEDS OF THE ASD COMMUNITY?

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

INTRODUCTION

Appropriate research infrastructure is critically important to the success of the *IACC Strategic Plan*, and progress toward the Aspirational Goal has been rapid over the past 8 years. New databases are being built to leverage recent genetics findings, and efforts to share biospecimens among multiple research efforts are intensifying. This increased availability of resources has advanced the efficacy and speed of ASD research. Surveillance systems have also progressed over the past 8 years, with new efforts focused on tracking more descriptive symptoms as well as a binary diagnosis. As the diagnosis of autism has broadened, more children are being identified who do not have co-occurring cognitive disability, and additional resources have been focused on serving the needs of people across a diverse spectrum. Furthermore, many government and private organizations regularly share lay-audience-friendly summaries of research findings to raise community awareness, including Simons Foundation, Autism Science Foundation, Autism Speaks, the Interactive Autism Network (IAN), the National Institutes of Health (NIH), and the Centers for Disease Control and Prevention (CDC).

In 2010, the IACC decided to track investments and evaluate progress in this area in the same organized, rigorous manner that is used in the rest of its *Strategic Plan*. From 2009-2015, a total of \$302 million dollars has been invested in building and maintaining ASD research infrastructure, including surveillance efforts. While many of the original infrastructure needs identified in 2010 have been accomplished, continued investment is critical in order to maintain, develop, and build on these valuable resources. Specifically, there must be a focus on enhancing the biorepository infrastructure, the data infrastructure, the human infrastructure, and surveillance activities in order for autism research to be successful.

BIOREPOSITORY INFRASTRUCTURE

Biological materials repositories collect, process, store, and distribute biospecimens to support scientific investigation. In the autism research community, biorepositories have been developed to support collection and dissemination of brain tissue, fibroblasts, and other tissues. Greater participation in brain and tissue banking is needed from members of the autism community in order to obtain enough samples to meet research requests. Outreach campaigns to encourage families to donate brain and other tissue need to be expanded and enhanced.

BRAIN BANKING

The **NIH NeuroBioBank** was formed in 2013 to address the increasing demand for postmortem human brain tissue for research purposes.¹ Although this resource provides tissues for wide-ranging neurological and neurodevelopmental disorders, there is high demand for tissue from donors diagnosed with autism spectrum disorders. The NIH NeuroBioBank supports six independent brain and tissue repositories; the University of Maryland site collects and distributes the majority of ASD tissue. The collection has been highly sampled over the years and continues to grow through outreach activities and collaborations with other organizations.

A more autism-focused effort was undertaken in 2015 by the **Autism BrainNet**, supported by the Simons Foundation. Autism BrainNet is focused exclusively on creating a collection of ASD and control brains. The program supports four nodes throughout the United States (New York, Massachusetts, Texas, and California) and one in the United Kingdom that share standardized protocols for tissue

harvesting, storage, and tissue dissemination. Autism BrainNet has a robust public awareness campaign to encourage donation, led by the Autism Science Foundation, fulfilling one of the longstanding goals of the *IACC Strategic Plan*. The NIH NeuroBioBank and Autism BrainNet work closely together to ensure that tissue acquisition, processing, and distribution from both resources are conducted with the highest standards possible.

TISSUE BANKING

The **NIMH Repository and Genomics Resource (NRGR)** provides a centralized national biorepository that plays a key role in facilitating ASD research. The repository contains thousands of biospecimens from ASD families, and accompanying genotypic and phenotypic data are available to qualified researchers worldwide. Biomaterials are stored at the Rutgers University Cell and DNA Repository, supported through a cooperative agreement from the National Institute of Mental Health (NIMH). Clinical projects funded by NIMH that propose to collect biospecimens are strongly encouraged to submit the samples to NRGR. Submissions typically consist of whole blood draws along with the necessary phenotypic data relevant to these samples. The NRGR also accepts plasma, DNA/RNA/cDNA, biopsied material, and human-derived cell lines such as induced pluripotent stem cells (iPSCs) and lymphoblastoid cell lines (LCLs). Other types of biospecimens (e.g., saliva) may be accepted on a case-by-case basis. There are currently 18,822 ASD samples across all diagnoses of ASD in the NRGR Autism distribution. Another 12,606 have been received and will be released in future distributions.

DATA INFRASTRUCTURE

Data infrastructure refers to data collection, storage, sharing, and consumption to support autism research, services, and policy development. Autism is a highly heterogeneous disorder requiring large sample sizes to make significant findings. Thus far, tens of thousands of research subjects have consented to make their genomics, imaging, and clinical research data available to scientists in the hope that those data will help lead to important research discoveries. These datasets have become very large (i.e., millions of gigabytes) and will likely grow exponentially in the coming years with the rapid advances in technology (e.g., raw imaging, whole genome sequencing), new methods of data acquisition (bio-tracking), and the integration of patient-directed reporting applications (e.g., IAN and SPARK). Other research communities have established related data repositories and funded data sharing initiatives making those datasets broadly available for use by the autism research community. Given the size of these data and the complexity of the software, algorithms, and analytic methods used, it is essential that all the data and associated metadata be shared when a result is published or a significant finding is announced. Ensuring that all data is shared will increase the rigor and reproducibility of findings, a core responsibility of publicly funded research.

DATA BANKS

New findings, technologies, and research methods have emerged that can drive autism research forward, capitalizing on advances in participant engagement through electronic portals and the collection of large data sets. Together, these participant-powered and clinical data networks can be further leveraged for rapid research on large numbers of participants throughout the country, offering the potential for a broad and rich view of the health and well-being of those with ASD and their families.

The **National Database for Autism Research (NDAR)** was implemented in 2008 to harmonize research data and share results for all human subject research studies, by supporting a de-identified research subject identifier – the NDAR Global Unique Identifier (GUID), and a precise method for associating research data with publications/results.² NDAR also supports common data definitions, a standardized set of data collection measures ensuring that results across studies can be accurately combined or compared. Initially implemented to support data sharing for the NIH Autism Centers of Excellence, NDAR was expanded to support data sharing of any autism research data funded by NIH extramural programs beginning in 2010. In 2013, NDAR was rebranded as the NIMH Data Archive (NDA) and now supports data sharing of all human subject research data related to mental health. Today, research data from over 600 research projects, representing a public research investment of over \$1.4 billion, are being shared. Overcoming limitations on restricted use datasets or the sharing of human subject research data across international borders, the NDA allows for the availability of research data funded by Autism Speaks, the Simons Foundation, and the Autism Science Foundation. Investment is still needed to extend this infrastructure to support big data analytics better and to integrate with biobanks and genomics data repositories more fully.

Another mechanism for data sharing is the **Autism Sequencing Consortium (ASC)**, an international group of scientists who share autism samples and genetic data.³ Currently, ASC has whole exome sequencing (WES) data for 29,000 samples, many of which are derived from DNA samples in the NIMH repository. Summary data is available for all samples, as is raw and called data for

samples with appropriate consents. Permission to re-contact research participants from completed studies exists for many of the samples within the ASC, managed by the contributing site.

In 2016, the Simons Foundation launched **SPARK (Simons Foundation Powering Autism Research for Knowledge)** to recruit, engage and retain a cohort of 50,000 individuals with ASD, as well as their family members, to participate in autism research. To participate in SPARK, families enroll online, provide saliva samples for genetic analysis, and agree to be re-contacted for future research opportunities. SPARK participants are being sequenced and genotyped to identify new genes associated with autism risk. Clinical, behavioral, and genetic data on the SPARK cohort are available to all qualified investigators, and SPARK participants can be invited to participate in other ASD research studies. Thus far, SPARK has enrolled over 48,000 individuals, including 19,000 individuals with ASD.

In 2016, the Autism Science Foundation launched the **Autism Sisters Project** to collect and distribute DNA from the unaffected female siblings of individuals with autism. Current research suggests that genes implicated in autism are equally distributed in boys and girls, but that many girls who carry the autism genes do not express clinical symptoms of autism due to a “female protective effect.” The goal of this new project is to collect DNA samples to enable researchers to discover and characterize this “female protective effect.”^{4,5}

DATA SHARING

When all research projects share their data, the quality of the accumulated data increases. For example, when a new research participant is enrolled in a research study, that person may also have registered previously with one or more data or biorepositories. If the data are linked and widely accessible to researchers (with appropriate privacy protections in place), the potential richness of

the information available on that participant is thereby enhanced. Care should be taken to ensure that all stakeholders across the research enterprise understand the importance of data sharing and that those sharing the most used and highest quality datasets be credited for their contributions. To facilitate data sharing in research involving human participants, an identifier or code is used to identify and link each individual to his or her specimens and perhaps also to associated medical information; use of a de-identified code (i.e., a code that does not reveal the identity of the individual) maintains privacy of the individual’s information. The GUID was developed to provide an easy method of identifying the same research participant across various data repositories and biobanks while maintaining the privacy of their personal information. The advantage of the GUID is that it enables linkage of data and specimens for a given individual over multiple studies, which can enrich the data set and prevent unnecessarily repeating the collection of the same types of samples from a given individual for multiple studies. While most data repositories have standardized identification of research participants using the GUID, adoption of this method has been less consistent across biobank repositories. Compounding this problem is the fact that most of the biobanks hold samples that are consented for restricted use (e.g., a study of autism and schizophrenia would require separate access) and are shared in separate repositories with different access restrictions and policies. The result is that it is often easier to request a tissue or sample from a biobank, re-sequence or re-analyze it, and then share the data with a new and different identifier, causing unnecessary (and often undetectable) duplication. For genomics, tools have been developed to eliminate this duplication, and attempts have been made to provide similar safeguards for imaging data. Though these additional tools exist, it is strongly encouraged that all data and biobank repositories maintain the use of the GUID and that those publishing genomics- or biobank-related studies provide a publicly available manifest of subject GUIDs and links to phenotypic

data locations when publishing, even if the data are only available as restricted use datasets. This action will provide standardization allowing data from the same individual to be linked across repositories, eliminate data duplication, and help minimize redundant sample and tissue requests, thereby conserving precious resources.

Supporting the increasing emphasis on the importance of data sharing, NIH has established a two-tiered approach for the **sharing of NDA research data** involving human subjects. First, observational and raw data is to be defined and shared using established data standards (data dictionary and a GUID). All data related to research results are expected to be submitted prior to publication. Data supporting other aims remain embargoed until publication, protecting ongoing research. This approach directly follows the long-established research process of sharing results and data at the time of publication. Where data collected by other researchers are used, this system automatically provides a mechanism showing data provenance and providing credit. All repositories supporting autism research should implement a similar program, even if the datasets shared are summary datasets, are not easily harmonized with established data repositories, or have restricted use limitations. As a community, by responsibly sharing high quality data at the appropriate times, it will increase the return on the collective research investment, protect the intellectual contribution of the best scientists, and help accelerate research discovery in autism and related disorders. Collectively, open data sharing offers the best opportunity to reach the sample sizes that are likely needed to improve understanding of autism and related disorders.

Several national surveys and administrative efforts collect information about people with ASD. Many of these surveys are Federally funded through agencies such as CDC [National Health Interview Survey (NHIS)], the Health Resources and Services Administration (HRSA) [National Survey of Children's Health (NSCH)], and the Department of Education [National Longitudinal Transition Study 2012 (NLTS 2012)]. Although each responsible agency may focus on its own research priorities when collecting and analyzing the data, synchronization of the national data sources will maximize their utility. Concordance of questions and sampling across surveys and administrative data could add greatly to the comparability of research undertaken across these national platforms. Additionally, infrastructure for linking these surveys to other sources of data is essential. The precedent for linkage already exists: for example, the CDC links the NHIS to administrative records from the Department of Housing and Urban Development (HUD), which allows for the addition of detailed housing information for those NHIS participants who use HUD services. Additionally, Federal Statistical Research Data Centers make national data from the Census bureau, CDC, and the Agency for Healthcare Research and Quality (AHRQ) available to researchers in one place. More projects like these, and additional means of capitalizing on the data that has already been collected and funded, are a key priority in order to generate an expansion of the information available on autism to a nationally representative sample.

HUMAN INFRASTRUCTURE

Human infrastructure refers to the development of human resources necessary to support autism research. These include developing a professional workforce to conduct research and provide services, as well as encouraging individuals with autism and their family members to participate in autism research. In addition, systems must be developed to share research findings with community stakeholders and translate research findings into policy and practice.

Individuals with autism and their families participate in research studies at relatively low rates, hampering the ability of researchers to fully understand ASD and develop interventions. Coordinated efforts are needed to educate stakeholders from diverse backgrounds on the importance of participating in research. Research should also be conducted to understand the barriers that discourage participation. Efforts should also be made to encourage families from diverse backgrounds to donate biological samples for research.

RESEARCH TRAINING AND WORKFORCE DEVELOPMENT EFFORTS

There are a number of efforts underway to enhance research training and workforce development. Private funding agencies such as Autism Speaks and the Autism Science Foundation support research fellowships that focus on attracting and nurturing early career investigators as they pursue innovative ASD research projects and begin their careers. Great emphasis is placed on building relationships with experienced mentors and on encouraging multidisciplinary avenues of exploration. NIH also offers research training opportunities including, but not limited to, training and career development grants and travel awards for early career investigators to attend research conferences.

While these initiatives represent mechanisms for the general support of trainees and early career ASD investigators, an area of need and opportunity identified by the IACC is for these up-and-coming researchers to have better access to existing datasets for conducting secondary data analysis. Hundreds of millions of Federal and private donor dollars have been spent on ASD research, which has led to the collection or federation of data on tens of thousands of ASD cases. A modest investment aimed at improving access to these data would not only maximize the return on substantial financial and human capital investments represented by decades of ASD research, but would also provide a fast-tracked training mechanism ideally suited to early career investigators, who often lack the resources to collect primary data.

Workforce development is an area of immense need as the number of identified individuals with autism continues to grow. While progress has been made in the area of early detection and intervention, and in the support of children on the spectrum, much less effort has been expended on adult services, as tens of thousands of children with autism transition to adulthood. Further, there is a dearth of trained medical professionals that are knowledgeable in providing care to the autism community, particularly the adult community. The *Autism Collaboration, Accountability, Research, Education, and Support Act*, IDEA Part C, and Title V Maternal and Child Health Block Grants all provide some amount of Federal funding intended to target workforce training and development programs. However, resources remain scarce, and it is not immediately clear how some of those resources are being utilized, particularly regarding whether there is any standardization in the delivery of workforce development efforts across communities. In some cases, it is unclear what training programs are

being implemented, if they are evidence-based, and how they are evaluated. There seems to be an immediate need for evidence-based best-practice guidelines in the development and implementation of such training programs.

INTERNATIONAL COLLABORATION

A 2012 IACC report titled *Autism Spectrum Disorder Research Publication Analysis: The Global Landscape of Autism Research* highlighted the expanding web of ASD research collaboration and publications across the globe; researchers from over 50 countries published papers during the analysis period. While there has been an increase in ASD research conducted and published outside of the US and other developed countries, the report also called attention to the fact that while research efforts are robust in the US, Canada, Europe, Australia, and China, many other countries around the world are lacking in capacity to conduct research or provide opportunities to participate in research. More attention and investment toward fostering international research collaborations have the potential to change this situation and provide benefits for people with autism and other developmental disabilities worldwide. Diverse settings can afford unique research opportunities to investigate risk factors (e.g., air pollution) and populations (e.g., higher genetic homogeneity) that may not be present in countries from which most of ASD research is currently published. Further, international research collaborations not only present opportunities to disseminate and implement evidence-based science and services in diverse settings around the world, but also allow the ASD research community to learn about how diverse populations, including those from low-resource settings, have addressed issues such as limited research infrastructure and large service gaps. For these reasons, it is imperative that international research efforts and collaborations continue to be promoted and supported.

DISSEMINATION OF SCIENCE

Increasing and improving mechanisms for dissemination of research findings after publication should be a priority for the autism community. It is vital that findings and data become more accessible to researchers, practitioners, families, and the general public. Training to improve science communication skills should be more readily available to researchers who wish to share their work with lay audiences. Particularly important is risk communication in the interpretation of research findings, as the information disseminated to the public is sometimes contradictory, oversimplified, overstated, or sensationalized. This misinformation can confuse the risk, disenfranchising members of the public, and have a negative impact on research participation. Mechanisms that allow for the summation of the evidence base into actionable recommendations such as systematic reviews and meta-analysis are encouraged, though research funders often overlook the potential for these types of analyses because they are based on existing rather than new data. Much of this work will be more feasible as the data sharing infrastructure further develops and expands. NDAR provides an infrastructure to make data broadly accessible through a universal platform and federation with other data sources. To make NDAR the most useful resource possible for the community, autism researchers must improve both the consistency and quality of data shared, especially those data supporting published results, allowing the infrastructure to be better utilized and supporting the dissemination of scientific advances. NDAR and similar data sharing efforts can help maximize the return on Federal and private investment in autism research made over the last decade by providing the research community with richer datasets and opportunities for research that would not have been possible without the coordination of these data.

Technology can play a key role in improving the dissemination of science, and advances in technology have made it increasingly possible to handle the troves

of “big data” that have been collected in ASD research. In addition to combining, storing, and analyzing data, technology affords new avenues of information collection and dissemination, for example, in the form of mobile applications (apps). Researchers can better collect data and do so more consistently across research studies by utilizing technology-based research platforms. Similarly, practitioners can better collect clinical data using the same or similar platforms. Making this technology more accessible and promoting the development of new technology for data collection and sharing should be prioritized by the research community to help optimize autism research studies. Further, technology to promote dissemination

and implementation of intervention and support services, via telehealth or e-learning, is critically important to improving the capacity to deliver the latest in evidence-based services throughout the US and around the world. Lastly, with growing awareness of ASD around the world and an increase in the number of local organizations supporting people with ASD in their communities, it is an opportune time to begin building stronger international collaborative efforts around ASD. Such initiatives have the potential to enhance communication and cooperation between governments, researchers, service providers, and advocates and to aid in dissemination of research findings and best practices globally.

SURVEILLANCE

Population-based surveillance for autism spectrum disorder is essential for monitoring time trends in prevalence, assessing patterns by demographic factors and level of support necessary, characterizing co-occurring conditions, estimating resource needs, and stimulating research into potential risk factors. For the data provided to be used effectively, surveillance should be as complete and valid as possible. Population-based studies of the prevalence and characteristics of autism spectrum disorder in the United States have been conducted among children, but continued collection is necessary to monitor trends. In addition, there is a pressing need for surveillance studies among adults.

There are several different methodologies currently used for estimating the prevalence and characteristics of autism spectrum disorder among children, including: 1) use of administrative records; 2) parent or caregiver surveys; 3) expert review of records from multiple sources; and 4) screening and examination of children. Each of these methodologies has strengths and limitations. Administrative records are readily available and cost-effective to use, but

are collected for other purposes and do not always contain adequate and pertinent information. Health surveys are nationally representative, generate data relatively quickly, include extensive questions on service needs and utilization, include a comprehensive age range of children, and are cost-effective in terms of the marginal cost of adding ASD-related questions; however, the validity of parent/caregiver-reported ASD has not been established, and declining response rates have raised concerns about bias. Expert review of records from multiple sources, including healthcare and education records, can ascertain records-based data on a number of factors such as demographics, educational placement, intellectual and adaptive function, and behavioral phenotype. However, this methodology is dependent on data in children’s records, focuses on a few specific ages, and is resource- and time-intensive and so currently cannot be done at a national level. Finally, screening and examination of children using a standardized and validated ASD diagnostic tool is a rigorous methodology that attempts to give all children

in the selected population an opportunity for ascertainment. However, this methodology is also resource- and time-intensive and cannot currently be done on a national level. In addition, low response rates in previous studies suggest a potential for bias.

Continued ASD surveillance among children is essential to monitor prevalence trends (including disparities in prevalence by demographic factors), characterize co-occurring conditions, estimate resource needs, and stimulate research into potential risk factors. ASD surveillance systems should be complementary, offering unique strengths and contributions that will further the understanding of the population of individuals with ASD. Where appropriate, data collection should be designed to allow comparisons across systems. Linkage of surveillance data with other state and Federal datasets should be encouraged to leverage the surveillance efforts and expand the scope and utility of the information collected.

While many research studies are focused on understanding and meeting the needs of children with ASD, much less effort has been expended on adults. There is an urgent need to expand ASD surveillance to adults to characterize prevalence, adolescent/young adult transition needs, employment and housing, co-occurring conditions, premature mortality, and other lifespan issues. In particular, investigating ASD prevalence in adults will help researchers understand how the interaction of ASD and co-occurring conditions impacts the ability to adults with ASD to live and work.

A systematic community survey in the United Kingdom estimated that approximately 1% of adults surveyed met the criteria for ASD, a rate similar to that in children.^{6,7} None of the adults with ASD identified in this study had been previously screened or diagnosed, further confirming the need for ASD surveillance in adults. The researchers involved in the study noted several challenges to their methodology, including low response rates to the survey

and the potential high cost of initial screening. Nevertheless, a comprehensive adult surveillance in the United States would be desirable, subject to available funding.

CURRENT SURVEILLANCE PROGRAMS

Autism and Developmental Disabilities Monitoring Network

The **Autism and Developmental Disabilities Monitoring (ADDM) Network** is a population-based surveillance program for ASD and other developmental disabilities based on expert review of behavioral characteristics documented in developmental evaluations contained in children's healthcare and educational records. CDC has been conducting surveillance for ASD among 8-year-old children through the ADDM Network every 2 years since 2000 at between six and 14 sites throughout the United States. Recent surveillance cohorts have included approximately 350,000 8-year-old children. In 2010, the ADDM Network was expanded to include surveillance for ASD among 4-year-old children in six sites of the ADDM Network. Data have been linked to various sources such as environmental pollutant monitoring, juvenile justice records, and others. Additional linkages to data from state and Federal agencies would enhance the usefulness of the ADDM Network data. The ADDM Network methodology has remained stable over time and so is able to assess prevalence trends. The most recent prevalence estimate for 2012 was 14.6 per 1,000 8-year-old children.⁸ The ADDM Network methodology also allows for assessment of the effect of changes in diagnostic criteria for ASD, and an evaluation of the effect on ASD prevalence and characteristics of the change from DSM-IV-TR to DSM-5 is underway.

National Survey of Children's Health

The **National Survey of Children's Health (NSCH)** is currently administered by the Maternal and Child Bureau of HRSA. This nationally representative telephone survey

of children's health and development based on parent/caregiver report includes questions on whether the child currently had an ASD as well as whether a healthcare provider ever informed the parent or caregiver that the child had an ASD. Data are also collected on a variety of topics including the child's health, health as an infant, recent healthcare service, experiences with healthcare providers, health insurance coverage, sociodemographic factors, and the child's learning, home, and family environment. The most recently published report presented data for over 90,000 children aged 6-17 years; ASD prevalence was 2.00% for children aged 6-17 years in 2011/2012. Beginning in 2016, this survey was moved to a mail-invitation, online survey based on a US Census Bureau sampling platform. This survey has been combined with the previously fielded National Survey of Children with Special Healthcare Needs. The new combined survey will be conducted every year and include approximately 100,000 children aged 0-17 years. It is anticipated that state-level estimates will be available for many variables, and for other variables data will be combined from several study years to provide state-level estimates. Linkages to data from other Federal agencies should be encouraged to expand the scope and usefulness of the data collected.

National Health Interview Study

CDC conducts the **National Health Interview Survey (NHIS)**, a nationally representative survey of parents/caregivers that provides data on the health of children in the United States, including information on whether a healthcare provider ever informed the parent or caregiver that the child had an ASD. The US Census Bureau is the data collection agent and the data are collected through personal household interviews. Data are collected on children aged 0-17 years every year; the most recently published survey year, 2014, presented data on ASD prevalence and characteristics for approximately 13,000 children aged 3-17 years. Data are also gathered on a

variety of topics including the child's health status, healthcare access and utilization, and a mental health screener (the Strengths and Difficulties Questionnaire), as well as family factors, including sociodemographic factors. ASD prevalence was 2.24% for children aged 3-17 years in 2014. The questions that establish a child's ASD status were recently revised to be the same as those in the NSCH. As with NSCH, linkages to data from other Federal agencies should be encouraged to expand the scope and usefulness of the data.

South Carolina SUCCESS

The **South Carolina Children's Educational Surveillance Study (SUCCESS)** is an Autism Speaks-funded screening-based initiative designed to help improve the precision of US ASD prevalence estimates by reducing reliance on service records alone to make ASD diagnoses, addressing the chief limitation of the ADDM Network approach. It has been suggested that this methodological approach is subject to missed cases, particularly among populations with less access to services, and in sites with fewer record types. SUCCESS was designed as a replication of the first-ever total population study of ASD prevalence in South Korea which found 2.64% of 7-9 year-old children, or 1 in 38, had an ASD.⁹ SUCCESS similarly implements a direct-screening protocol of all eligible school children in the catchment area, to both augment and compare to the records-based case ascertainment methodology of the South Carolina ADDM Network site. In addition to improving the estimation of the prevalence of ASD within a US site, SUCCESS intends to characterize the factors contributing to why cases may be missed using current best surveillance practices. It is also the first study to compare DSM-IV and DSM-5 prevalence using a population-based methodology in the US. The findings, currently in preparation, will better guide ASD surveillance practices in the US, including resource and infrastructure needs, moving forward.

SUMMARY

Continuing to build the infrastructure necessary for autism research is an important priority. In particular, researchers must make efforts to standardize their data collection and share with others in order to build higher-powered studies across multiple areas of research. Research institutions must continue to support biobanks and databanks, and to work towards integrating common collection and processing methods. Efforts to increase the participation of individuals with autism and their families in research and contributions to biorepositories are important, as information and samples gathered have the potential to

make significant contributions to our understanding of ASD. Inclusion of people on the autism spectrum and their families in research planning is also important, as it will help ensure that studies maintain a focus on issues that matter most to those who are impacted by ASD. Finally, funding agencies should continue to devote resources to ensuring dissemination of research findings and best practices, gaining better understanding of ASD prevalence across the lifespan, and training the next generation autism researchers, clinicians, and care providers.

OBJECTIVES

OBJECTIVE 1: Promote growth, integration, and coordination of biorepository infrastructure.

Examples:

- Promote biological sample donation to ensure that demand for research studies is met.
- Develop and expand programs and outreach campaigns to encourage families from diverse backgrounds to participate in ASD research, join registries, and donate biological samples.
- Create incentives to encourage standardization and sample sharing across data and biorepository banks.

OBJECTIVE 2: Develop, enhance, and link data repositories.

Examples:

- Adopt a de-identified research participant/subject identifier, such as the GUID, across all research initiatives in order to reduce the likelihood of sample duplication.
- Use common data definitions in order to standardize data collection, and responsibly share all the data supporting any findings when those findings are announced.

OBJECTIVE 3: Expand and enhance the research and services workforce, and accelerate the pipeline from research to practice.

Examples:

- Expand and enhance programs that provide funds to train current and future researchers on innovative research techniques.
- Provide service providers with training in evidence-based ASD services across multiple settings from clinics to communities.
- Develop programs to translate and disseminate ASD research findings into actionable recommendations and real-world practice.

OBJECTIVE 4: Strengthen ASD surveillance systems to further understanding of the population of individuals with ASD, while allowing comparisons and linkages across systems as much as possible.

Examples:

- Expand surveillance efforts to include the adult population in order to gain a better understanding of needs and concerns over the lifespan.
- Expand surveillance efforts to collect more descriptive data regarding co-occurring conditions, including cognitive disability, seizure disorders, anxiety, and depression to increase understanding of the prevalence of these conditions in the ASD population.

BUDGET RECOMMENDATION

*In the preceding chapters, the Interagency Autism Coordinating Committee (IACC) has provided information about recent research progress and services activities as well as 23 new strategic objectives to guide future efforts to better understand and address the needs of people on the autism spectrum across the lifespan and all levels of ability and disability. Under the **Autism CARES Act**, the IACC is also required to include “proposed budgetary requirements” in the Strategic Plan. The following information provides supporting background information and the IACC budget recommendation for the 2016-2017 Strategic Plan for Autism Spectrum Disorder (ASD).*

ASD is a lifelong condition, and as such, it results in significant human costs across the lifespan, not only in healthcare and services costs, but also in lost economic productivity, and reduced individual quality of life. These true costs reflecting lost human potential have recently begun to be described by thorough analyses. One of the most notable studies to date has estimated that the total lifetime cost (including spending and lost productivity) for supporting a person with ASD in the United States averages \$2.4 million for ASD with intellectual disability, and \$1.4 million for ASD without intellectual disability.¹ Another study estimated that the additional costs of healthcare, education, therapy, services, and caregiver time associated with caring for a child with ASD aged 3 to 17 years is about \$17,000 per year.²

The total annual cost of ASD in the United States – including medical, non-medical, economic, and lifetime costs, among others – has been estimated to be at least \$236 billion. Of the estimated \$236 billion, the cost of supporting children with ASD was at least \$61 billion per year, and the annual cost for adults with ASD was at least \$175 billion.¹ Another study has suggested that in 2015 the combined medical, non-medical, and lost productivity costs were in the range of \$162-\$367 billion, or 0.89-2.0% of the US gross domestic product.³ By contrast, the Interagency Autism Coordinating Committee (IACC) portfolio analysis data from 2015 indicates that combined autism research funding among Federal and private sources totaled \$343 million – only 0.09-0.21% of the estimated total annual cost of ASD.

While it is evident that more work needs to be done to fully understand the impacts of ASD on our society, there are several ways in which investment in research may be able to effect long-term benefits to individuals and society, as well as cost savings. Research on the biological basis of ASD may lead to the identification of modifiable risk factors that could reduce disability associated with ASD, as well as enable earlier diagnosis and improved interventions. There is already evidence that the costs of research and services that enable delivery of effective early intensive behavioral interventions in childhood can result in cost savings over the lifespan by reducing the need for costly long-term care and support.^{4,5} A recent study found that the health-related costs of the Early Start Denver Model were fully recouped after only a few years because children receiving the intervention required fewer other services, such as applied behavior analysis.⁶ In addition, we know that an estimated four out of ten young adults with autism do not transition to a job within the first years after completing high school, and those who do find work are often relegated to part-time or low-wage jobs.⁷ It is therefore also likely that more investment in research to improve adolescent and adult services and supports would improve the economic productivity of individuals over their entire lifetime, while also improving their sense of purpose and quality of life.⁸

Although there was significant growth in autism research funding from 2008 to 2010, and additional Federal funding from the *American Recovery and Reinvestment Act (ARRA)* provided a welcome boost in 2009 and 2010, ASD research funding levels have since become relatively flat. The loss in momentum has been accelerated by the loss of purchasing power over time due to inflation, resulting in what was effectively 15% of funding that was lost to inflation in 2015 alone (**Figure 1**). At the same time, never before have there been such promising scientific advances in ASD research, as well as a recognition of the full range of ASD research that will require attention and resources in order to truly improve the lives of individuals across the autism spectrum and lifespan. In the *2016-2017 IACC Strategic Plan*, the IACC has identified 23 new strategic objectives that represent areas of significant opportunity in the autism field and with enhanced funding have the potential to address critical needs of the autism community.

With these goals in mind, the IACC considered historical ASD funding trends and projected the budgets that will be necessary to propel ASD research forward and ensure there is meaningful progress on the priorities identified in this newly updated *IACC Strategic Plan*. Given the tremendous needs of the autism community as well as the promising opportunities for research and services that have been outlined in this *Strategic Plan*, the IACC recommends doubling the 2015 combined Federal and private autism research budget level of \$343 million to \$685 million by the year 2020. To accomplish this goal with steady and predictable annual funding increases, a roughly 14.85% increase in the autism research budget would be required each year (**Figure 2**). It is important to point out that this budget recommendation applies to ASD research budgets only; an IACC analysis of services budgets will be forthcoming in future years. Furthermore, the research funding increases recommended by the IACC would not be sufficient to accomplish all of the research goals identified in this *Plan*. However, a specific effort to double the autism research budget in 5 years would represent an aggressive, yet realistic jump-start to support research that can significantly move the field forward.

As evidenced by the analysis of the autism research portfolio from 2008 to 2015, an infusion of resources would be wisely and efficiently leveraged, with many areas of autism research well-poised to capitalize on additional investment. While all areas of the autism research portfolio require increases in funding, the areas identified by the IACC that are in particular need of resource growth include:

1. Research to support development and delivery of new and improved treatments and interventions
2. Research to enable development and delivery of evidence-based services
3. Research on lifespan issues, especially to understand and address the needs of transition-age youth, young adults, and older adults on the autism spectrum.

In addition, the investment of resources targeting these areas would serve not only to incentivize research on these topics, but also to encourage additional well-trained scientists to specialize in these research areas of significant need.

THE OVERALL ASD RESEARCH BUDGET HAS PLATEAUED AND LOST PURCHASING POWER FROM 2008-2015

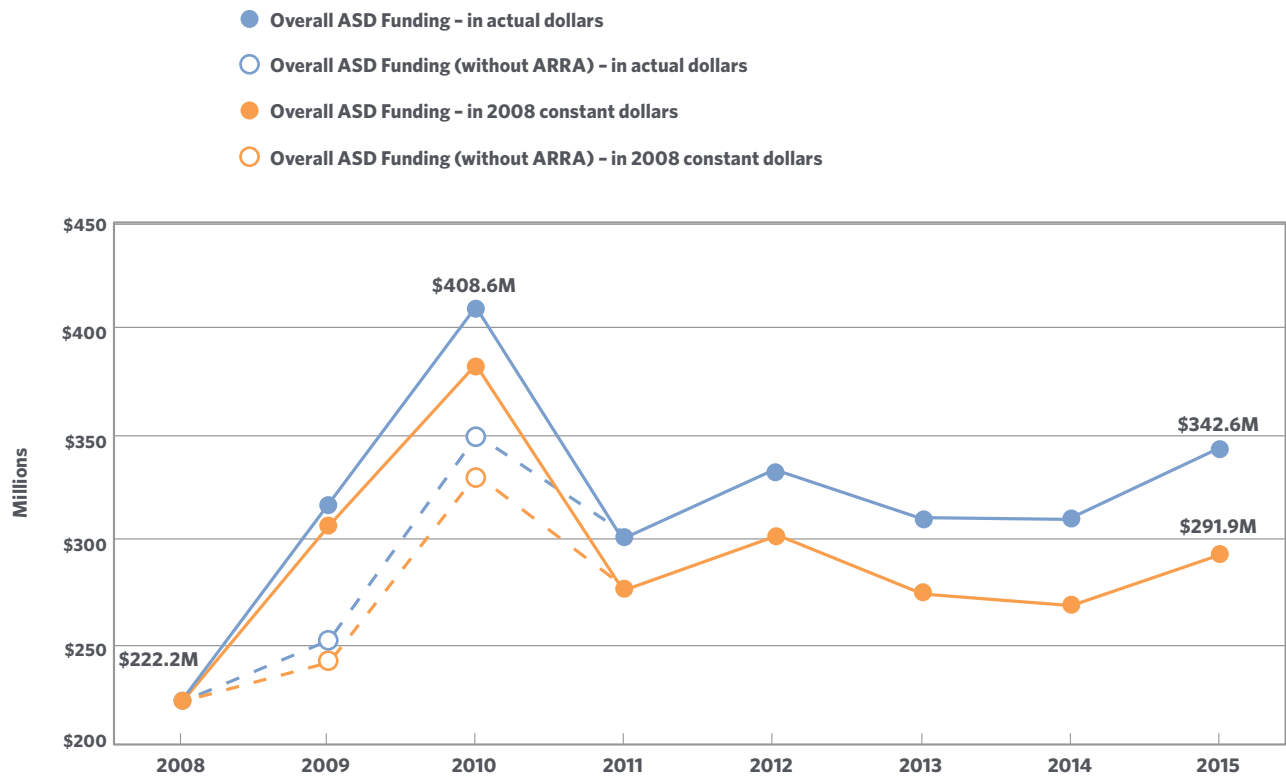


Figure 1. The history of combined Federal and private autism research funding from 2008 to 2015 in actual (blue) dollars and 2008 constant (orange) dollars shows that after experiencing an initial increase, the ASD research budget became relatively flat and lost purchasing power due to inflation in recent years. The dotted lines indicate funding levels excluding *American Recovery and Reinvestment Act (ARRA)* stimulus funds, which provided supplementary funding in 2009 and 2010. Inflation effects were calculated using the Biomedical Research and Development Price Index (BRDPI).⁹

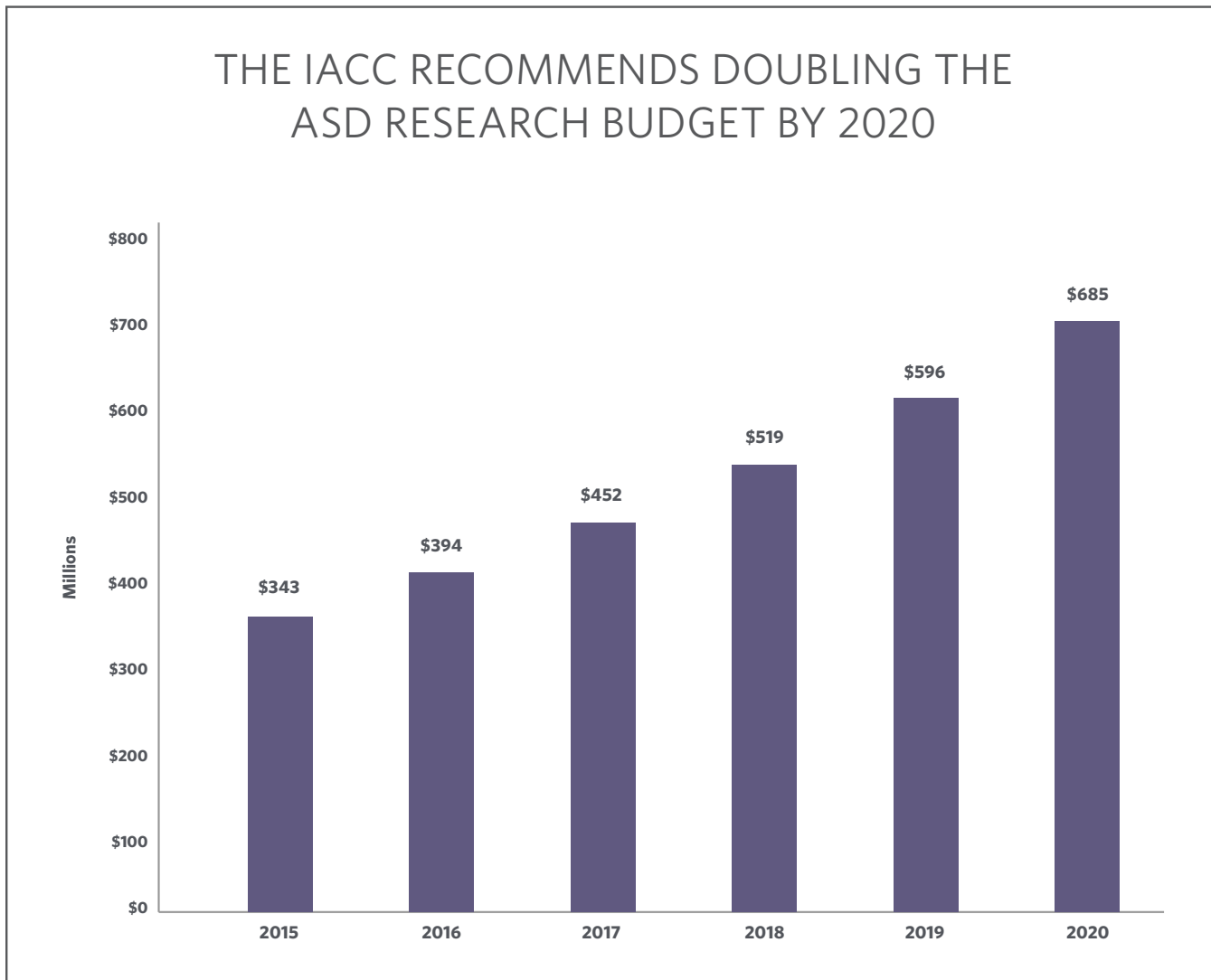


Figure 2. The IACC believes doubling the combined Federal and private ASD research budget to \$685 million would spark progress on the 23 new *Strategic Plan* objectives. A steady and predictable path to doubling the 2015 ASD research budget by the year 2020 would require an overall budget increase of about 14.85% each year.

STATEMENT ON DUPLICATION OF EFFORT

The *Autism CARES Act* requires the IACC in its *Strategic Plan* to provide “Recommendations to ensure that autism spectrum disorder research, services and support activities, to the extent practicable, of the Department of Health and Human Services and of other Federal departments and agencies, are not unnecessarily duplicative.”

The 2016-2017 IACC *Strategic Plan for ASD* offers wide-ranging objectives that are designed to address gaps in ASD research, services, and support activities. The IACC’s intention is that each broad-based objective will be accomplished through multiple projects addressing various aspects of these complex issues, which will be funded by multiple agencies in a coordinated fashion. The IACC is charged with ensuring that coordination, which is achieved by fostering dialogue among Federal agencies and private organizations and engaging their input in the development of plan objectives. The IACC believes that in the case of scientific research, coordinated efforts by multiple public and private agencies to fund different types of projects within the same objective represents cooperation and collaboration, not duplication. In addition, the scientific process requires that studies be independently replicated in order to ensure reproducibility and validate findings. Replication of an experiment or approaching a single problem using different methods can corroborate findings and help researchers distinguish between false leads and important discoveries. Replication also contributes to efficiency in research funding by ensuring the creation of a solid base of validated findings that establish the rationale for later-stage, larger, and potentially more costly research efforts. For these important reasons, replication of research is valuable and should not be considered duplication of effort.

In 2013, the US Government Accountability Office (GAO) released a report entitled *Federal Autism Activities: Better Data and More Coordination Needed to Help Avoid the Potential for Unnecessary Duplication* (GAO-14-16). The GAO report suggested that the IACC should more fully take advantage of research project data collected to identify opportunities to enhance coordination and prevent duplication. The *Autism CARES Act* provided more specificity in requiring the IACC to make recommendations about ways in which duplication could be avoided in its *Strategic Plan*. In the process of preparing this *Strategic Plan*, the IACC reviewed funded research projects to monitor the extent to which strategic objectives are being accomplished, including changes in funding over time. The IACC explicitly asked each of the seven working groups assisting with preparation of content for the *Strategic Plan* to identify issues related to duplication and to propose suggestions for avoiding unnecessary duplication.

The IACC did not find any specific instances of duplication among projects in the 2013 portfolio of funded autism research projects, but it noted that there are several instances of the opposite of duplication within the portfolio – gaps in research where too few projects are being supported to answer key questions in the field. Examples include the lifespan area in Question 6, which has received relatively little funding over the years that the *Strategic Plan* has been in place, resulting in gaps in knowledge about the needs of youth and adults on the autism spectrum and research to develop innovative services and supports.

The Committee also identified a broader issue that provides an opportunity to reduce duplication - the need for closer coordination of large genomic sequencing efforts. Several different research organizations are building genetic databases, and there is concern that different databases may be sequencing the same individuals, which could result in poor stewardship of funds as well as the time and effort of research participants. To reduce duplication of effort in sequencing, the IACC encourages organizations building databases to publicly share their “manifests” which include information on whose DNA is in each database, to use global unique identifiers (GUIDs) to tag data in order to help researchers know when they are working with an individual who already has been sequenced, and to share data by federating with or contributing to the National Database for Autism Research. As technology advances, there may be instances where resequencing the same individual is necessary to expand coverage or gather additional data that were not gathered previously. Ideally, in an environment where data sharing is maximized, researchers will be able to be more efficient with genomics research funding and participation of subjects in research so as to reduce duplication of effort.

CONCLUSION

Much progress has been made in the autism field since the launch of the first *IACC Strategic Plan* in 2009. At that time, researchers and other professionals in the field were starting to explore and push toward the possibility of earlier diagnosis and intervention, to understand whether genetics or the environment play a larger role in etiology, to determine why autism was becoming a more common diagnosis, and to understand what were the major challenges of autism in adulthood. Since then, through research and service work in the community, we have learned that: children at risk for ASD can be identified as early as the first year; early intervention does lead to improved outcomes for many children; myriad genetic and environmental factors interact closely resulting in the observed heterogeneity of ASD; multiple factors may be influencing prevalence estimates and more children with milder forms of ASD are being detected; and there are tremendous unmet service needs for adults on the autism spectrum. While research and services activities have moved the field forward in many ways, as represented in the aforementioned examples, they have also brought to light many challenges that still need to be addressed.

Before developing the *2016-2017 IACC Strategic Plan for ASD*, the IACC reviewed research progress and analyses of recent data describing the portfolio of ASD research funding in order to assess trends in funding and determine potential areas of opportunity. Overall funding for the autism research portfolio increased, from \$222 million in 2008 to \$343 million in 2015. Over the years the Committee has monitored the research portfolio, it has not identified any concerns about unnecessary duplication of effort across the portfolio, but it has monitored gaps and used this information to inform the development of the *2016-2017 IACC Strategic Plan*.

Strategic investments in the autism portfolio have produced promising scientific advances over recent years. For example, since the last *Strategic Plan Update* in 2013, research findings have provided several new insights, such as a better picture of existing autism services and service needs, improved identification of genetic risk factors for ASD, and a more accurate representation of the broader ASD community - including girls and women, individuals with intellectual and language disabilities, adolescents, and aging adults. This new knowledge has further illuminated several areas ripe for future efforts and investments - investments that have the potential to improve quality of life while also producing long-term cost savings for individuals, families, and society. The 23 new objectives in this *Strategic Plan* describe priorities for autism research, services, and supports that reflect the most important opportunities and needs in the current autism landscape. Included in these objectives are a focus on detecting autism earlier and improving access to early intervention; advancing understanding of the biology of autism and co-occurring conditions across the lifespan; integrating genetic and environmental information to understand autism risk; developing a wide array of new treatments and interventions that will address needs across the spectrum and across the lifespan; implementing interventions in community settings and improving access to services; improving transition services and quality of life for adolescents and adults; and enabling data sharing and expanded surveillance.

The IACC continues to coordinate autism research efforts and reaffirms its commitment to our core values: responding with urgency to the needs and challenges presented by ASD, pursuing excellence in research, building a spirit of collaboration, remaining focused on the needs of the community, developing strategic partnerships, and striving for equity. As the IACC looks to the future and considers the outlook for its strategic goals, the Committee believes the autism field is poised to experience significant progress toward addressing the critical needs of the autism community in the coming years.

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QUESTION 2: WHAT IS THE BIOLOGY UNDERLYING ASD?

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QUESTION 4: WHICH TREATMENTS AND INTERVENTIONS WILL HELP?

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QUESTION 6: HOW CAN WE MEET THE NEEDS OF PEOPLE WITH ASD AS THEY PROGRESS INTO AND THROUGH ADULTHOOD?

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QUESTION 7: HOW DO WE CONTINUE TO BUILD, EXPAND, AND ENHANCE THE INFRASTRUCTURE SYSTEM TO MEET THE NEEDS OF THE ASD COMMUNITY?

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BUDGET RECOMMENDATION

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