Autism Speaks
Strategic Plan for Science
2013-2017

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Acknowledgements

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I. INTRODUCTION

Autism is one of today’s most urgent public health crises. The estimated prevalence of autism spectrum disorder in the US is 1 in 88, greater than Type 1 Diabetes (1 in 400), childhood cancer (1 in 2000) and cystic fibrosis (1 in 3500) combined, and represents a larger burden to society based on the World Health Organization’s measure of burden of disease (Disability Adjusted Life Year). The annual cost of autism to society is now estimated to be $137 billion, most of which is for adult care. Empirically-based practices such as early intensive behavioral intervention have been shown to significantly reduce these costs, but unfortunately, many barriers exist to accessing such services. Individuals with autism and their families are struggling with unmet needs and a lack of effective treatments. There has never been a greater need for focused, cost-effective, and innovative research into the causes, treatment, prevention, and cure of autism. Moreover, research on the most effective means of implementing empirically-based practices is urgently needed.

In this document, we outline Autism Speaks 2013-2017 Strategic Plan for Science. The purpose of the strategic plan is to help guide AS science goals and funding priorities and to communicate the philosophy, values, and intentions of the Autism Speaks science department. Such values and intentions reflect the input of many individuals, including the scientific, clinical, and stakeholder communities. People with autism and family members are a central voice in shaping the plan.

Our mission is to improve the future of those struggling with ASD by funding research and developing resources that will accelerate discovery, development, and dissemination of methods for prevention, treatment, and cure.

The mission of Autism Speaks is “to improve the future for all who struggle with autism spectrum disorders. We are dedicated to funding global biomedical research into the causes, prevention, treatments, and cure for autism; to raising public awareness about autism and its effects on individuals, families, and society; and to bringing hope to all who deal with the hardships of this disorder.” The strategic plan for science must be fully aligned with the overall mission of the organization. The goals of the strategic plan must not only serve to accelerate scientific research, attract new scientists to the field, and increase the knowledge base about autism. Our strategic vision must strive to change the future for all who struggle with autism spectrum disorders.

The core values reflected in Autism Speaks’ mission statement are (1) recognition that individuals with autism spectrum disorders (ASD) and their families are struggling, which inspires a sense of urgency; (2) commitment to discovery through scientific excellence; (3) the critical role of families and individuals with autism spectrum disorder (ASD) as partners in shaping this effort; and (4) a fundamental tenet that the direction of our funding should always be aimed at helping individuals with autism and their families. As we align our compass, people with ASD and their families are the true north toward which we are oriented.
Tactics

To achieve our strategic goals, we utilize a core set of tactics. First, we recognize that new breakthroughs will require creative interdisciplinary collaboration. We encourage fluid and flexible interaction among different disciplines at all levels. Furthermore, we recognize the importance of close collaboration between basic scientists and clinicians. Such collaboration is not only necessary for the translation of basic science findings into clinical practice, but also for the fertile opportunity for discovery that clinical practice provides. Although it has long been recognized that the usefulness of scientific findings rests in their translation into practice, it is also true that the results of clinical trials and the observations of clinicians in the field often lead to critical breakthroughs and new fruitful directions. Also, scientists studying ASD on a macro level are encouraged to talk with those studying ASD at a molecular level. Interdisciplinary collaboration is encouraged through interdisciplinary workshops organized around a specific topic, through initiatives that focus on interdisciplinary studies, and through Requests for Application (RFA) mechanisms that solicit interdisciplinary proposals.

Second, it is crucial that we adopt strategies that are highly leveraged. By looking for opportunities to partner with governments and private agencies world-wide, we can multiply our efforts and resources for greater results. Thus, in developing a strategic plan we aim to coordinate our efforts with US organizations, such as the National Institutes of Health (NIH) and Simons Foundation, as well as international organizations, such as the World Health Organization. Such partnerships often not only increase the reach our results but also accelerate them. The NIH has developed its own strategic plan for autism research (as mandated by the Combating Autism Act). Geraldine Dawson, Chief Science Officer for Autism Speaks, is a member of the Interagency Autism Coordinating Committee (IACC) that is responsible for creating the National Institutes of Health (NIH) Strategic Plan for Autism Research.

Third, sharing of data across investigators and institutions worldwide is an important tactic in achieving our strategic goals. Data sharing refers to a wide range of data, from ideas to biological samples. One of the greatest challenges in developing effective treatments for autism is its tremendous heterogeneity. It is now recognized that there exist many different “autisms” with many different causes. To parse apart this heterogeneity, large data bases are needed. Efforts should focus on ensuring that all data are captured, cleaned, and ready for analysis, and that analytic methods are available and easily and flexibly applied by investigators. A thoughtful, comprehensive, and collaborative bioinformatics plan is an important part of any strategic plan for autism research. Information on the two largest data bases that Autism Speaks oversees,

Fourth, a balance between long-term and short-term goals is needed. While impact related to some goals will require considerable time, we believe that many aims can be achieved in the near term that will have a significant impact in changing the lives of individuals with autism and their families today. As an analogy, although the cure for cancer has yet to be found, our progress in treating cancers and improving the outcomes of individuals with cancer has increased dramatically. Examples of initiatives that reflect longer terms goals are the Autism Genome Project and the Autism Tissue Program. Examples of initiatives that reflect shorter term goals include (1) the Autism Speaks Autism Treatment Network - a network of 17 hospitals that are involved in the daily care of individuals with autism - that is developing and implementing standards for clinical practice for ASD, and (2) the United States and Global Autism Public Health Initiatives aimed at disseminating empirically-validated screening, diagnostic, and treatment protocols for individuals with ASD worldwide. For both short- and long-term goals, however, there is a need for near-term markers of success, measurable outcomes that will allow us to determine whether we have reached or are making progress toward reaching our goals.

Fifth, we recognize that an important role of Autism Speaks is to encourage innovation in the field by funding higher risk studies and setting up rapid review mechanisms that can respond quickly to new opportunities and discoveries. Most of the funding opportunities at the NIH do not provide a rapid response to highly innovative ideas. Autism Speaks has an important role to play in funding the engine of new discovery by supporting research on higher risk pioneering ideas.

We need to clearly define what success looks like for each of our defined goals. We hold ourselves accountable by asking: what are the metrics for measuring success, and how would we know if we achieved success? We need to monitor whether our strategy is working, correcting our course, if necessary. Thus, we adopt the “SMART” paradigm: We strive to develop goals that are Specific, Measurable, Acceptable (to both the stakeholders and those achieving the goals), Realistic, and Timely.

**How the Plan Was Formed**

Two communities had significant impact on the priorities described in this plan. First, the scientific community, especially Autism Speaks’ Scientific Advisory Committee (SAC), had a significant role in shaping the plan. The SAC meets in person annually and quarterly by phone to discuss the strategic directions of research funding. The SAC ([http://www.autismspeaks.org/science/boards/scientific-advisory-committee](http://www.autismspeaks.org/science/boards/scientific-advisory-committee)) is comprised of scientists and clinicians with a wide range of expertise pertinent to autism research. One-third of members of the SAC also have family members affected by autism spectrum disorders. The SAC identified the following areas as high priority for investment:

- Biomarkers, genetics, genomics and their clinical utility
- Environmental risk factors and gene-environment interactions
- Preclinical research aimed at understanding pathophysiology, target identification and validation, including immune mechanisms in autism
Clinical characterization, stratification of clinical samples using gene-phenotype algorithms

Novel Treatments

Effectiveness studies and dissemination science

Biorepositories and bioinformatic support, and other resources to accelerate research

The broader scientific community also played an important role in influencing the plan as members of Autism Speaks various steering committee and scientific consultants provided advice and leadership for Autism Speaks’ initiatives. Members of the Autism Speaks Autism Treatment Network’s Executive and Family Advisory Committees, the Autism Clinical Trial Network Steering committee, and the Autism Genetic Resource Exchange Steering Committee provide ongoing guidance for our efforts.

The broader stakeholder community also had substantial input into the strategic plan. Family members and persons on the autism spectrum serve on our steering and advisory boards. However, we also sought feedback from the larger stakeholder community. In early 2012, Autism Speaks took the unprecedented step of directly involving our lay community in prioritizing our research goals for the years ahead. We created an innovative web-based crowdsourcing platform. Here, supporters could submit and discuss their own research proposals. The MyResearchIdea campaign drew nearly 1,000 participants. They submitted 180 research ideas and ranked them by casting more than 2,000 votes. The results (See Figure 1.) are now part of the research priorities laid out in this Science Strategic Plan.

Figure 1. MyResearchIdea Community-Sourcing Results

The ideas that received at least 100 votes from the community are illustrated in the figure above and include a strong interest by the community in the role of immune dysfunction in the underlying biology of autism and its implication for therapeutic interventions. The community also recommended research into the environmental risk factors that can predispose individuals to autism. In the area of treatment, the community expressed wanting research into complementary approaches to address autism symptoms and associated medical conditions such as GI distress. They also recommended more research focused on developing more
Effective FDA-approved medicines that could reduce the core symptoms of autism, including social communication impairments and repetitive behaviors, in both children and adults. Research on more effective medicines to ameliorate associated symptoms, such as sleep disorders and seizures, were specifically prioritized. Finally, the lay community prioritized adult services – especially effective support systems for transitioning to independence and employment. The priorities recommended by both the SAC and community are clearly reflected in the goals of this strategic plan. The strategic planning process is illustrated below:

<table>
<thead>
<tr>
<th>Year</th>
<th>Event</th>
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<tbody>
<tr>
<td>2011</td>
<td>• Benchmarking: Funding models used by other non-profit research organizations</td>
</tr>
<tr>
<td>2011</td>
<td>• Autism Speaks staff retreat to discuss and draft strategic priorities</td>
</tr>
<tr>
<td>2011</td>
<td>• Small strategic planning group including members of Scientific Advisory Committee and Autism Speaks leadership meet to discuss key questions shaping new funding model</td>
</tr>
<tr>
<td>2011</td>
<td>• Web-based survey of the community, including families and individuals with ASD, for their suggestions and priority research areas</td>
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<tr>
<td>2011</td>
<td>• Outline of 2013-17 Strategic Plan presented to Scientific Advisory Committee for initial feedback and input</td>
</tr>
<tr>
<td>2012</td>
<td>• Plan drafted by Autism Speaks science staff</td>
</tr>
<tr>
<td>2012</td>
<td>• Penultimate version provided to Scientific Advisory Committee and members of the community for final feedback</td>
</tr>
<tr>
<td>Spring 2013</td>
<td>• Strategic Plan presented to Autism Speaks Leadership</td>
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II. SCIENTIFIC CONTEXT FOR THE STRATEGIC PLAN AND DESCRIPTION OF PRIORITY GOALS

The Rapidly Changing Landscape of Autism Research

In the four years since the previous strategic plan for science was written, the landscape of autism research has rapidly changed. Several new developments helped shape the current plan, including powerful new and emerging tools for scientific inquiry and a number of key scientific advances. A full understanding of a complex disorder such as autism requires understanding and integration of information on multiple levels: molecules, cells, synapses, circuits, behavior, and social systems. Over the past decade, the fields of genomics and genetics have provided important clues into the neurobiology of autism, including clues for potential targets for drug discovery. Fortunately, the costs of sequencing DNA have rapidly decreased such that it is now feasible to map the full human genome. We now understand that autism is not one condition, but rather it is many conditions with many causes and underlying biological patterns. Research is focused on discovering biomarkers that can stratify autism into its various subtypes so that the right treatment can be delivered to the right person. We are moving toward an era of personalized medicine for individuals with ASD which matches patients with the safest and most effective treatments to improve neurobehavioral and medical functioning.

Increasingly, there is an appreciation for how the environment influences brain development and risk for autism. Whereas previously autism was considered largely a genetic disorder, it is now appreciated that environmental influences, especially those that occur during the prenatal and early postnatal period, play a larger role than was formerly recognized. Of great interest are epigenetic mechanisms, whereby a wide range of environmental factors, from toxins to diet to stress can influence how genes are expressed. Over the past 5 years, several environmental factors that increase risk for autism have been identified, including very low birth weight, exposure to certain medications and toxins during pregnancy, maternal metabolic conditions such as obesity, infection or fever during pregnancy, winter season of conception, and short interpregnancy interval. The first protective factor has also been identified as use of folic acid before and during early pregnancy. The study of gene-environment interactions will figure prominently in the research that is funded during the next 5 years.

Imaging methods have gained sophistication, which allows scientists to obtain a much more detailed and accurate picture of how the brain develops and functions. Optogenetics allows scientists to activate specific brain circuits in an animal model with precision using beams of light. Magnetic resonance imaging of the human brain allows researchers to map how the
brain develops and the functioning of large-scale neural circuitry. The field of “connectomics” has emerged with a goal of understanding how brains become wired over development. This is particularly relevant to autism as recent discoveries indicate that autism is a disorder of the connections between neurons – the synapses – and that many functional impairments, as well as unusual talents associated with autism, can be explained in terms of differences in short and long range connections between different brain regions. Diffusion tensor imaging, a method derived from MRI that allows one to quantify the development of white matter – the fiber tracts that connect one brain region to another – recently revealed differences in neural circuitry by 6-12 months of age in infants who later developed autism. The availability of predictive biomarkers that could index risk for autism before onset of symptoms raises the possibility that, one day, interventions can begin before or at the onset of symptoms, thereby preventing its disabling symptoms from ever developing. Fortunately, over the past 5 years, Autism Speaks funded several clinical trials focused on developing new methods for early behavioral intervention that are appropriate for evaluating infants as young as 10-12 months of age. Although this is still a new area of research, initial results are promising in showing more positive outcomes with very early intervention.

Research has shown that autism can result from processes that either increase or decrease the strength of the synapse (long term potentiation and long term depression). The balance between the activity of excitatory and inhibitory neurotransmitters at the synapse has been found to be dysregulated in autism. Thus, a great deal of research activity is directed toward testing therapeutics that could restore that balance and improve synaptic functioning. Undoubtedly the most breathtaking finding in the past 5 years was that, in animal models of neurodevelopmental disorders associated with autism – such as Fragile X and Neurofibromatosis – substantial improvements in function can result when the molecular deficits are reversed, even when these treatments are started in adult animals. Substantial improvements have also been seen in a Rett syndrome mouse model by performing competent microglial cells into the mice; this improvement resulted from phagocytosis of cellular debris rather than from any specific targeting of the MECP2-related synaptic defect. Such findings marked a paradigmatic shift in the way we envision treating autism and have spurred tremendous excitement in the possibility of creating medicines that could treat the core symptoms of autism, even in adults with the condition. Pharmaceutical companies, such as Roche, Novartis, and Seaside Therapeutics, now have active research units exploring novel therapeutics for autism. By the time this plan is published, the results of the first major clinical trial testing a disease-modifying drug for autism will have been revealed. During the next 5 years, enticing industry into the field of autism drug discovery and development by de-risking their investment opportunities will be a key goal for Autism Speaks.

A transformative discovery that opened up new lines of inquiry is the ability to derive neural stem cells from skin tissue. This has allowed scientists for the first time to feasibly study
how the actual brain cells of a person with autism function and respond to both environmental toxins and therapeutics. The use of induced pluripotent stem cells to gain insight into the neurobiology of autism is a rapidly developing methodology that has the potential to revolutionize our understanding of the neuroscience and treatment of autism.

There is now a greater appreciation for the high prevalence and clinical significance of associated medical conditions in autism, including such conditions as gastrointestinal distress, sleep disturbance, immune dysfunction, and seizures, among others. For the first time, empirically-based physician guidelines for the assessment and treatment of many of these conditions have been published, and research on the nature and treatment of these conditions is increasing. Treatment of associated medical conditions can have an immediate and profound impact on quality of life, including improved behavior, attention, and learning.

Another area of new research focus is adulthood in autism. As research increasingly focuses on adults with autism, we are learning more about factors related to variation in outcomes in adulthood, in areas that include health, employment, and community and social involvement. The increasing prevalence of autism creates urgency for better treatments, services, and supports for adults as many individuals are transitioning from adolescence to adulthood, when they typically lose many supports and services. It is now recognized that the transition to young adulthood is an especially vulnerable period that sets the stage for later adulthood, having a profound impact on the trajectory of adult life.

Finally, the application of technology to improve the quality of life for people with autism is an extremely exciting field of research, with new apps becoming available to promote communication, learning, social skills, among other domains. As people from the tech industry apply their skills to “hack autism,” the possibilities for new interventions and supports are endless.

The Challenges Ahead

At the same time that significant strides have been made over the past 5 years, a number of challenges lie ahead that must be addressed in the next 5 years. They include the following:

**Which treatments are most effective for which people? Biomarkers needed to stratify ASD**

**Addressing the heterogeneity of autism.** A number of major exome-sequencing efforts – the sequencing of the coding regions of the genome that contain genes that are translated into protein – revealed the sobering finding that autism likely results from hundreds of small-effect and rare risk genes. Many of the genetic mutations associated with risk for autism appear to be de novo rather than inherited; in other words, rather than being passed from parent to child, these mutations are present for the first time in the egg or sperm of one of
The findings have changed the way we think about autism genetics. Whereas a decade ago, it was hoped that a few inherited autism risk genes of major effect would allow us to understand the causes and biology of autism, it is now understood that the genetics of autism is exceedingly complex. This complexity is not irreducible, however, because the autism risk genes that have been identified appear to influence a potentially tractable set of common pathways in the brain. Major challenges ahead include the development of analytic methods for understanding the effects of different genes on biology and the identification of biomarkers for stratification of autism subtypes for targeted therapeutics.

The challenge of “big data”. The promise of whole genome sequencing brings with it the enormous challenges of storing, distributing, and analyzing remarkably large data sets. The application of computer science and information technology to yield meaningful information from large sets of biological information – bioinformatics – will play a central role in scientific discovery over the next decade. Mathematical and computing approaches will be used to glean insights into the biology of autism from large data sets.

Reducing risk aversion on the part of the pharmaceutical industry toward investments in medicine development for autism. Recent scientific breakthroughs, such as reversal of impairments of neurodevelopmental disorders in animal models, have enticed some pharmaceutical companies to invest in autism and related disorders. Yet many are reluctant to devote resources to a disorder that currently lacks a clear understanding of its pathophysiology and has a high level of heterogeneity, few clear biomarkers, and poorly developed outcome measures for clinical trials. The Gulf between a basic discovery and the development of a new treatment is so overwhelming that it has been called “a valley of death” by some. Scientists are ill equipped to develop the technologies that are required for translational research, and historically, funding of such research is lower priority relative to discovery-focused research at the NIH. Fortunately, the NIH has begun to prioritize translational research, including the development of new technologies that will accelerate the progression from basic animal research to human clinical trials. Francis Collins, the director of NIH, spearheaded the creation of a new center, the National Center for Advancing Translational Sciences (http://www.ncats.nih.gov/), which has as its mission to catalyze the generation of innovative methods and technologies that will enhance the development, testing and implementation of diagnostics and therapeutics across a wide range of human diseases and conditions. An important role for Autism Speaks will be to facilitate and de-risk translational research through data sharing policies, partnerships with for-profit organizations, multi-disciplinary collaboration, and targeted funding on needed technological and knowledge advances that will help pave the way to treatments, prevention, and cure.

Understanding gene-environment interactions. As the role of environmental risk factors becomes increasingly appreciated, the need for large data sets that contain genomic and detailed environmental exposure data is great. Also necessary is data on environmentally vulnerable intermediate physiology that can serve as biomarkers of impact, which is important in settings where many environmental factors converge upon smaller numbers of physiological pathways, amplifying the environmental impact in an aggregate fashion even when any specific exposure may not be great. This level of intermediate metabolism or physiology (which includes measures of oxidative stress and immune dysfunction that commonly ensue from many environmental triggers) may lead to medical interventions sooner than environmental or genetic data because existing treatments may prove useful to treat problems at this level, which
may strongly leverage function at higher levels such as behavior. Collection of exposure data can be difficult and costly, particularly for risk factors that operate within the home, and therefore are not available in existing databases (e.g., pollution monitoring networks, or prenatal medical records). Furthermore, although a variety of types of methods for analyzing gene-environment interactions have been developed, techniques incorporating high-dimensional (genomic) data and/or multi-dimensional environmental factors require new methodologies. Similarly, approaches for epigenetic influences, which serve as the nexus between genes and environment, are still under development.

**Bridging the gap between knowledge of evidence-based practices and implementation.** One of the great success stories of the past decade has been the demonstration that early diagnosis and early intensive behavioral intervention have a dramatic impact on outcome, increasing cognitive, language, and social abilities while reducing autism symptoms. However, the gap between what is known based on several efficacy studies and a few effectiveness studies and what is available to children in the real world is huge. Whereas intervention studies now enroll children as young as 18 months of age, the average age of diagnosis of autism in the US is 4 years, and at least 50% of children in the US do not receive the early intervention services they need. The gap in developing countries is even more substantial; close to 85% of children do not receive adequate services. While the success of Autism Speaks’ efforts toward insurance reform have had a significant benefit in addressing the financial barriers to access to services, many others remain. The grand challenge is this: How does one scale up interventions that require a high level of professional training and a high intensity of delivery so that these interventions can be available not only in the US but worldwide? Dissemination and implementation of evidence-based practices is one of the most important challenges ahead of us. The hope is that by identifying the core active ingredients and using innovative methods for delivery and training – such as web-based training – we can make significant strides in increasing access to much-needed services to the many people that need them. Similarly, the past 5 years have witnessed great progress in the identification and treatment of associated medical conditions that affect quality of life for persons with autism. Yet, it is clear that most children and adults with autism, even in the US, do not receive the kind of comprehensive healthcare that is needed to address these medical conditions.

**Adults with autism.** Finally, we are facing a tsunami of individuals with autism who are about to transition from adolescence into adulthood, and we are ill-prepared to provide them with what they need to live successful, satisfying, and productive lives. A few sobering facts:

- Adults with autism are often socially isolated and unengaged despite having a desire to be with others
- Less than 1/5 of high functioning adults with ASD are able to find employment after high school
- Depression and anxiety are key factors affecting success in the workplace
- Mortality rate in individuals with autism is 6X higher than general population
- Among the health-related challenges adults with autism face are heart disease, obesity and epilepsy
- Almost nothing is known about aging in autism
Identifying the factors that promote positive outcomes in adults will be a key priority in addressing what is one of the biggest and most important challenges we face in the next 5 years.

**Funding Priorities for the Next 5 Years**

There is a multitude of worthy goals but not enough money to fund significant work toward all of them. It will be important to set priorities so that funding decisions can be made effectively and strategically. Issues that need to be taken into consideration when setting priorities include (1) the balance and relationship between short- versus long-term impact, (2) level of risk tolerance that is acceptable to Autism Speaks, (3) stakeholders’ priorities, (4) the need to respond to current “hot topics”, (5) cost, (6) feasibility, and (7) collaborative and complementary funding relationships with other funding agencies, such as the Simons Foundation, the CDC, and the NIH. With respect to the latter, the priorities and objectives identified in the federal government’s IACC Strategic Plan for ASD Research represent potential areas of collaboration or complementarities between the NIH and AS. Geri Dawson’s participation as a member of the IACC (http://iacc.hhs.gov/) facilitates coordination between the goals of Autism Speaks and the federal government.

The funding priorities for the next 5 years will focus on *providing resources and facilitating collaboration* that will accelerate scientific discovery and dissemination of those findings to real world application, and *funding research to address the following five goals:*

1. Identify risk factors for ASD that can lead to prevention and improved diagnosis and treatment
2. Reduce age of detection and improve access to early intervention for children with ASD
3. Enhance quality of, and access to, healthcare for individuals with ASD
4. Promote the development of safe, effective interventions and medicines to reduce core and associated symptoms of ASD throughout the lifespan
5. Improve the health and outcomes of adults with ASD from a lifetime perspective

Sections that follow will describe these goals in more detail.

**Our priority is to provide scientific resources, facilitate collaboration, and fund research to address these five goals:**

1. **Identify risk factors for ASD that can lead to prevention and improved diagnosis and treatment**
2. **Reduce age of detection and improve access to early intervention for children with ASD**
3. **Enhance quality of, and access to, medical care for individuals with ASD**
4. **Promote the development of safe, effective interventions and medicines to reduce core and associated symptoms of ASD throughout the lifespan**
5. **Improve the health and outcomes of adults with ASD from a lifetime perspective**
III. LOOKING BACK: AN OVERVIEW OF PAST AUTISM SPEAKS RESEARCH FUNDING

Since its inception in 2005, Autism Speaks has made enormous strides, committing over $180 million to autism research. In support of its mission to improve the future for all who struggle with ASD, Autism Speaks provides funding along the entire research continuum – from discovery to development to dissemination – for innovative projects that hold considerable promise in significantly improving the lives of persons with autism. Annually, Autism Speaks accepts applications through a number of grant funding mechanisms for investigator initiated research projects. This includes cornerstone mechanisms such as Basic and Clinical Research Awards, Treatment Research Awards, Pre- and Post-doctoral Fellowship Awards, as well as the Suzanne and Bob Wright Trailblazer Awards and the Faith and Philip Geier Award for Environmental Sciences. These are described below.

Investigator-Initiated Award Programs

Autism Speaks offers several types of grant mechanisms that target critical areas of autism research, all of which pass through three levels of review. The Scientific Advisory Board (http://www.autismspeaks.org/science/boards/scientific-advisory-board) or Treatment Advisory Board (http://www.autismspeaks.org/science/boards/treatment-advisory-board) reviews each proposal for scientific merit. Proposals deemed to be of high scientific merit are then reviewed by the Scientific Review Panel (http://www.autismspeaks.org/science/boards/scientific-review-panel), which makes the final recommendation to the Autism Speaks Board of Directors based on a review of how each proposal fits Autism Speaks’ overall priorities. These boards serve to solicit feedback from the world’s best scientists as well as consumer advocates such as parents and persons on the autism spectrum. The objective is to facilitate and promote efforts that will produce significant findings related to the diagnosis, cause, prevention, treatment, and cure of autism that will lead to improvements in the lives of people with autism and their families.

Basic & Clinical Research Grants stimulate the exploration of new avenues of basic and clinical research through awards aimed at testing novel ideas. These grants can serve to bring new investigators into the field and allow researchers to collect preliminary data through our pilot level funding, which can permit them to compete for larger grants in the future. Projects may also build upon established research in a broad range of autism-related areas by providing researchers with larger full-level awards in order to pursue leads that have already shown promise in pilot studies.

Treatment Research Grants address the urgent need to develop effective therapies to treat those living with the disorder today by supporting research focused on all aspects of treatment, including behavioral, psychosocial, biomedical and technological interventions. Similar to the Basic & Clinical mechanism, Treatment awards can be for pilot or full levels of funding.

Dennis Weatherstone Pre-Doctoral Fellowships are awarded to support highly promising graduate students with an interest in devoting their careers to autism research. Established in 2009, the fellowship program attracts young, talented scientists into the field of autism research and offers opportunities for networking with other fellows through annual events.
Postdoctoral Fellowships in Translational Autism Research are designed to support promising, well-qualified postdoctoral scientists in their pursuit of research training that involves translation of biological discoveries toward novel and more effective methods for treating or diagnosing ASD. This is accomplished by encouraging multidisciplinary collaboration among basic scientists, applied researchers, and clinicians. Dual mentors in both basic and clinical sciences allow exposure to methods from bench to bedside.

Suzanne and Bob Wright Trailblazer Awards are designed for highly novel ideas that will significantly accelerate the pace of autism science. In commemoration of Autism Speaks’ fifth anniversary and to honor the organization’s pioneering co-founders, Suzanne and Bob Wright, the Trailblazer Award is designed to respond quickly to highly novel projects that have the potential to be transformative and/or that will eliminate significant research roadblocks. No preliminary data are required. Investigators are encouraged to submit study proposals that are generally high risk, but if successful, would also yield a high reward. The application deadline is rolling and includes a rapid review process that allows Autism Speaks to respond quickly to unique and important opportunities.

Faith and Philip Geier Award for Environmental Sciences. This award is given each year to a research project focused on environmental science research that is particularly noteworthy, innovative, and promising.

Exploring Autism Speaks Funded Research

In 2011, Autism Speaks developed and launched a web-based search program that allows users to query the database of Autism Speaks’ funded projects. Users are able to search for science grants using a host of different key words depending on the desired results. There is an open field that allows for the entry of multiple keywords or search terms such as an area of science (e.g. genetics, environment) or the name of an investigator or institution. Grants can further be searched for by location by typing in a city, state, or country. Searches can also be filtered by a number of preset subcategories such as grant year, award type, general topic, and subject area.

All results can be displayed as either a list or on a map by toggling between views. In the list view, the user can mouse over a grant title to be provided with a preview of the grant’s
description, or abstract. Selecting a particular project will bring the user to a detailed view of the grant with start and end dates, amount, award type, and a lay description of the project. Also listed are keywords used to describe the project, which in turn serve as links to all projects that meet that keyword criteria. In the near future, visitors to the grants search will also be able to find descriptions of outcomes from completed projects as well as links to full-text articles published as a result of Autism Speaks grants, which are subject to the organization’s free, public access policy.

**Autism Research Funding to Date**

As of November 2012, Autism Speaks has committed more than $185M to supporting autism science, including research grants, initiatives, meetings, and workshops, since the organization was launched in 2005. More than 1,137 awards have been made since 2006 totaling just over $150M. This includes 259 Basic & Clinical Research Awards totaling approximately $32M, 213 Pilot Research Awards (which were a separate mechanism prior to 2011) totaling $12M, and 75 Treatment Awards for $7.9M. 249 total fellowships have been awarded including 109 Postdoctoral and 140 Pre-doctoral awards that total $5.25M and $4M respectively. The Suzanne and Bob Wright Trailblazer Award has resulted in 8 funded projects totaling just over $1.4M for highly innovative science with significant potential for yielding high-impact findings.

Beginning in 2007, Autism Speaks expanded its science portfolio from largely investigator-initiated awards to a greater mix of targeted initiatives and clinical resources. Specific areas of high priority were identified by Autism Speaks to explore understudied research areas, issues of great relevance and/or opportunities that leverage ongoing resources and programs. While targeting funding toward specific priorities and opportunities is an effective strategy for maximizing impact and addressing specific needs, it is important to continue to support investigator-initiated projects to ensure that novel ideas and potentially transformative project areas are explored and new talent is nurtured. A balance between “top down” and “bottom up” strategies is needed. Approximately $62.8M has been committed to nearly 170 targeted awards supporting initiatives such as the Autism Genome Project, the Autism Speaks Autism Treatment Network, and Innovative Technologies for Autism. These targeted efforts have been highly successful. For example, the Autism Genome Project (AGP) is the largest study ever conducted to find the genes associated with genetic risk for autism. The ultimate goal is to enable doctors to biologically diagnose autism, utilize genomic information to inform personalized approaches to treatment, and gain insight into the underlying biology of autism that can lead to novel therapeutics. AGP is a public/private research partnership involving approximately 50 academic and research institutions that have pooled their DNA samples in a collaborative effort. To date, Autism Speaks has committed over $9M in funding to the AGP that has led to close to $70M in additional funding from other agencies.

The Autism Speaks Autism Treatment Network (AS-ATN) is a network of hospitals and medical centers working together to improve the quality of care for individuals with autism. The clinicians in the AS-ATN provide comprehensive, coordinated, multi-disciplinary care to families in their communities, and are dedicated to establishing standards of care for autism that can be shared across the wider medical community. Currently, Autism Speaks is supporting 17 AS-ATN sites in the United States and Canada, and over its history the AS-ATN has received $18M in
direct funding, which has leveraged over $24M of federal dollars for research and guideline development.

**Autism Speaks Funding in the Context of Federal Funding for Autism Research**

The IACC, a committee comprised of both federal and public members that monitors and guides federal autism research, was established in accordance with the 2006 Combating Autism Act. The IACC annually releases a portfolio analysis of autism research funding in the United States. Specifically, it analyzes funding of both federal agencies and private organizations and is used to monitor progress in fulfilling the objectives of the IACC Strategic Plan. The analysis is also intended to help guide future funding priorities by outlining gaps and opportunities in ASD research.

<table>
<thead>
<tr>
<th>Funding Agency/Organization</th>
<th>Number of Projects</th>
<th>Total Funding</th>
</tr>
</thead>
<tbody>
<tr>
<td>National Institutes of Health (NIH)</td>
<td>545</td>
<td>$217,143,701</td>
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<tr>
<td>The Simons Foundation (SF)</td>
<td>122</td>
<td>$53,729,921</td>
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<tr>
<td>Health Resources and Services Administration (HRSA)</td>
<td>82</td>
<td>$43,303,150</td>
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<tr>
<td>Department of Education (ED)</td>
<td>139</td>
<td>$90,432,564</td>
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<tr>
<td>Centers for Disease Control and Prevention (CDC)</td>
<td>30</td>
<td>$19,698,839</td>
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<tr>
<td>Autism Speaks (AS)</td>
<td>228</td>
<td>$18,476,890</td>
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<tr>
<td>National Science Foundation (NSF)</td>
<td>69</td>
<td>$12,222,206</td>
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<tr>
<td>Department of Defense (DoD)</td>
<td>58</td>
<td>$7,082,059</td>
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<tr>
<td>Administration for Children and Families (ACF)</td>
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<td>$1,877,959</td>
</tr>
<tr>
<td>Agency for Healthcare Research and Quality (AHRO)</td>
<td>4</td>
<td>$1,548,053</td>
</tr>
<tr>
<td>Center for Autism and Related Disorders (CARD)</td>
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<td>$906,482</td>
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<td>Environmental Protection Agency (EPA)</td>
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<td>$756,802</td>
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<td>Autism Research Institute (ARI)</td>
<td>15</td>
<td>$386,905</td>
</tr>
<tr>
<td>Centers for Medicare &amp; Medicaid Services (CMS)</td>
<td>3</td>
<td>$376,159</td>
</tr>
<tr>
<td>Autism Science Foundation (ASF)</td>
<td>13</td>
<td>$245,000</td>
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<tr>
<td>Organization for Autism Research (OAR)</td>
<td>12</td>
<td>$191,590</td>
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<tr>
<td>Coalition for SafeMinds (SafeMinds)</td>
<td>8</td>
<td>$128,979</td>
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<td>Southwest Autism Research &amp; Resources Center (SARRC)</td>
<td>5</td>
<td>$70,000</td>
</tr>
<tr>
<td><strong>GRAND TOTAL</strong></td>
<td>1367</td>
<td><strong>$408,577,276</strong></td>
</tr>
</tbody>
</table>

Table 1: 2010 IACC Portfolio Analysis (Published July 2012).

Autism Speaks ranked second in the total number of projects funded (228) behind the National Institutes of Health (545). Autism Speaks also ranked second in total funding dollars among private foundations ($18,476,890) behind The Simons Foundation ($53,729,921). Autism Speaks ranked sixth in total research funding behind the NIH, Simons Foundation, HRSA, Department of Education, and the CDC. For all funding organizations, biology, risk factors, and treatments were the top three funding areas.

As funding for autism research has increased, rates of publications have also steadily grown over the past decade. A report by IACC\(^1\) indicated that ASD publication growth matched broader publication growth until the late 1990s, with the sharpest increase starting in 2000 and continued growth thereafter, outpacing publications in similar health-related topics. The overall, a total of $408,577,276 was spent on autism research in 2010. This year is unusual because it includes temporary 2-year stimulus funding based on the American Recovery and Reinvestment Act. Thus, overall, there was a $93 million increase from 2009. Eighty two percent (82%) ($334,441,512) reflected federal funding, whereas 18% ($74,135,764) came from private foundations. As shown here in Table 1, in 2010, of the 18 total funding organizations, 82% of the total funding came from federal agencies.

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majority of publications focus on biology, with research on treatments and risk factors tying for the second most frequent type of publication.

As the IACC report points out, in 2000, the Children’s Health Act called for increased research funding and improved surveillance. At that time, NIH devoted about $50 million to autism research. The Combating Autism Act, passed in 2006, called for continued autism research funding. About that time, the Simons Foundation launched its autism research initiative, and Autism Speaks began to provide about $25 million in annual autism research funding. By 2010, federal funding for autism research reached approximately $334 million and private foundation funding exceeded $74 million.

Although the increase in research funding is encouraging, the parallel increase in prevalence of autism means that we still are not adequately addressing the scale and urgency of the public health crisis that autism represents. The prevalence of ASD has increased 78% in the past six years and the estimated annual cost of autism has more than tripled. The 78% increase in ASD prevalence was met by only a 43% increase in federal funding. The per capita autism federal research funding has deceased from an estimated $62 per person in 2007 to $47.50 per person with ASD today. Thus, there continues to be a great need for more research funding, especially for certain neglected research areas, such as research on adults and treatment.

Assessing the Impact of Investigator-Initiated Research Grants

Assessing the outcomes of our grant funding is crucial for assessing the return on our investments. Autism Speaks developed a system for assessing the outcomes of its investigator-initiated awards (e.g. Basic and Clinical Research Awards, Treatment Research Awards, Pre- and Post-doctoral Fellowships) as well as the impact of those outcomes, including return on investment. The outcomes information is collected using a custom-designed online reporting system where researchers can enter information about their findings and other achievements of their projects on an annual basis. By the summer of 2012, the survey had been conducted on 240 grants awarded between 2006 and 2010 and completed by summer of 2012. More than two-thirds (77%) of respondents reported the major finding to be a novel discovery while only 5% reported a negative result. The remaining 19% cited a replication of previous results as the chief outcome. Respondents were asked to classify the areas upon which their findings had impact to help us understand how research topics were distributed across projects and identify gaps. Figure 2 shows the top five impact areas of our first 240 investigator-initiated awards (not mutually exclusive).
As shown in Table 2, the 240 completed research grants resulted in 2,364 presentations or publications. To ensure that new knowledge resulting from Autism Speaks supported research can be accessed, read, applied, and built upon, the organization implemented a Public Access Policy stating that all peer-reviewed articles supported in whole or in part by its grants must be made available for free to the public in the PubMed Central online archive.

We were also interested in the outcomes of our fellowship grants that aim to attract new scientists to the field of autism; 73% of the first 78 fellows funded reported that it was their first experience in autism research, and 88% intended to stay in the field. A total of 935 research assistants were also funded, 73% of which were new to autism research, with the vast majority intending to stay in the field.

Finally, as shown in Table 3, the initial investment of $36 million for the first 240 grants was highly leveraged. An additional $237,800 million was secured in federal and other types of funding based on the data collected in these initial grants.

### Assessing the impact of our investments in resources and initiatives

The analysis reported above focuses on investigator-initiated awards and does not assess the outcomes of our investments in various resources, such as the Autism Genetic Resource Exchange, and initiatives, such as the Baby Siblings Research Consortium. A few statistics reflecting the productivity and outcomes of these investments are provided in Table 4.
<table>
<thead>
<tr>
<th>Initiative</th>
<th>Outcomes to date</th>
</tr>
</thead>
</table>
| Autism Genetic Resource Exchange | Used by 353 scientists  
Genetic data downloaded by scientific community 28,433 times  
201 publications  
Discovery of several autism risk genes  
AGRE cited in Time Magazine Top 10 Medical Breakthroughs of 2010 |
| Autism Genome Project | Supported >50 institutions and >100 investigators  
>200 publications  
Discovery of several autism risk genes  
$8M investment leveraged, resulting in >$76M in additional federal funding |
| Autism Tissue Program | Used by 151 scientists  
128 publications |
| Autism Speaks Autism Treatment Program | Supports 350 clinicians/scientists  
Competed successfully for $24M in additional federal funding  
Recognized in 2012 US News and World Report on US Best Hospitals |
| Baby Siblings Research Consortium/Toddler Treatment Network | Supports collaborative activity of 24 members at 22 research sites worldwide  
Published largest study on recurrence rates for siblings  
Developed new ASD screening tools for infants and toddlers  
Established a repository of the largest collection of longitudinal information in high risk siblings, including both behavioral data and biological specimens  
Developed first interventions appropriate for infants and toddlers with ASD |
| Global Autism Public Health Initiative | United Nations and World Health Organization have begun major focus on autism  
Collaborations with Autism Speaks established in 23 countries  
$29M in new funds committed by other countries toward services and research  
Up-to-date analysis of cost of autism established for US and UK  
First time prevalence estimates in several countries established |
| Environmental Epidemiology Initiative/International Collaboration on Autism Registry Epidemiology | Brings together 78 researchers from 29 studies in 14 countries  
Created first standardized tool for tracking environmental exposures for use in autism research  
Built infrastructure to combine health registries from 7 countries to study prenatal risk factors; led to $12M in federal funding to continue this research (NIH ACE Network) |

The investments in investigator-initiated awards, resources, and initiatives have resulted in several significant advances over the past several years. Examples of such advancements
include:

• Multiple autism risk genes were discovered, leading to identification of drug targets for reducing autism symptoms.
• It was shown for the first time that autism symptoms can be reversed in animal models.
• The largest twin study to date was conducted, demonstrating larger impact of environmental risk factors for autism.
• Several environmental risk factors were identified, some of which are modifiable (e.g. folic acid taken during the preconception period can reduce risk).
• Screening tools for autism for infants and toddlers were developed.
• Infant-toddler treatments are now available, which can be delivered by parents.
• New behavioral interventions for adolescents and adults to address anxiety and social skills were developed and validated.
• Treatments for medical conditions, such as sleep disturbance, were developed and tested.

Looking forward: Investigator Initiated Funding and Priority Goals

One of the objectives of Autism Speaks’ science program is to identify and support promising research with the hope that results from these efforts will produce findings that will make significant contributions to the larger field of autism science. Ultimately, the aim is to enhance the capacity for research by attracting new talent, train researchers in methods critical to conducting autism research, and disseminate the findings in a rapid and meaningful manner. It is further anticipated that the research funded by Autism Speaks will lead to additional research support from government or other funding agencies.

Each year Autism Speaks solicits a variety of investigator-initiated applications to support many different types of projects, each critical for advancing all phases of autism research, from basic and clinical to treatment. These grants are crucial for allowing investigators to gain enough data to be able to attract even larger, multi-year commitments from the NIH and other traditional medical research funding organizations. Each year, we also identify critical areas that need added attention, and these typically address research questions that directly address the challenges ahead.

In an effort to stay on the cutting edge of autism science, Autism Speaks goes through an annual process of assessing current and identifying future emphasis areas for investigator-initiated awards. This process highlights areas that are notably understudied or underfunded that hold promise for important scientific discovery. Autism Speaks research funding is fully aligned with the priority goals outlined in the strategic plan for science; however, each year, the targeted research emphasis areas for investigator-initiated awards can remain flexible to emphasize specific types of research that are expected to accelerate progress toward the overall goals. These emphasis areas apply to all investigator initiated grants as well as any special targeted projects.

There is also a critical need to attract and nurture talent in autism research. Fellowships provide the necessary resources to support and encourage the development of young scientists who benefit from the mentorship of prominent researchers. The investment in autism research training will grow exponentially as many of our fellows later assume teaching roles and join departments around the country and the world, many of which currently have no representation in autism research. Currently Autism Speaks supports fellows at the pre-doctoral
and post-doctoral level, with the post-doctoral awards focused on translational research.

In the next sections, we review each of the priority research goals for 2013-17, describing the initiatives that address these goals, specific objectives, strategies, and metrics for measuring success. The priority goals are:

1. Identify risk factors for ASD that can lead to prevention and improved diagnosis and treatment
2. Reduce the age of early detection and improve access to early intervention for children with ASD
3. Enhance quality of, and access to, healthcare for individuals with ASD
4. Promote the development of safe, effective interventions and medicines to reduce core and associated symptoms of ASD throughout the lifespan
5. Improve the health and outcomes of adults with ASD from a lifetime perspective
IV. IDENTIFY RISK FACTORS FOR AUTISM THAT CAN LEAD TO PREVENTION AND IMPROVED DIAGNOSIS AND TREATMENT (GOAL # 1)

Autism is estimated to affect one out of every 88 children in the United States today including one in 54 boys (CDC, 2012). This represents a 78% increase in prevalence reported from 2007-2012, and a nearly 1000% increase over the past two decades. Furthermore, it is believed that this may still be an underestimate of autism prevalence in the U.S. An economic analysis funded by Autism Speaks revealed that the costs of autism have also increased dramatically, with annual costs to society of caring for individuals with ASD in the U.S. now reaching $137 billion a year. For each individual with autism, the lifetime cost is a staggering $1.4 million, and for individuals with autism and intellectual disability those costs can reach $2.3 million. Recent international epidemiological research showed that more than 2.5% of children (1 in 38) in South Korea were affected, using a rigorous school-based screening approach to identify autism cases. Autism Speaks is supporting the Centers on Disease Control and Prevention to implement a similar approach to identify the barriers to receiving an autism diagnosis in the U.S. and to better estimate prevalence of autism in the US.

Researchers are still unclear on what is causing the dramatic rise in autism prevalence. A number of reports suggest that a portion of the increase may be due to factors such as changes in the way autism is diagnosed and in the awareness levels of autism among families and doctors. However, there is also agreement that factors such as better identification alone cannot account for the entire increase in prevalence. Other factors, including environmental exposures and their interaction with genetic susceptibility, are likely playing a role in the increase, and one of Autism Speaks targeted goals is to identify these factors that may increase the risk for autism. However, understanding the increase in prevalence is not the only reason to study environmental and genetic risk factors. Prevention strategies rely strongly on understanding these factors and their mechanism of interaction. For example, preliminary research out of Baylor College of Medicine suggests that about 1% of individuals with ASD carry a mutation that disrupts metabolism of cartinine. If replicated, it is theorized that cartinine supplementation, when identified early, may prevent some ASD symptoms. In an animal model, mutations of one carbon folate metabolism, also seen in some cases of ASD, result in behaviors similar to neurodevelopmental disorders. Early dietary supplementation of folate partially protected against some of these deficits. Furthermore, use of genetic markers and understanding of environmental risk factors may hasten early behavioral intervention which would secondarily prevent ASD symptoms.

In addition to identifying environmental risk factors through epidemiological approaches, it is crucial to understand their mechanism of action and/or interaction with genetic markers. An understudied area of research is the role of environmental factors on epigenetic gene expression. Many new therapeutics in cancer are targeting epigenetic factors. More effort
should be focused on discoveries in the environmental epigenetics of ASD, how they can be studied and what different fields of science can contribute to creating the “environmental epigenome of ASD”.

Background and Initiatives

Genetics and genomics

**Autism Genetic Resource Exchange (AGRE).** Over the last 15 years, advances in genetic sequencing technologies have led to enormous growth in the amount of data generated by the scientific community. As developers of the Autism Genetic Resource Exchange (AGRE; [http://research.agre.org/program/descr.cfm](http://research.agre.org/program/descr.cfm)), Autism Speaks and its predecessors have been pioneers in the development and support of large-scale phenotypic and genetic databases and the creation of tools that serve to store, organize, and flexibly query such datasets. While the AGRE database is currently the largest private open resource for ASD research, advances in genetic technology, computational biology tools, and other novel analytic approaches demand even larger samples for more powerful genomic analyses. Larger data sets and improved analytic tools will allow scientists to better parse subgroups and make critical discoveries despite the substantial etiological and clinical heterogeneity of ASD.

Until recently, the majority of AGRE’s efforts have focused on the collection of phenotypic and genotypic information on families with 2 or more individuals affected with ASD (multiplex families). This collection, largely the result of a significant public-private partnership between Autism Speaks and the National Institute of Mental Health (NIMH), is regarded as a major genetic resource for the study of ASD. This is evidenced by the productivity of the researchers using AGRE over the last 15 years. Since its inception, over 400 researchers from 36 countries have used the resource, generating 200 scientific papers published in the best scientific journals and revealing significant new findings on autism risk genes. In fact, the majority of significant genetic findings in the last decade have benefitted from the resource, attesting to its utility to the field.

However, as Autism Speaks looks towards the future, the landscape for translational research and genomic medicine requires a much different approach that relies on extremely large sample sizes (>20,000) with a focus on the generation of “big data” to inform research and treatment. In order for AGRE to keep pace with and continue to properly support the research pipeline, it is critical and timely that Autism Speaks position the resource to better meet the emerging needs of science. To achieve this objective, AGRE has changed its model from a single source data collection model focused on multiplex family data collection to a data coordinating center model (AGRE DCC). The AGRE DCC is bringing together all of Autism Speaks-supported rich genetic and clinical data under one umbrella and supporting a suite of database resources and services for researchers to ensure maximum accessibility to data funded by Autism Speaks. The new vision for the AGRE DCC is to serve as a central data management, curation, and distribution center for the broader Autism Speaks community of researchers. Figure 3 illustrates this centralized model. The AGRE DCC will work to integrate metadata and phenotypic data across all the resources funded by Autism Speaks. Where biospecimens are available, the AGRE DCC will also create a central mechanism for accessing those samples. The AGRE DCC will remain the “honest broker” in the field and both promote and hold steadfast to broad data sharing and collaboration.
Table 5 below illustrates the suite of services that the new AGRE DCC will support.

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<th>SERVICES</th>
<th>AGRE DCC</th>
<th>BSRC</th>
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<td>DATA SYSTEM RESOURCES</td>
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<td>Patient tracking</td>
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Specifically, this suite of services currently includes 1) data management capabilities, including support for phenotype data, genomic data, and data federation; 2) biorepository management and support; 3) data system resources including patient tracking, electronic data capture and web-based clinical data acquisition; 4) subject recruitment and re-contact for families in the multiplex, twin, and AS-ATN collections; and 5) study management capabilities for external researchers who wish to collaborate with the AGRE DCC.

Currently, few research programs have the necessary infrastructure to support the management and distribution of the volumes of data that are needed and are being generated through industry and private universities worldwide. In 2011, Autism Speaks launched the 10K Genome project, a partnership between Autism Speaks and the Beijing Genomics Institute (BGI). Our long term goal is to generate whole genome sequencing data on 10,000 individuals from the
AGRE multiplex collection as well as the Autism Genome Project trio collection. The volume (petabytes) of whole genome sequencing data alone will require solutions that will exceed the current capacity. Autism Speaks aims to address this need by establishing core computing and informatics infrastructure capacity that will leverage the power of cloud computing.

In 2009, Autism Speaks received funding from the NIMH to build capacity for AGRE to serve as a data federation site for the National Database for Autism Research (NDAR). Since that time, AGRE has worked closely with federal partners to create an active pipeline for researchers to access both AGRE data as well as other federated datasets. This mechanism has allowed AGRE to harmonize data across other international or proprietary repositories without having to store and host the data locally, tripling the number of individuals available to the research community.

To further improve the core infrastructure and data basing capacity available through AGRE, Autism Speaks partnered with Prometheus Research, a leading provider of data management services for behavioral and biomedical research, to develop a series of integrated data systems to support the integration and centralization of several of these data and biospecimen repositories. The Prometheus Research Exchange Database (RexDB®) platform lends itself to data analysis across collections, and there are plans to make the software stack open source by 2012. Through this partnership, Prometheus is also developing a web-based system that will allow research participants to more easily participate in studies via user-friendly web-based technologies. Current and future studies using the AGRE DCC will benefit from the technology developed through this partnership and will contribute further to NDAR to create an even more comprehensive database for autism research.

**Establishing an Autism Biorepository in China.** Our knowledge of the genetics of autism has been gained almost exclusively from the studies conducted in Caucasian populations in the U.S. and European countries. Remarkably few studies from other populations or countries have been reported in the English literature.

Because of increased public health concern for ASD in China over the last decade, autism research has gained national attention both at the public and academic levels. A national survey conducted in 2001 by the Chinese Disabled Person Federation, a government social welfare agency, reported a rate of 8 per 10,000 children identified with autism or atypical autism. Another recent study found that 1.1 per 1,000 children met criteria for an ASD. This is in contrast to the much higher prevalence in the U.S. as well as a recent report from South Korea that reported 1 in 35 school-age children in that territory were diagnosed with an ASD. Explanations for why the prevalence of ASD in Chinese-speaking populations would be significantly lower than Caucasian or other populations include differences in patterns of diagnosis and ascertainment of samples, environmental risk factors, and population-specific genetic factors.

To this end, Autism Speaks partnered with Fudan Children’s Hospital in Shanghai, China to standardize the evaluation and centralized collection of phenotype data and biospecimens. This pilot project will focus on the recruitment of families from the Shanghai region that will be made available to the broader autism community through AGRE. The proposed autism repository will be the first one in China and also is believed to be the first among other Chinese-speaking territories including Taiwan, Hong Kong, and Macao. The project will serve as a model
for expansion to other major cities or at the national level in China and other Chinese-speaking territories. The autism registry will be immediately available for studies of natural history, validating diagnostic tools, relevant epidemiology studies, and genetics studies. The ASD biorepository will provide a valuable resource for investigators both in China and the U.S. who are interested in cross-cultural comparative ASD studies. Recently, the Ministry of Health of China approved funding to link 8 regional children’s hospitals in the country to establish a national clinical research and training network to (1) provide training for autism screening and diagnosis, (2) conduct an autism prevalence study in the country, and (3) provide training of service providers for behavioral intervention. The network’s expertise and infrastructure may someday be leveraged to create a national surveillance network akin to that overseen by the CDC in the U.S., and to serve as a platform to spur basic and translational research in autism. Autism Speaks staff are serving as technical consultants to this national initiative with the goal of replicating the AGRE-China model across the network.

**Autism Genome Project.** The Autism Genome Project (AGP) ([http://www.autismgenome.org/](http://www.autismgenome.org/)) is a consortium of over 100 leading autism geneticists and clinicians from 19 countries. Since 2004, they have collaborated to combine their large collection of multiplex and trio families to advance our understanding of the genetic architecture of autism. As of the end of 2011, members of the consortium had published over 200 papers, including seminal reports in high impact journals such as Nature that identified autism risk genes and the biological processes and pathways in which they play a role. At least $76 million in additional grants from U.S. and international funding agencies have been leveraged focused on analysis of the AGP data and training of new researchers. The number of samples currently in the AGP data set is shown below in Table 6. In recent years, the AGP’s scientific focus has evolved from basic research toward translational efforts. While consortium members and samples continue to play a key role in signature discovery efforts like the NIH-funded Autism Sequencing Consortium and the collaboration between Autism Speaks and Beijing Genomics Institute, they have also been active in exploring the development of diagnostics and novel therapeutics.

Recognizing AGP’s unique collection of over 6,000 families representing nearly 24,000 individuals as an important resource for high impact research to be carried out by the consortium as well as the broader scientific community, AGRE has recently assumed the role of data coordinating center for the consortium. Aiming to facilitate consortium activities and informing other key research community priorities going forward, the migration of the AGP data coordinating center to AGRE is firmly aligned with AGRE’s current reorganization as an informatics hub for autism research in the coming years.

Table 6: AGP Database “footprint” (as of September 2011)

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<tr>
<td>Number of Families</td>
<td>6,095</td>
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<tr>
<td>Number of Individuals</td>
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<tr>
<td>Phenotypic data points</td>
<td>2,200,000</td>
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<tr>
<td>Total footprint</td>
<td>260 GB</td>
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<tr>
<td>Total archival storage</td>
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**Informatics.** The key to major discoveries that have near-term clinical impact lies at the confluence of (1) genomics, (2) detailed clinical characterization, and (3) bioinformatics, with all three elements at unprecedented scales of coverage and functionality. The landscape for translational research and genomic medicine for autism requires a much different approach that
relies on extremely large sample sizes (>20,000) with a focus on the generation of large-scale datasets to inform clinical research. To date, university-led efforts have been too small and underpowered, and while the whole could eventually become greater than the sum of its parts, the lack of centralized coordination suggests that the path to breakthrough is likely to be costly, long and underwhelming. Instead, the field needs a bolder, more nimble effort that can serve as a catalyst for scientific discovery independent of any single university or academic setting.

Autism Speaks brings unique leverage for success in two of the three key areas described above (genomics and detailed clinical data) through two existing initiatives. First, AS has developed the Autism Speaks Autism Treatment Network (AS-ATN) that coordinates the collection of comprehensive behavioral and medical information from over 5,000 children with autism at 14 academic medical centers across the United States and Canada. In addition, through a collaborative partnership with BGI, AS has outsourced the genomic sequencing of over 2,000 families with autism to amass the world’s largest collection of autism and control genomes, a collection that will total over 10,000 in 3 years. With these two efforts already under way, the goal is to develop the third critical piece, bioinformatic capacity, which will provide the computing and analytic platform to integrate these elements into a comprehensive center for genetic and clinical discovery.

To this end, Autism Speaks plans to develop a national center for autism genomics and bioinformatics research by leveraging Autism Speaks’ existing substantial clinical and biospecimen resources and enhancing Autism Speaks’ bioinformatics resources and expertise. There will be three primary areas of focus and activity:

1. Computational infrastructure development & expansion
2. Genomics data generation
3. Data analysis & clinical discovery research

Our goal is to offer the scientific community the data and computational infrastructure and expertise that will accelerate the translation of genomic information into clinical applications for improving diagnosis and treatment of ASD.

**Autism Epidemiology Initiative**

**Prevalence and risk factors.** The Autism Epidemiology Initiative was established in 2004 with the goal of better understanding the prevalence of autism globally and identifying the factors that increase risk for autism. As one part of this initiative, Autism Speaks, in partnership with the CDC, established a collaborative network – the International Autism Epidemiology Network – to identify common approaches and facilitate coordination of epidemiologic research activities across investigators from multiple countries. International research presents unique opportunities to study autism across diverse populations and environments. Epidemiologists can make comparisons of autism prevalence as a means of generating clues about the involvement of genes or environmental exposures that would not be possible by looking in the U.S. alone. Additionally, some nations have special resources, such as population health registries and surveillance systems, which can generate unique large datasets and make research on rare risk factors possible.
Autism Speaks has supported epidemiological research in more than a dozen countries around the world including first-ever prevalence studies in Bangladesh, India, Mexico, South Africa, South Korea, and Taiwan. In addition, Autism Speaks supports a highly innovative project that links population health registry data from seven countries – Australia, Denmark, Finland, Israel, Norway, Sweden, and the United States – to create the largest autism data set in existence. Supported in 2008 by Autism Speaks, the International Collaboration for Autism Registry Epidemiology (iCARE) focuses on pre- and perinatal risk factors for autism including birth weight, gestational age, and parental age. There are a potential 20,000 cases in one birth year that can be analyzed using registry data. This project has since received a substantial Autism Centers of Excellence (ACE) Network Award from the NIH to expand its investigation of early life risk factors. Many of the international epidemiology research efforts have served as the catalyst for many of the activities of Autism Speaks Global Autism Public Health Initiative (described in detail below).

**Environmental Epidemiology of Autism Research Network.** Also part of the Autism Epidemiology Initiative is a network of investigators focused specifically on environmental risk factors, the Environmental Epidemiology of Autism Research Network (EEARN). EEARN was formed in partnership with the National Institute of Environmental Health Sciences (NIEHS) in 2010 with the encouragement of researchers in this area. The objectives of the network are to 1) support and encourage collaborations across research sites using different methodologies, especially those that involve rare subgroups or exposures, 2) provide a mechanism for information and protocol sharing, including a web portal as well as disseminating topics of interest such as statistical methodology and 3) create opportunities for new researchers, specifically in analyzing data sets that may provide insight on undiscovered findings using existing data studying environmental risk factors and gene/environment interactions. Among the risk factors being studied are maternal and paternal age, gestational age, medication use during pregnancy, certain chemical exposures and indoor and outdoor pollution.

Though the number of studies examining environmental factors is not large, they alone have already been highly successful. To date, well-conducted epidemiologic research has shown associations between risk for ASD and air pollution, pesticide exposures, short interpregnancy intervals, maternal nutrition, maternal metabolic conditions including obesity, conception in winter, acute infections or fever during pregnancy, use of SSRIs, and vinyl flooring. Some of this research has identified large effects (e.g., pesticides, viral infections, short interpregnancy intervals). Certain others have shown interactive effects between genes and environment, i.e., have demonstrated a genetic susceptibility that alone has no impact, but combined with an environmental factor (the low intake of folic acid in the periconception), alters the risk dramatically. To date, none of the research has clearly identified a clinical phenotype that correlates with an environmental exposure. Thus, despite heterogeneity of phenotype, the field is not yet able to link environmental etiology in a one-to-one correspondence with severity or specific symptomatology. Given the diverse and expansive nature of data collection, as well as the heterogeneity of ASD, multi-site and multi-disciplinary collaboration will be important. An example of an ongoing collaboration is provided by the international autism registry projects in epidemiology (iCARE, described above).

In 2011, two multisite projects of the EEARN network were launched, both supported by Autism Speaks. The first utilizes the AGRE dataset together with the hazardous air pollution database to examine the relationship between air particulate matter and autism risk, including
dimensional features of ASD. The second aims to develop and validate a standardized exposure questionnaire that can be used in a number of research studies, especially those primarily focused on genetic or clinical outcomes, to better study gene/environment interactions. This questionnaire is currently being used by the Baby Siblings Research Consortium (BSRC) sites participating in the first phase of the BSRC repository, as described below.

**Other approaches to identifying risk factors: studies of high-risk siblings**

**Baby Siblings Research Consortium.** Autism Speaks has been facilitating collaboration and funding specific research projects within a network of investigators studying at risk siblings of children with autism. Such siblings are at much higher risk for ASD than the general population. The Baby Siblings Research Consortium (BSRC) is a group of 25 researchers across 21 research sites that share their data on very early markers of ASD outcome. They focus on investigations of infants at risk for autism spectrum disorders (ASD) using a variety of methods. Building upon the diverse, yet integrally aligned, set of investigators, the BSRC supports the independent efforts of individual researchers and research groups while at the same time creating a framework for collaborative research activities (with new or existing funding at each site) and data sharing through this collaboration. In 2011, Autism Speaks awarded a grant to UC Davis to house a legacy database of information on over 2,500 high risk siblings and 1,000 low risk siblings. In mid-2011, this database was used in a major publication updating the recurrence rate of these younger siblings. This recurrence rate of 20% has been instrumental in helping families with autism create awareness with their health care providers around early signs and symptoms.

In the next 5 years, the consortium plans to address other questions around early signs and symptoms of autism using this database. This will include a) expansion of data collected and entered into the common database, and b) increasing the number of collaborative projects using consortium data through this database and linking to existing databases and shared data repositories. The topics of these collaborative projects include environmental exposure information, biological data including EEG, early motor symptoms, and trajectories of development in ASD using existing datasets.

In 2011, in partnership with the Simons Foundation, the BSRC funded a biorepository of 445 families across 6 sites in the US and Canada. In addition to collecting genetic information on families with at least one sibling tracked from 12 – 36 months of age, the repository will house extensive phenotypic and environmental exposure information on families. Cell lines and clinical and other data will be available through AGRE. As the current number of high risk sibs in the consortium is reaching 4,000, this repository is only one piece of the biological and environmental exposure risk information that is being currently collected. A future goal of the repository, through the interaction with AGRE, will be to bring existing and future samples together in one larger collection.

**IBIS-EARLI collaboration.** In 2008, the NIH funded two Autism Centers of Excellence Awards to prospectively follow cohorts of infant siblings of children with autism – the Infant Brain Imaging Study (IBIS; [http://www.ibisnetwork.org/](http://www.ibisnetwork.org/)) directed by Joseph Piven at the University of North Carolina at Chapel Hill and the Early Autism Risk Longitudinal Investigation (EARLI; [http://www.earlistudy.org/](http://www.earlistudy.org/)) directed by Craig Newschaffer at Drexel University. Each network involves collaboration among several academic centers following high-risk siblings. IBIS
is focused on studying early brain development with brain imaging (MRI, Diffusion Tensor Imaging, MRS) conducted at 6, 12, and 24 months of age. EARLI is focused on a number of environmental exposures, ranging from suspected neurotoxicants to medications taken during pregnancy. Multiple longitudinal direct exposure assessment coupled with detailed phenotyping in a high risk cohort allows more detailed analysis on the relationship between genetic and environmental risk factors to be ascertained. In 2010, Autism Speaks and the Simons Foundation provided additional funding to enrich and combine the data from the two projects. Simons Foundation funds allow enhanced brain imaging measures. Autism Speaks provided funding to enable the collection of DNA on all family members, collection of a core set of comparable measures of environmental exposures across the two networks, and methods for combining and analyzing the data to study gene-environment interactions. In 2011, the IBIS team reported brain imaging differences evident at 6 months in high risk infants who later developed autism. Published in the American Journal of Psychiatry, it was found that infants who met criteria for autism had differences in early white matter fiber tract development – pathways that connect brain regions – as measured by fractional anisotropy (see http://www.sciencedaily.com/releases/2012/02/120217101048.htm).

During the next 5 years, these longitudinal studies will begin to come to fruition with infants reaching the age at which a diagnosis can be made. In addition, based on additional funds from both NIH and Autism Speaks, the sample size on these studies will be increased and additional brain imaging measures using electrophysiology will be added. Biological samples and certain behavioral endpoints will become available to researchers through AGRE. These studies are designed to identify: 1) very early risk predictive biomarkers for autism that may be evident before the onset of the full syndrome, 2) genetic and environmental risk factors for autism, 3) the interaction of environmental factors on systems, including the endocrine and metabolic system in ASD, and 4) a detailed examination of the earliest behavioral signs of autism in infants.

**Targeted research projects on risk factors**

Over the past 5 years, several environmental factors have been identified which contribute to risk of ASD. The ultimate goal of identifying environmental risk factors for ASD is to determine those that may be modified by change of exposure on either a personal level, a community level, or a regional level. There is mounting evidence that some of these risk factors include diet, nutrition, medical interventions and some chemical and toxic exposures. In certain cases, these environmental risk factors may lead to knowledge about how they can be avoided, or introduced, to mitigate the risk of ASD.

In addition to risk factors which may be modifiable, the effects of these risk factors on biological mechanisms which can be reversible is crucial for better understanding how certain factors relate to outcome, and how reduction in exposure modifies risk. For example, changes in epigenetic markers which control gene expression are modulated in different times during brain development and can be identified in a variety of biospecimens. These epigenetic changes may be modifiable, so future studies should incorporate longitudinal assessment of epigenetic and environmental variables so that these modifiable risk factors can be better characterized. In addition, by focusing on the underlying mechanism of action, researchers will be better able to discriminate relevant risk factors from confounds which may also be involved with the same pathway.
There are very few studies that focus on how specific genetic modifiers of autism risk interact with environmental factors in epidemiological studies. With more expanded use of genetic analyses in research settings and certain medical settings, some previously undetected risk or protective factors may emerge. It will be crucial to communicate the role of these risk factors to the public in an ethical and scientifically sound way to minimize unintentional harm. In addition, as many of these findings are relevant to risk itself, Autism Speaks should ensure that research findings relating to these discoveries are communicated in an ethical, justifiable way that looks towards how families interpret and understand this information. Autism Speaks will continue to engage a broad array of expertise, from bioethics to risk communication to clinical services, to provide ongoing assessment and evaluation of how this crucial information is being comprehended.

**Faith and Philip Geier Autism Research Award in Environmental Sciences.** To stimulate research on environmental risk factors, in 2012, Autism Speaks launched the Faith and Philip Geier Research Award in Environmental Sciences. The award is given annually to an outstanding researcher seeking to uncover environmental risk factors for autism. The inaugural grant was awarded to M. Daniele Fallin for a three-year project on environmental epigenetics by funding a genome-wide examination of DNA methylation in a large cohort of individuals with ASD versus controls.

**In-depth study of autistic regression.** Although it has long been validated that a subgroup of children with ASD follow a normal or near-normal early developmental trajectory and then experience regression and loss of skills, there is still relatively little known about the etiological and biological differences between children with ASD with regression versus those with early onset of symptoms. An in-depth study of children with ASD with and without regression will be carried out, which will include a detailed environmental exposure, developmental and medical history, as well as comprehensive medical evaluation including whole genome sequencing, immune profile, and assessment of co-morbid medical conditions.

The role of immunizations in autistic regression was identified as a priority by the Interagency Autism Coordinating Committee based on recommendations by the National Vaccine Advisory Committee. Many studies have been conducted to determine if a link exists between vaccination and increased prevalence of autism, with particular attention to the measles-mumps-rubella (MMR) vaccine and those containing thimerosal. These studies have not found a link between vaccines and autism. It remains possible that, in rare cases, immunization might trigger the onset of autism symptoms in a child with an underlying medical or genetic condition. Autism Speaks is funding studies on the underlying biology of autism, including studies to better understand medical and genetic conditions that are associated with autism that could potentially be linked to adverse responses to immunization.

**Looking Ahead to 2013-2017**

**Objectives**

- Accelerate discovery of genetic and environmental risk factors, diagnostic methods, predictive and early efficacy biomarkers, and drug target identification and validation through more detailed genomic information and enhanced bioinformatics expertise and resources
- Accelerate discovery of modifiable risk and protective factors through various types of research, including but not limited to: population-based epidemiology, high-risk
subpopulation designs, animal models, molecular studies in well-characterized populations, mechanistic investigations

- Identify and explain genetic and environmental risk factors for ASD, including those that may be population specific, as well as those that can be modified by population or individual changes in exposure
- Investigate and understand, through various study designs, the roles of the following: maternal nutrition before and during pregnancy, and during breastfeeding; maternal metabolism and how it impacts the fetus; chemical toxins both in and outside the home environment, their routes of exposure and their persistence; microbiological influences on development through immune or other mechanisms; paternal exposures during late spermatogenesis and both the cause and the role of de novo mutations in relation to risk for ASD; hormonal factors, both exogenous and endogenous; and other classes of non-inherited risk and protective factors
- Describe gene/environment interactions and their mechanisms, including environmental epigenetics, and their role in autism spectrum disorders
- Delineate which risk and protective factors are shared with other developmental disorders and which are specific to ASD
- Identify genetic and environmental risk factors influencing heterogeneity and comorbid disorders, including epilepsy and immune dysfunction.
- Understand the underlying causes and biology of autistic regression with a long term goal of developing more effective strategies for prevention and treatment
- Use research discoveries and advances to disseminate knowledge and influence policy, communication of findings, clinical practice, and individual behavior

**Strategies**

- Expand research partnerships in the study of environmental epigenetics and resources needed to investigate these studies
- Create large and diverse data base of whole genome sequence data to serve the autism scientific and clinical communities through a partnership with BGI
- Migrate Autism Genome Project data base to AGRE and establish platform for investigators to have access to these data
- Build a more robust and flexible platform for investigators to access genomic and clinical data through AGRE through partnership with Prometheus
- Continue to accrue diverse genetic data sets as part of AGRE
- Continue to collaborate with NDAR and the Simons Foundation to build federated genetic data sets
- Hire additional expertise in the area of bioinformatics at Autism Speaks
- Establish a national center for autism genomics & bioinformatics research that will provide a state-of-the-art computational framework, genomics analysis pipeline, and data import procedures
- Establish an Autism Biorepository in China and replicate this model elsewhere
- Collaborate with our international partners to facilitate and fund epidemiological studies focused on prevalence and risk factors outside the U.S.
- Look for and take advantage of unique international opportunity to better understand risk factors for ASD
- Promote collaboration and provide funding for investigators involved in environmental epidemiological research
• Capitalize upon existing environmental research programs by funding add-ons that multiply the impact of such resources, particularly biobanks, with opportunities for exposure determination and establishment of early biomarkers
• Provide incentives to attract established investigators from other areas who can bring unique insights into the field of autism research
• Continue to support young environmental health investigators seeking a career in autism research
• Establish a standardized environmental exposure assessment tool that can be readily used by a wide range of investigators, including studies on genetics
• Promote research and collaborations focused on risk markers younger than 12 months of age through the BSRC and EARLI, with a stronger focus on biological risk markers, including electrophysiological risk markers
• Conduct in-depth study of the etiology and biology of autistic regression
• Launch new studies using existing and expanded datasets on high risk infants
  o Identification of biological risk marker(s)
  o Link with environmental exposure(s)
  o Study of protective factors or factors which confer resilience
• Fund research on environmental epigenetics, including windows of susceptibility for epigenetic modification of gene expression

**Metrics for measuring success**

• Significant expansion of diverse clinical, genetic and environmental data, including international data sets, will become available to the scientific community and significantly accelerate and expand the discovery of genetic and environmental risk factors for ASD, including epigenetic mechanisms.
• Genomic information will be used to personalize treatment approaches for patients, including those served through Autism Speaks Autism Treatment Network.
• Enhanced computational and analytic resources will be available and lead to the identification and validation of biological pathways affected in autism and novel drug targets, as well as new diagnostic approaches.
• Biological markers for risk for autism that can be used before autism symptoms are fully manifest will be available.
• Infant ASD screening methods will be validated and distributed for use.
• Identification, through both discovery and replication, of modifiable risk factors that can explain 10-20% of cases of autism, followed by appropriate dissemination of this information to stakeholder communities, as a first step towards prevention.
• Deeper understanding of the neuropathophysiologic mechanisms by which modifiable factors influence risk for autism, opening the door to pathway-oriented research and prevention strategies.
• Improved understanding of the cause and biology of autistic regression will lead to more effective ways of preventing and/or treating this condition.
• Prevalence estimates for autism will exist in countries outside of the US and Europe, allowing those countries to begin to build and address the public health needs of individuals with ASD globally.
• A standardized assessment tool to collect information on environmental exposures across studies will be implemented.
• Information on modifiable risk factors for ASD will begin to change public health policy.
V. REDUCE AGE OF EARLY DETECTION AND IMPROVE ACCESS TO BEHAVIORAL INTERVENTIONS (GOAL #2)

Background and Initiatives

Autism can now be reliably diagnosed at approximately 18-24 months of age, yet the median age of diagnosis is about 4 years or older. Furthermore, despite the existence of effective behavioral interventions, many children still lack access to such services. There is a clear gap between the state of the science and the clinical services that are implemented in practice. This is especially apparent when looking to the international community. Many countries have minimal infrastructure and services for child mental health conditions, particularly autism. Although we plan to implement an increased focus on closing the gap in early detection and services, a number of existing initiatives have provided a foundation for this work, as described below.

Baby Siblings Research Consortium. The High Risk Baby Siblings Research Consortium, or BSRC, was established in 2003 through collaboration between Autism Speaks and the Eunice Kennedy Shriver National Institute of Child Health and Development (NICHD). This group has grown to 24 researchers at 21 research sites in 4 countries, including the United States, Canada, the United Kingdom and Israel. Each of the investigators focus on studies of infants at risk for autism spectrum disorders (ASD) using a variety of methods, including behavioral and neurobiological measures. Building upon the diverse, yet integrally aligned, set of investigators, the BSRC not only fosters projects of individual researchers and research groups, but also creates a framework for collaborative research activities. This collaborative framework is built on an Autism Speaks-funded database which includes data on over 3,000 high risk and 1,000 low risk siblings through 36 months of age. The consortium is now poised to better identify early signs of autism to help reduce the age of detection.

Toddler Treatment Network. In 2007, Autism Speaks formed the Toddler Treatment Network (TTN) to study the efficacy of interventions delivered to children under the age of 24 months. The original group of 8 studies has now expanded to over a dozen different projects worldwide. These projects share a common goal of using randomized clinical trials to understand the efficacy of parent-implemented naturalistic interventions targeting the earliest autism behavioral symptoms. As such, they are heavily focused on communication, including joint attention, imitation, gestures and language. The interventions involve techniques that can be implemented outside the clinic, allowing parents and caregivers to use them in different settings, decreasing the time between parents’ initial concern and the start of an intervention, thus hopefully improving developmental outcomes in the long run. The TTN utilizes the individual strengths of researchers studying the feasibility and efficacy of interventions delivered at the youngest ages through individual research projects, collaborative data sharing activities such as a meta-analysis of the original 8 studies, an annual public meeting, and workgroups on specific topics such as methodology and dissemination. These interventions hold promise in helping more families begin intervention as early as possible and improving behavioral outcomes through cost effective, parent-mediated services.

The Toddler Treatment Network is now in a position to help disseminate evidence-based interventions into community settings. As part of the TTN, a multi-stakeholder network to improve the quality of early intervention services for children with ASD will be established.
The overall objectives of the network will be to reduce population disparities in access to intervention and enhance the use of evidence-based practices in early intervention programs for children with autism. Through this network, Autism Speaks will lead a number of both collaborative and dissemination/implementation activities. Collaborative activities include exploring partnerships between community-based early intervention providers, administrators and the research community to implement community-based participatory research activities to address network objectives; developing partnership models to be tested by a wider community in various areas of the U.S.; and funding a pilot project involving model collaborations. Dissemination and implementation activities include developing and testing a set of quality measures for early intervention providers; examining challenges in transition/maintaining care continuity for toddlers in early intervention as they enter the school system; and encouraging and supporting the development and refinement of strategies (e.g. parent-mediated, train the trainer, telemedicine) for the delivery of evidence-based practices to improve outcomes.

**Reduce age of diagnosis and increase access to intervention.** Through the discoveries and advances in research made by researchers involved in the BSRC and the TTN, great strides have been made in developing autism screening and diagnosis tools and methods for early behavioral intervention that can be utilized with very young children. Screening tools are available that can be used with infants as young as 12 months of age, and infant-toddler interventions are being developed and evaluated. Multiple studies now support the reliable diagnosis of autism by 18-24 months of age. Randomized controlled trials have shown that early intensive behavioral intervention can significantly alter the trajectory of cognitive, language, and social development, resulting in more positive outcomes by elementary school age. It is important that we galvanize our efforts to make a noticeable, measurable difference in reducing the age of autism diagnosis and improving access to early intervention.

In recognition of this large public health challenge, as well as the current efforts of partners like the CDC and the American Academy of Pediatrics (AAP), there is a need to develop a strategic, coordinated effort both within and outside of Autism Speaks. A multi-pronged strategy will be implemented, including developing a collaborative strategic approach, targeting awareness and advocacy efforts, creating and testing innovative solutions to increase access to diagnosis and intervention, and understanding and addressing disparities in access to diagnosis and intervention.

All Autism Speaks departments across the organization are involved in this initiative. For example, in partnership with the Ad Council, Autism Speaks has developed a media campaign targeting underserved groups, such as Spanish-speaking communities, to increase awareness of the importance of early diagnosis and treatment. The campaign will be launched in the spring of 2013 and is the organization’s first ever media campaign developed for and targeted at an underserved community. Other key ongoing activities include Autism Speaks efforts related to insurance reform to improve reimbursement for behavioral health interventions, including early intensive behavioral intervention, and autism screening. As the number of walks and regional chapters increases, this will also mean greater awareness and reach. Social media also plays an important role. The Autism Speaks website will be redesigned to optimize its usefulness for families with a concern or with children who have been recently diagnosed. The Family Services team is actively engaged in outreach to the broader autism community through the development of new toolkits and the promotion of the video glossary to educate families on the first signs of autism. In addition, an online version of the Modified Checklist for Autism in
Toddlers (M-CHAT) is now available on the Autism Speaks website. Over 2,000 individuals fill out the MCHAT on a monthly basis. In August of 2012, Autism Speaks launched an annual conference that brings together families and professionals that will improve awareness in the areas of early diagnosis and screening. Continuing education credit, based on lectures from the National Conference, will be offered during the conference and later on the Autism Speaks website. Targeted research emphasis areas for investigator-initiated awards include “enhancing the diagnosis of underserved and understudied populations” as well as “disseminating and implementing evidence-based clinical practices to the community worldwide”. The Global Autism Public Health Initiative (described in greater detail below) is designed to facilitate these goals in communities outside of the United States.

In order to develop a coordinated, strategic plan among Autism Speaks departments and outside partners and stakeholders, Autism Speaks hosted a strategic planning meeting in 2012 that included experts in the areas of early detection and early intervention for autism, representatives from the CDC, AAP and New York State Department of Early Intervention, and experts in areas outside of ASD, such as breast cancer and technology applications for dissemination and implementation. The participants gathered for 2 days to 1) identify priorities, opportunities, and barriers to achieving a reduction in age of diagnosis and access to intervention in the U.S; 2) consider how current efforts can be leveraged to achieve these goals; 3) define the partnerships that are key to success; 4) identify knowledge gaps that must be filled; and, 5) pinpoint strategic investments that are needed to increase the evidence-base and speed dissemination and implementation. The meeting began by reviewing the landscape and current activities pertaining to early detection and intervention in the areas of awareness, screening and diagnosis. This was followed by presentations on challenges and barriers and innovative technologies. The presentations were supplemented by a summary review of the literature on all strategies to date related to enhancing early detection and increasing access to care in both autism and in other disease areas, such as ADHD, epilepsy, depression and cancer. This meeting set the stage for subsequent development of key strategies and objectives of the initiative, as shown in Figure 4.

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Figure 4.
Global Autism Public Health Initiative. Evidence suggests that autism knows no cultural, ethnic, or geographic boundaries. It affects more than 1% of children in the United States, and converging research from around the world suggests that autism affects at least 1% of the global population. Just as the high prevalence of autism has driven its emergence as a public health priority in the United States, increased awareness of autism has simultaneously increased the demand for services around the world. However, unlike countries in Western Europe and North America that, in general, have some capacity to help meet the needs of individuals with autism, access to services can be extremely insufficient in many countries around the world.

In 2008 Autism Speaks launched the Global Autism Public Health Initiative (GAPH) to facilitate the development of systematic and sustainable solutions for enhancing global autism awareness, research, and service delivery. The strategies through which GAPH aims to accomplish these goals, as well as the specific focus areas of this initiative, are illustrated in Figure 5. Since GAPH’s inception, Autism Speaks has established collaborations with stakeholders from over 42 countries, including parents, professionals, and governments, who are dedicated to making lasting change in their communities. When possible, GAPH aims to facilitate regional collaboration to address shared challenges across partner countries in a comprehensive and coordinated fashion. To date, Autism Speaks has facilitated the establishment of the Southeast European Autism Network (SEAN), South Asian Autism Network (SAAN), and the Gulf Coast Countries Consortium (GCC).
GAPH is rooted in scientific research and evidence-based practices. To date, most autism research has taken place in select areas of relatively developed nations and communities. Very little is known about the occurrence and treatment of autism in low-resource settings and among underserved populations with limited capacity for research and public health services. By addressing these barriers and enhancing the quality of research around the world, investigators can not only learn more about autism and its causes, but also communities can benefit from improved capacity for autism detection and services.

Research is also a mechanism for capacity building in itself. Internationally, among the steps necessary to conducting research is the training of individuals to diagnose autism, and in some cases, deliver interventions. By studying autism in settings with different cultures and resources, GAPH affords the opportunity to develop new diagnostic and treatment services that are easier and less costly to administer, or test existing evidence-based practices in a variety of settings. The results of such research can have implications for underserved populations around the world, even in more developed countries such as the U.S. In 2011, Autism Speaks announced a targeted RFA that resulted in the support of 5 projects aimed at disseminating and implementing best practices in low resource settings around the world, including one project in the United States.

Epidemiological research and the larger field of public health allow investigators to measure the magnitude of a public health problem and to monitor trends over time. In addition, they can be used to evaluate access to services and factors that influence it. Such information provides a platform on which advocates and decision-makers can build a case for health policy reform and appropriate resource allocation. Understanding the economic impact of autism, for example, can help researchers and advocates gauge the impact of autism on societies, including the quality of life of affected individuals and families. Beginning in 2011, Autism Speaks announced support of a series of research projects designed to 1) provide a more accurate and updated measure of the cost of autism to society annually and the lifetime cost to individuals in the U.S. and U.K.; 2) develop a cost-calculating model that can be used by other societies to measure the economic burden of autism in their countries; and 3) evaluate the cost effectiveness of early intervention services. The impact of early diagnosis and early intervention on the economic burden of autism can further make the case for increased service support to both general and underserved populations in the U.S. and abroad. This information can serve as a means to promote increased access to low-cost and widely available services.

International autism research not only sheds light on the scope of the autism challenge around the world but also serves to raise global awareness of autism and reduce stigma. Thus, enhancing awareness is another core focus of GAPH. Increased awareness can galvanize communities that can, in turn, use public health research findings to advocate for health policy that can immediately and sustainably benefit previously underserved communities.
Approaches to autism detection, diagnosis and treatment across the globe may vary as a function of differences in levels of awareness and availability of resources. Given the diversity of basic infrastructure, understanding and knowledge of autism across the globe, the approach to address detection, diagnosis and intervention for ASD may vary across regional settings. However, there are common overlapping themes across the domestic and international initiatives that fit together under goal #2. For example, all initiatives emphasize the importance of forming partnerships to improve capacity for the creation and sustainability of programs and services. A common theme of partnership and collaboration across the world to facilitate research can be seen across these programs and initiatives. In particular, efforts to reduce the age of early detection and access to services in the US share a number of commonalities with the larger GAPH initiative in the areas of awareness, screening and diagnosis, and service delivery. Both initiatives emphasize the importance of using population-based methods for estimating prevalence and cost of autism to society. In addition, both rely on available data sources for surveillance and monitoring of prevalence and associated outcomes for entire populations and population sub-groups. In the area of screening and diagnosis, both focus on the development and validation of rapid diagnostic and case confirmation methods as well as the examination of effective, sustainable strategies for broad adoption of evidence-based screening and diagnostic practices. And in the area of service delivery, the development and evaluation of efficient models of early behavioral interventions and the exploration of the feasibility and effectiveness of delivering evidence-based interventions via nontraditional channels—including distance-learning, train the trainer models, and parents—are major foci of both the U.S. and global efforts.

In sum, lowering the age of diagnosis of ASD and improving access to early intervention is going to require: 1) focused research on early detection and effective interventions, 2) dissemination of findings to community settings, and 3) implementation of evidence-based
practices tailored for a global audience. As such, the overlapping objectives, strategies and examples of metrics for success will be:

Looking Ahead 2013-2017

Objectives

- Raise awareness in the U.S. and worldwide among professionals and the public of:
  - Prevalence
  - Early detection and intervention
  - Evidence-based treatment practices
- Increase the number in the U.S. and worldwide of:
  - Toddlers who are screened for ASD
  - Children who receive early intervention services in a timely manner
- Reduce the time from parents’ first concern to diagnosis of ASD in the U.S. and worldwide
- Empower families and professionals to access and share information in the U.S. and worldwide through internet-based mechanisms
- Develop valid, novel methods for detecting ASD in infants and toddlers, disseminate this knowledge to practitioners, and evaluate its use
- Develop a stronger evidence base for early interventions appropriate for infants and toddlers, making these interventions more likely to be covered by insurance and more readily available through standard clinical practice
- Develop cost-effective, scalable methods for dissemination and implementation of evidence-based practices in low resource communities in the U.S. and worldwide
- Make available accurate estimates of the costs of autism and the cost savings associated with provision of early intervention and transition services from adolescence to young adulthood

Strategies

Awareness:

- Utilize existing resources and develop new resources to monitor change in age of diagnosis and access to care
- Target awareness, tool kits, resources, and research toward under-served populations, including ethnic minority, rural, and remote populations
- Make better use of local community resources for dissemination and implementation, including resources available through Walk Now for Autism Speaks walk communities and the Autism Speaks Autism Treatment Network

Collaboration:

- Coordinate and engage with national (e.g. CDC, AAP) and state partners to leverage and create synergies among different efforts with similar goals
- Use parents and professionals as dissemination channels

Dissemination:

- Explore whether existing practices for professional training developed at the state level can be brought to scale
- Promote physician referrals to appropriate providers by enhancing and disseminating Autism Speaks Resource Guide and Tool Kits (e.g. 100 Day Kit).
• Explore novel, scalable, and cost-effective methods for training more providers, such as web-based approaches, including:
  o Expanding on the use of web based training and information and patient navigators
  o Funding a project that explores the utility of telemedicine or telehealth
  o Funding web-based training modules for diagnosis and treatment of ASD appropriate for professionals in the U.S. and worldwide

Research:
• Facilitate research opportunities and international research networks by providing technical assistance and funding for conferences that bring together the academic, government, professional, and family communities
• Isolate and expand on the active ingredients of naturalistic behavioral interventions and further refine existing interventions across a wider range of ages and developmental outcomes

Capacity-building:
• Enhance capacity for screening, diagnosis and early intervention in U.S. and international settings through the following:
  o Conducting a situational analysis of autism in at least 2 countries outside of the U.S. in collaboration with local stakeholders including parents, professionals, and government officials
  o Building on the success of state-based initiatives to improve early detection and intervention practices, pilot a more expansive use of these evidence-based practices
  o Implementing web-based intervention training in at least 2 countries outside of the U.S.
  o Developing and disseminating 2 community based autism intervention packages for underserved communities and populations

Metrics for measuring success
• Average age of diagnosis of ASD in the U.S. is decreased significantly from a median age of 4 years to closer to 24 months
• The time between screening and diagnosis in the U.S. is significantly reduced
• ASD screening practices in the U.S. are widely implemented in community settings as evidenced by:
  o Increase in the number of service providers screening for ASD at 18- and 24 months
  o Increase in the number of service providers using strategies to enhance follow-up after a positive screen
  o Increase in the number of services providers who are providing referral and other supportive and educational information for families whose children have screened positive for ASD
  o Improvement in the opportunities for children to get screened. For example, on-line screening and referral resources are readily available and utilized widely in professional settings
• Increased capacity for diagnostic and intervention services in the U.S. and worldwide, as evidenced by:
  o Increased number of providers competent to diagnose and provide early intervention autism
  o Increased number of countries using valid and reliable instruments to screen and diagnose autism
  o A reduction in the disparities in access to early diagnosis and intervention based on geography, socioeconomics, and ethnicity

• The scale and scope of autism's impact in different countries are better understood as evidenced by:
  o Established public health statistics in at least 2 additional countries around the world, including those from low and middle income countries
  o Established up-to-date estimates of the economic cost of autism to individuals and society in the U.S. and at least one other country, especially the cost effectiveness of early intervention
VI. ENHANCE THE QUALITY OF, AND ACCESS TO, COMPREHENSIVE HEALTHCARE FOR INDIVIDUALS WITH ASD (GOAL # 3)

Background and Initiatives

Many individuals with ASD have symptoms associated with medical conditions, including seizures, sleep problems, gastrointestinal (GI) disorders, psychiatric conditions, nutritional deficiencies, and metabolic conditions. When left untreated, these conditions may not only compromise general health, but also affect behavior, development, and educational outcomes. For nonverbal children, identifying and monitoring medical conditions becomes even more challenging. Among the healthcare concerns for children and adolescents with ASD is a need to strengthen the awareness and treatment of associated medical conditions with standardized, comprehensive approaches for evaluation, treatment, and monitoring, as well as individualized follow-up.

Children and adolescents with ASD encounter difficulties obtaining appropriate and necessary healthcare services. They have decreased access to medical specialists and increased unmet needs compared with other children with special healthcare needs and typically developing children. Furthermore, the underlying biology of ASD may change the manifestations of various medical conditions and their response to treatment. Thus, special attention to these conditions is crucial for improving the quality of life for individuals with ASD. Autism Speaks has recognized the need for a systematic, comprehensive strategy to address this gap among children and adolescents with ASD, as well as the many gaps in knowledge among providers regarding the general healthcare challenges of these individuals.

Autism Speaks Autism Treatment Network (AS-ATN)

Since 2005, the AS-ATN has been a significant driver of evidence-based practice and comprehensive and coordinated care for children and adolescents on the spectrum. Much of the earlier work of the AS-ATN focused on better characterizing the occurrence and nature of medical conditions in ASD. In 2007, Autism Speaks tripled the size of the network (shown in Figure 6) with the goal of improving the health and quality of life for individuals with ASD by developing a sustainable model of care influenced by research and the generation of evidence across a variety of critical areas of concern to families.

Figure 6. Autism Speaks Autism Treatment Network Sites
Specifically, the AS-ATN represents a collaboration of clinicians across major children’s hospitals and academic medical centers dedicated to developing and delivering a comprehensive model of care for over 28,000 children and adolescents with ASD annually. The 17 participating sites have institutional commitment to support a multidisciplinary, family-centered care model providing access to a collaborative care team that includes pediatricians, psychologists, pediatric neurologists, gastroenterologists, sleep specialists, and genetic/metabolic specialists, as well as access to ancillary care services such as speech and occupational therapy. One of the key aspects of the AS-ATN model is that access to care is managed and coordinated for the family.

The four emphasis areas for the AS-ATN are Quality, Access, Research, and Leadership as shown in Figure 7.

AS-ATN activities are supported through Autism Speaks and by significant leveraged funding from federal agencies including the National Institute of Mental Health (NIMH) and the Health Resources and Services Administration (HRSA), which together have provided $24.9M in federal funding for biospecimen collection (NIMH) and for the AS-ATN to serve as the Autism Intervention Research Network on Physical Health (AIR-P) (HRSA). Some of the significant accomplishments are outlined below.
Quality and Access:

Quality Assurance: As part of its AIR-P funded activities, 14 AS-ATN centers are engaged in the Autism Collaborative, a partnership with the non-profit National Initiative for Children’s Healthcare Quality (NICHQ). This collaborative focuses on targeted site-specific initiatives aimed at continually improving the quality of care that families receive at AS-ATN centers. Since 2011, the 14 sites have engaged in initiatives to improve: 1) implementation of the principles of the AS-ATN care model; 2) adherence to standards and guidelines in delivering care, specifically using the AS-ATN sleep and GI clinical guideline algorithms and 3) the integration of families in both care decisions and in decision-making policies for the clinic. This latter aim has been enhanced by constituting a formal Family Advisory Committee (FAC) which includes two members from all 17 AS-ATN centers. This committee, led by two family member co-chairs, has engaged in quality improvement endeavors, established a strategic outline for better integration of families, and established family representation on each of the AS-ATN clinical committees.

Guidelines: AS-ATN subspecialty experts have developed ASD-specific clinical guideline algorithms for physicians in the areas of sleep (insomnia), GI (constipation), medication choice and monitoring, neurology, metabolic disorders and genetics. The guidelines for sleep, GI, and medical treatment of ADHD symptoms in ASD were published in November 2012 in a special supplement of Pediatrics.

Toolkits: The AS-ATN has developed tool kits and informational resources for families and clinicians. AS-ATN/AIR-P Tool kits are now available on medication management, blood work, sleep management, use of visual supports, toileting, Applied Behavioral Analysis and behavioral health. These can be downloaded for free on the Autism Speaks website: [http://www.autismspeaks.org/family-services/tool-kits](http://www.autismspeaks.org/family-services/tool-kits). Table 7 shows the number of downloads since their release starting in Q3 2011 through 2012.

Table 7: Number of Downloads of AS-ATN/AIR-P Toolkits

<table>
<thead>
<tr>
<th>TOOL KIT</th>
<th>Download to Date</th>
</tr>
</thead>
<tbody>
<tr>
<td>Visual Supports</td>
<td>9338</td>
</tr>
<tr>
<td>Sleep Booklet (Parent's Guide)</td>
<td>4631</td>
</tr>
<tr>
<td>Medication Decision Aid</td>
<td>4371</td>
</tr>
<tr>
<td>ABA</td>
<td>3724</td>
</tr>
<tr>
<td>Toileting</td>
<td>3342</td>
</tr>
<tr>
<td>Behavioral Health Treatments</td>
<td>2746</td>
</tr>
<tr>
<td>Dental Guide (Professionals)</td>
<td>2670</td>
</tr>
<tr>
<td>Phlebotomy (Parents)</td>
<td>2308</td>
</tr>
<tr>
<td>Phlebotomy (Professionals)</td>
<td>1085</td>
</tr>
</tbody>
</table>
• **Research:**
  - The AS-ATN Patient Registry includes data on over 5,400 children between ages 2-17 seen at AS-ATN centers that includes longitudinal follow-up data. Thirty abstracts have been presented at professional conferences (IMFAR, PAS, AAP) and 17 publications have been generated from the AS-ATN Registry.
  - The AS-ATN has also established a biorepository through collaboration between the NIMH and AGRE that includes biospecimen collection from affected children and their families. A total of 456 families will be collected across two studies scheduled to complete in May 2013 and January 2014, respectively. Over 190 families have been enrolled to date.
  - Fifteen AS-ATN-specific studies funded through the AIR-P are now recently completed or on going with over 1,500 children enrolled across the studies. These clinical and treatment research studies have focused on areas related to medical health and care issues including sleep, GI, nutrition, metabolic issues, medication side effects, epileptiform abnormalities, bone density, measuring outcomes and experiences with emergency medicine. Twelve abstracts and 10 publications have resulted from these studies.

• **Leadership:**
  - AS-ATN’s leadership goals center on being the “go-to network” where families and clinicians can go for information on medical issues for children with ASD. All sites participate in both local and national conferences and events, and reach over 30,000 families and professionals annually. AS-ATN clinicians are regular contributors on medical topics in Autism Speaks’ blog and webchats.
  - The AS-ATN was featured in *U.S. News and World Reports 2012 Best Hospitals* edition.
  - The AS-ATN played a pivotal role at Autism Speaks’ first national conference for families and professionals. This event, held Aug. 3-4, 2012 in Columbus, OH focused on comprehensive care that integrates behavioral and medical approaches. This conference was hosted as part of an on-going partnership with Nationwide Children’s Hospital, the American Academy of Pediatrics, The University of Ohio Wexner Medical Center, and the Health Resources and Services Administration. Ten of the 19 featured speakers came from the AS-ATN centers or the AS-ATN advisory committee. AS-ATN leadership and site members played key roles in the planning committee. This inaugural conference offered science updates and interactive workshop sessions for over 400 family and professional attendees from 33 states and 6 countries. Continuing education credits were offered for professionals in psychology, medicine, nursing and speech language pathology. Session videos and online credits will be made available on the Autism Speaks website.

**Looking Ahead: 2013-2017**

The AS-ATN is undertaking the revision of its programmatic strategic plan, and has engaged the consulting firm Accenture to assist with this process. The specific aim of this collaboration is to provide fresh thinking on new strategies and approaches particularly focused on the (1) dissemination of the AS-ATN model of care, improved support for families, research to better understand how to identify and treatment medical co-morbidities, and the transition
of care for adolescents as they become young adults. Some of the key objectives identified for the AS-ATN are included here.

**Objectives**

- Increase the ASD community’s access to services based on the AS-ATN Care Model
- Improve the quality of care standards and provision of care at tertiary medical centers
- Increase awareness of the AS-ATN Model, AS-ATN resources (e.g. tool kits) and AS-ATN guidelines in the family, health care and research communities
- Develop and implement an educational training program for the healthcare community
- Continue targeted development of tool kits and training materials (video tools) in the AS-ATN area of expertise that are relevant to family needs
- Develop a model for the provision of services for adolescents and young adults and the transition of services to adult care providers
- Develop and implement a strategic research agenda for the AS-ATN

**Strategies**

**Objective 1:** Increase the ASD community’s access to services based on the AS-ATN Care Model

- Develop and implement a new network structure that relies on regional AS-ATN Centers of Excellence and community networks starting in 2014
- In quarter 1 of 2013, release a Request for Applications for centers to apply for membership under the new funding requirements
- Use existing telemedicine resources to integrate regional community physicians

**Objective 2:** Improve the quality of care and provision of care at tertiary medical centers

- As part of the AIR-P Autism Collaborative, sites will be starting a new quality improvement initiative focused on improving outcomes in the areas of sleep, GI and access to care. The aim will be to work on small tests of change in how care is managed in order to measure improvements in sleep and GI problems for children identified with these issues and to decrease wait times to access the clinics.
- Family Advisory Committee (FAC) members will continue involvement in the quality improvement teams.
- Publish results of the initiative as a means to disseminate findings on practice improvement

**Objective 3:** Increase awareness of the AS-ATN Model, AS-ATN resources (tool kits) and AS-ATN guidelines in the family, health care and research communities

- AS-ATN FAC project to increase awareness and visibility of the AS-ATN in their local communities, including improving strategic integration with Autism Speaks local staff and volunteers
- Leverage existing AS outreach mechanisms through field staff, family services, government relations, and social media
- Change the name of the network from the Autism Treatment Network (ATN) to Autism Speaks Autism Treatment Network (AS-ATN) to leverage “brand awareness” of Autism Speaks
• Implement the Autism Speaks National Conference annually with a continued focus on medically related issues, updates on AS-ATN resources, and inclusion of AS-ATN clinicians
• AS-ATN FAC project to developing broader, family-friendly mechanisms for outreach and dissemination of AS-ATN resources
• Complete and ensure broad dissemination of the findings from the 15 AS-ATN/AIR-P research studies
• Complete pilot and make biorepository resources available to researchers through AGRE

**Objective 4:** Develop and implement an educational training program for the health care community

• Implement the Autism Speaks National Conference annually with a continued focus on medically related issues, updates on AS-ATN resources, and inclusion of AS-ATN clinicians
• Develop and implement more centralized AS-ATN-specific curricula and topics for local presentations funded through the AIR-P
• Offer continuing education credits through various means such as online modules, AS National Conference and telemedicine
• Collaborate with existing LEND, DBP and AAP to develop AS-ATN-specific curricula for their trainee and professional training programs
• Utilize technologies such as telemedicine to expand the training capacity of the AS-ATN

**Objective 5:** Continue to increase targeted development of tool kits and training materials in the AS-ATN areas of expertise that are relevant to family needs

• Create a mechanism for integrated, strategic development of tool kits and resources with Autism Speaks Family Services, the AS-ATN FAC and the external stakeholders such as the AAP
• Develop new tool kits and video tools with AIR-P funding
• Complete and release tool kits in development with AIR-P funding: sleep tool kit for clinicians, feeding, medication FAQs, family-centered care, pica, constipation management, vision and eye doctor visits; and also video tools: providing feedback, clinician video guide for using the sleep tool kit, video tool for doctors to help them identify movement disorders in children with ASD
• Complete and release Spanish and French translations of existing and in-development tool kits with AIR-P funding

**Objective 6:** Develop a model for the provision of services for adolescents and young adults and the transition of services to adult care providers

• Develop, implement, and monitor outcomes of standards for transition planning as a component of the ATN Care Model
• Develop a pilot AS-ATN Care Model for the provision of services for adolescents and young adults
• Implement and track outcomes of the pilot model at select AS-ATN centers
Objective 7: Develop and implement a strategic research agenda for the AS-ATN

- Engage the AS-ATN Research Advisory Board to help identify critical content areas for AS-ATN
- Revise the AS-ATN Registry to support health related research projects and be more useful for the longitudinal characterization of children
- Establish a research core that will develop a program of health services research

Metrics for measuring success

Success in the AS-ATN is measured by metrics targeting both process (number of research studies, tool kits, guidelines, publications, presentations; Registry and research enrollment; adherence to AS-ATN Care Model) and impact (number of tool kits downloaded, number of families and professionals reached by presentations, family satisfaction, child quality of life, wait times for initial visits). During the next 5 years, milestones will include:

Objective 1: Increase the ASD community’s access to services based on the AS-ATN Care Model

- Launch of new regional centers of care with increased access to families within their region via collaborations with local institutions
- Develop a working model of PCP integration for AS-ATN centers. Regional centers officially engage 2-3 local partners in a formal training relationship

Objective 2: Improve the quality and provision of care at tertiary medical centers

- Improvement in children’s parent reported sleep and GI symptoms, reduced wait times for evaluative visits, measured by the availability of appointments and number of publications (at least one per area of focus for a total of three)
- Enhance care by ensuring that microarray genetic testing is conducted on all patients and that this information is used to guide healthcare, as appropriate, and help establish a robust patient registry that contains genetic data on patients in the registry. This will allow for clinical research that can stratify patients on the basis of genetic information.

Objective 3: Increase awareness of the AS-ATN Model, AS-ATN resources (e.g. tool kits) and AS-ATN guidelines in the family, health care and research communities

- AS-ATN FAC will increase awareness and visibility of the AS-ATN in their local communities based on an increase in the number of AS-ATN venues; establish working relationships between AS-ATN and AS field staff at all AS-ATN centers with an outreach plan; increased “recognition value” base on community surveys
- Name will be changed by Q4 2012 to leverage “brand awareness” of Autism Speaks
- Increase in number of families and clinicians reached through the Autism Speaks Annual Meeting both in-person and via online resources
- For research resources, success is measured by number of publications (one for each study) and the number of researchers using the AGRE resource
**Objective 4:** Develop and implement an educational training model for the health care community

- Implementation of the Autism Speaks National Conference annually with a continued focus on medically related issues, updates on AS-ATN resources, and inclusion of AS-ATN clinicians. Metrics include the number of continuing education credits awarded at the meeting and online, and number of attendees.
- Establishment of AS-ATN-specific curricula and topics for local presentations funded through the AIR-P by 2014; implementation launched in 2014 with formal collaborations with LEND, DBP and AAP to develop AS-ATN-specific curricula for their trainee and professional training programs by 2015.
- A training fellowship for community physicians is established and piloted that will be awarded in 2014.

**Objective 5:** Continue to increase targeted development of tool kits and training materials in the AS-ATN area of expertise that are relevant to family needs

- Establishment of mechanism for integrated, strategic development of tool kits and resources with Autism Speaks Family Services, the AS-ATN FAC and the external stakeholders such as the AAP.
- Development of new tool kits/video tools annually with AIR-P funding.
- Tool kits released in development with AIR-P funding: sleep tool kit for clinicians, feeding, medication FAQs, family-centered care, pica, constipation management, vision and eye doctor visits; and also video tools: providing feedback, clinician video guide for using the sleep tool kit, video tool for doctors to help them identify movement disorders in children with ASD in 2013 and 2014.
- Completion and release of Spanish and French translations of existing and in-development tool kits with AIR-P funding. Currently available tool kits complete by mid-2013. New tool kits complete within 4 months of release of the English version.

**Objective 6:** Develop a model for the provision of services for adolescents and young adults and the transition of services to adult care providers.

- Develop and operationalize the AS-ATN Care model criteria for managing transitions to adolescence and adulthood by 2014 that all sites follow.
- Increase in the number of tool kits for transition care between 2014-2017.
- Increase in the number clinicians and practitioners who are able to readily provide behavioral and medical health care for adults with autism.
- Launch of pilot AS-ATN Care Model for the provision of services for adolescents and young adults in 2016.
- Improved access and outcomes for adolescents at pilot AS-ATN centers.

**Objective 7:** Develop and implement a strategic research agenda for the AS-ATN

- Establish detailed research agenda and data analysis plan for the registry by Q3 2013.
- Redesign the data capture strategy for the registry to include greater age and ethnic/racial diversity by 2014.
- Fund a research core that will focus on health services research by 2015.
- Compete for another round of HRSA funding for continued AIR-P support in the 2nd quarter of 2014.
Background and Initiatives

The purpose of this initiative is to accelerate the translation of scientific discovery into evidence-based products that treat, diagnose or cure autism spectrum disorders. In evidence-based practice, the current pathway to improved outcomes involves a dynamic process of screening, diagnosis, assessment and intervention. Improvements in outcome for individuals with ASD are typically measured by increased level of independence achieved and improvement in the health, wellbeing, and quality of life for individuals throughout their entire lifetime. Medical products such as medicines, therapeutic devices, and diagnostics play an important role in achieving the goal of improved outcomes, working in concert with standards of care delivered with behavioral, psychosocial and educational interventions. Unfortunately, to date, and in contrast to other areas of psychiatry/neurology, the development of medical products for individuals with ASD has been largely ignored by requisite partners in the for-profit sector. This lack of approved products represents a significant unmet medical need for our community and is integral to defining our priorities for translational research over the next 5 years.

To illuminate the scale of the current unmet medical need, only two medications to date have been approved by the United States Food and Drug Administration (FDA) to treat symptoms in individuals with autism. These two agents, risperidone (Risperdal™) and aripiprazole (Abilify™) were approved in 2006 and 2009 respectively to treat a cluster of symptoms.
symptoms now labeled as ‘irritability,’ which include tantrums, self-injury, and aggression. Irritability is not a core feature recognized by the current DSM-IV; rather it is an associated set of co-morbid behavioral symptoms associated with autism. The pathway to regulatory approval for these two agents, which were originally developed, approved and marketed as treatments for schizophrenia, has been largely viewed as opportunistic lifecycle expansion of these established neuroscience franchises. Although these agents are clearly efficacious for many individuals with autism, clinical benefits are often overshadowed by the presence of a significant side effect burden.

In the absence of approved products, off-label use of psychotropic medications in autism is the norm and has been increasing in prevalence. Unfortunately, with few exceptions, the vast majority of medications used is not adequately supported or guided by reproducible evidence from the gold standard of large clinical research studies (RCTs). This has been emphasized by numerous published reviews on the subject, which indicate that for most classes of psychotropic medications in use clinically with ASD, there remains an inadequate body of published evidence to support claims of efficacy. This is not to say that physicians have not experienced clinical success with specific agents in individual patients; rather, this anecdotal evidence has struggled to be confirmed in the larger trials that inform wider use. In addition to concerns about claims of efficacy, insufficient evidence clarifying the prevalence of side effects and ensuring safety with clinical use of these agents in individuals with autism is sorely lacking.

Our efforts in the area of translational research at Autism Speaks seek to address these unmet needs by building strategy, programs and projects that facilitate the advancement of the field’s most promising science into the development chain that delivers new medical products. Developing medicines for autism will require partnership with organizations in the biotechnology and biopharmaceutical sector. Although academic centers and national laboratories are widely considered important engines for innovation and early discovery, these organizations are not positioned in the overall process of translation to bring new products to market and ensure they are delivered to patients who need them. As an organization, our translational research strategy for converting scientific discovery into products that will reach market must acknowledge the requisite participation of partners in the for-profit sector of biotechnology and biopharmaceuticals.

Unfortunately, the current level of engagement and investment in product development for autism by the biotech and pharmaceutical sector is inadequate to address the diverse medical needs of our community. This lack of engagement may be explained by a number of challenges facing medical product development in autism, which span the value chain of translational research from earliest decisions around target selection through navigating the unclear regulatory path(s) for autism. There is one element common to all of these challenges that has clearly influenced decision making among sponsors, namely, they view the investments as risky. The current financial landscape among medical product developers has already become increasingly difficult, leading to increased intolerance to risk with investment. Although the value proposition for developing products for autism has been recognized by many companies, most are unwilling or unable to take on the additional risk of entering into an unprecedented development space unless something is done externally to change the risk landscape. From a strategic perspective, therefore, we have chosen to focus on efforts that work to discharge the development risk, perceived or real, in order to stimulate engagement and investment by the
Looking Ahead 2013-2017

Strategic Priorities for Translational Research in Autism

Objectives and strategies

Broader objective: Standardize target selection

Target selection refers to a process that supports decisions by research organizations to pursue given targets as platforms for the development of therapeutics. Although every organization differs slightly in the criteria used to guide target selection, the decision to pursue a given target is considered an important early decision in the value chain of translational research because it represents the first significant commitment of organizational time and resources. Target selection is informed by the weight of evidence derived from available clinical and preclinical work, specifically implicating a target in a specific disease process, and the potential that modulation of the target can be exploited for therapeutic benefit. Preclinical evidence often originates from work undertaken in animal and cell-based models of the disorder. Perception of risk, and a subsequent unwillingness to invest resources, emerges when the feasibility of target validation research lacks clarity or is absent. The perception of risk is heavily influenced by the availability, quality, and standardized use of disease-relevant models. Over the next 5 years, we will work to develop open resources and participate in precompetitive partnerships that will specifically address these risks.
Specific objective 1: Develop and characterize a catalog of genetic rat models of ASD via partnerships with SAGE Labs and Richard Paylor, Ph.D.

- **Deliverables:**
  - 1-3 new rat models per year through 2017 are publicly available
  - Complete a standardized behavioral phenotyping for all lines
  - Complete a baseline transcriptional profiling of prefrontal cortex in at least 3 lines
  - Establish an online, open-access, and searchable rat brain gene expression atlas

Specific objective 2: Establish and operate a preclinical research consortium of leading experts to test novel targets using genetic animal models and standardized, reliable assay protocols

- **Deliverables:**
  - Establish a consensus battery of standardized, reliable preclinical test protocols involving both mouse and rat genetic models relevant to ASD
  - Develop a public database to disseminate testing results for all activities of the consortium
  - Partner with sponsors to evaluate 2-3 therapeutic mechanisms of action per year
  - Establish a program for dissemination of best practices that includes a mini-fellowship program

Specific objective 3: Invest and actively participate in a public-private partnership established by the European Innovative Medicines Initiative, namely, the EU-AIMS Initiative\(^2\). Specifically, we will be involved with work-packages 1 and 2 (WP01-02; in vitro and in vivo models, respectively) to ensure reliability and relevance for medications discovery

- **Deliverables:**
  - Establishment of induced pluripotent stem cell (iPSC) lines from at least 3 distinct genetic ASD patient populations
  - Consensus battery of standardized iPSC differentiation and phenotyping assays
  - Confirmation that shared iPSC lines and standardized protocols are advancing compound screening and/or mechanism testing at all WP01 industrial partners
  - Four novel animal models with robust phenotypes
  - Reliable, quantitative behavioral assays for characterizing novel animal models
  - Defined physiological deficits and biomarkers in novel animal models
  - Assessment of suitability for pharmacological intervention in novel animal models

\(^2\) European Autism Interventions - A Multicentre Study for Developing New Medications (EU-AIMS) - is the largest single grant for autism in the world, and the largest for the study of any mental health disorder in Europe. EU-AIMS involves a novel collaboration between nonprofit organizations and families (Autism Speaks), academia and Industry to develop the infrastructure underpinning new treatments for autism.
Broader objective: Support target prosecution

Target prosecution represents the phase of translational research activities that follow a decision to pursue a specific target as a platform for therapeutic development. This is a resource intensive activity that is principally focused on developing an investigational agent or prototype that can be advanced safely into human clinical research to test a specific therapeutic hypothesis. Prosecuting a target involves multidisciplinary teams of scientific experts including biologists, pharmacologists, chemists, toxicologists, and clinicians that work collaboratively to discover and optimize experimental medicines or prototype devices. Some of the greatest value-creating steps (producing intellectual property) in the translational research continuum occur during this target prosecution phase, which represents development activities undertaken by organizations large and small, from start-up entrepreneurs to large pharmaceutical companies. It is also a phase of activity that has significant financial risks associated with it. Currently, this essential phase of translational research for autism is undercapitalized, thus creating a financial obstacle for successfully moving breakthrough science forward along the value chain. Over the next 5 years, we will seek to develop innovative programs and projects to de-risk the landscape for target prosecution and incentivize investment in this critical phase of the value chain for new product development.

Specific objective 1: Develop and introduce novel research tools that facilitate/innovate the translational activities of sponsors working to develop products for ASD

- Deliverables
  - Develop 1-3 novel genetic rat models of ASD per year (including behavioral phenotyping battery)
  - Establish a Preclinical Autism Discovery platform to provide a standardized preclinical battery for characterizing novel pharmacological mechanisms of action

Specific objective 2: Establish vehicles for increasing investment in the discovery and development of medical products that improve outcomes for individuals with ASD

- Deliverables
  - Organize an annual conference for venture capital and philanthropic investors focused on exploring the opportunity landscape for translational research in ASD. This would help educate the investment community on the significant unmet needs of our community and establish an objective understanding of the value proposition for product development in areas such as medicines, therapeutic devices, diagnostics, and assistive technologies. It would be an important venue for entrepreneurs, new and established companies, and investors to network.
  - Establishment of a venture philanthropy affiliate to advance the science mission of Autism Speaks. The affiliate, Delivering Scientific Innovation for Autism (DELSIA), was established as a vehicle to more effectively enable partnership with for-profit organizations working to develop products aligned with unmet needs of our community. The goals of the affiliate’s activity are aligned with the science mission of Autism Speaks.
Broader objective: Improve clinical trial capability

The development of new medical products requires the availability of robust clinical research networks capable of conducting large multicenter trials and satisfying the demands of sponsors for recruitment, standardized protocols, and project management. The lack of organized research capability to conduct development programs internally or externally is viewed as a risk by sponsors who see opportunity in the autism space. Although networks have been established and maintained in the autism space previously (e.g. RUPP, START, ACTN), some of which have been utilized in the past to conduct industry-sponsored trials, the field currently lacks a dedicated clinical trials infrastructure for hosting product development programs in the autism space. Therefore, efforts to establish a clinical trials platform represent a significant strategic priority for the field.

Specific objective 1: Support the development of clinical research capability and capacity that serves the needs of development efforts specifically focused on bringing new products to market

- **Deliverables**
  - Establish a Medicines Development Network for Autism (MEDNA) that can serve as a platform for industry sponsored POC trials, studies aimed at exploring and validating novel biomarkers to support medical product development, and research aimed at validating new outcome measures
  - Develop an Autism Speaks Clinical Trial Consultancy Services Model to support experimental medicine efforts in industry and academia
  - Assist and support the development of patient registries among emerging autism research foundations

Broader objective: Develop and improve regulatory clarity for medical product development

In the process of medical product development, regulatory approval represents a penultimate step towards delivering the promise of translation for a given scientific breakthrough. Although medical product development is often focused on medicines or therapeutic devices, which in the case of ASD are likely to be developed in the next 10 years to treat a core or associated symptom of ASD, they also include molecular diagnostics or other technology that can be used to diagnose ASD early or more objectively. The development of so-called ‘wrap-around’ technologies that can improve prediction of treatment response or adverse events are also gaining increasing momentum in the translational research space. In addition to securing the marketing approval required by sponsors to recover a commercial return on financial investments needed to bring these products to market, regulatory approval has tangible value to our community by increasing the probability of reimbursement from payers. With the exception of approvals for Risperdal and Abilify as treatments for irritability in autism, there have been no regulatory approvals for medical products developed specifically for individuals with autism. This absence of regulatory precedent in ASD has introduced a significant perception of risk for developers of medical products. Autism Speaks has already spearheaded efforts to build expert consensus on the appropriateness of outcome measures that can be used to measure efficacy of medical products developed for social communication deficits, repetitive behaviors, or anxiety (hyperarousal) in autism, and also hosted discussions with the FDA to present these consensus and obtain feedback on behalf of the field. Over the next 5 years, we will need to continue building off this success and expand our efforts with:
Specific objective 1: Establish consensus statements on the state of outcome measures to support medical product development in ASD

- **Deliverables**
  - Sponsor and lead consensus-building workgroups focused on studying and delivering recommendations for use of specific outcome measures that can be used by sponsors to demonstrate efficacy of new medical products
  - Convene meetings with sponsors and relevant FDA divisions to present expert consensus recommendations on outcome measures and solicit feedback that can be used to improve current measures or identify areas of opportunity for continued collaboration
  - Author and disseminate consensus statements through published manuscripts, white papers, or other vehicles such as web-based reviews

Specific objective 2: Partner with FDA and other foundations to help prepare draft guidance(s) for the autism space to help stimulate research and product development

Broader objective: De-risk population heterogeneity for clinical trials

Autism is well-recognized as a heterogeneous clinical condition. This clinical heterogeneity, which can be observed through the lens of genetic risk, pathophysiology, core symptom severity, diversity of comorbid symptomology, response to intervention, and outcomes, presents significant challenges for research, diagnosis and treatment. These challenges also present hurdles for translation by introducing risk associated with the investment required to advance the most promising ideas forward through development. Improving our understanding of the factors underlying clinical heterogeneity offers the field, for example, opportunities for more effective patient stratification in clinical trials, prediction of treatment response, or management of adverse events. Over the next five years, we will work to leverage several ongoing programs and initiatives in efforts to accelerate research aimed at improving our understanding of heterogeneity through genetic risk discovery and biomarker validation.

Specific objective 1 (Genetics): BGI Project (See above under Goal #1 on Identification of Risk Factors for ASD), AGP, and AGRE efforts, including enhanced bioinformatics expertise, resources, and capabilities

Specific objective 2 (Biomarkers): Support the efforts of the Biomarkers Consortium for Autism, which is a precompetitive partnership intended to bring together the pharmaceutical industry, foundations/non-profits and academic researchers to explore and develop project proposals aimed at discovering and validating markers that could be used to help facilitate medicines development in ASD

- **Deliverables**
  - Participate in the workgroup development and launch of 2-3 new projects over the next 5 years

Metrics for measuring success

The penultimate, global measure of strategic success for our initiatives in the area of translational research will be the number and quality of medical products and related technologies that are brought to market, which increase the quality of health or life for
individuals living with autism. In order to achieve this goal, our strategic activities will focus largely on increasing engagement, productivity, and innovation in clinical development activity by requisite partners in the for-profit sector (e.g. entrepreneurs, small companies, established business, biotechnology and pharmaceutical industry). Measuring success for our strategies over the next five years can be defined indirectly based on evidence of desired changes in the level and direction of development activity in each of these focus areas.

**Measuring ‘Engagement’**. In order to realize the full potential of translation, the field requires a robust engagement by requisite partners in the for-profit sector who are capable of undertaking the scale of financial investments required to bring new products to market. For our purposes, companies capable of engaging in autism product development can be classified into one of three possible categories based on their current level of activity: ‘inactive,’ ‘exploratory,’ or ‘active.’ Transitions between these three activity states can be used to help monitor and define changes in the level of engagement by these organizations. ‘Inactive’ companies would be defined as for-profit organizations, capable of autism R&D investment, where no evidence of research investment, activity or interest can be determined through publically disclosed information or interactions with Autism Speaks (or its affiliate DELSIA). Organizations that are actively exploring opportunities in the autism space and participating in precompetitive consortium relevant to autism (e.g. EU-AIMS, Biomarkers Consortium, Arch2POMC) who may have nascent discovery efforts but no evidence of active clinical development programs in the area of autism (medicines, devices or diagnostics) would be classified as ‘exploratory.’ Organizations that have active clinical development programs working in the area of autism would be classified as ‘active.’ Companies such as BMS, which has a commercial franchise in autism with Abilify but no active development programs, would be considered ‘exploratory.’

- **Metric 1**: 500% increase in the number of companies that transition from an ‘inactive’ state of engagement to ‘exploratory.’ This represents a surrogate endpoint that helps measure how well our strategies and execution have been in initiating activity among inactive organizations.
- **Metric 2**: 300% increase in the number of companies that transition from the ‘exploratory’ to ‘active’ state. This represents a surrogate endpoint that helps measure how well our strategies and execution have been in facilitating the development or deployment of capabilities and capacity for clinical development.
- **Metric 3**: Less than 200% reversal in engagement state of companies currently classified as ‘exploratory’ or ‘active.’ This represents a surrogate endpoint that helps measure how well our strategies and execution have helped organizations maintain engagement in the face of challenges.

**Measuring ‘Productivity’**. The pathway to regulatory approval required to successfully deliver new medical products to market and the community is paved through a progression of well-defined development phases and clinical milestones. Formal tracking of activity in each of these phases is enabled though FDA-mandated reporting viewable online through clinicaltrials.gov. Using these public data sources, we can utilize registration of new development programs, phase transitions of registered programs, and applications for marketing approval as measurements of productivity in the for-profit R&D sector. These, in turn, can be used as indirect readouts of success for our efforts in the area of translational research.

- **Metric 1**: 300% increase in the number of investigational new drug (IND) or investigation device exemption (IDE) applications approved by FDA and registered in clinicaltrials.gov over the next five years. The primary goal of discovery research is to determine if the
experimental agent is reasonably safe for initial use in humans and if the compound exhibits pharmacological activity that justifies commercial development. After these discovery efforts determine an agent as a viable candidate for further development, the sponsor then moves to study the safety/efficacy in early-stage clinical studies. Approval from FDA, in the form of an IND, is required to enable this and represents this transitional milestone.

- **Metric 2**: 300% increase in the number of industry-run or industry sponsored development programs that successfully undergo a phase transition from phase 1 to phase 2A or 2B. This transition marks advancement to a stage of clinical development that is commonly referred to as ‘proof of concept’ (POC) studies, where the efficacy of an experimental agent or prototype is first investigated in a population of subjects with a particular disorder.

- **Metric 3**: 200% increase in the number of industry-run or industry-sponsored development programs that successfully undergo a phase transition from phase 2 to phase 3. Achieving a positive clinical POC in a phase 2 study is a significant scientific milestone but also a critical inflexion point for securing resources required to advance to larger and more expensive phase 3 trials.

- **Metric 4**: Regulatory filing for market approval from FDA of 2-3 new products relevant to autism from any of the following categories: Medicines (New drug application or NDA) or all classes of medical devices (Premarket approval or PMA), including diagnostics.

- **Metric 5**: Commercial launch of 1-2 new medical products (medicine, device, or diagnostic) relevant to autism. These could be considered the global success metric for all of our activities.

**Measuring ‘Innovation’**. It is important to recognize that many of the likely near term opportunities for product development in autism will arise from products that were originally developed and approved for another indication. An effort to reposition these agents based on new knowledge represents a modest but effective strategy for developing new products and is the result of innovative approaches. To support this direction of innovation, the Hatch/Waxman act offers incentives to sponsors who undertake new clinical investigations of drugs previously approved for non-related indications.

- **Metric 1**: 300% increase in the number of clinical development candidates entering the pipeline for autism indications that would be eligible for New Clinical Investigation exclusivity under the Hatch/Waxman act.

It is also important that we offer some means to measure the direction and quality of discovery as it impacts clinical development, working to facilitate innovation. In other words, one metric of success for our efforts would be to ensure that a diversity of mechanisms are entering clinical development, rather than having the pipeline dominated by large numbers of similar “me-tos.” Agents that have not been approved by the FDA in any other submitted application may apply for status as a new chemical/molecular entity (NCE or NME). NCEs typically represent the advancement of novel agent classes with mechanisms of pharmacological action distinct from those of currently approved medications. Subsequently, they can be considered as products of innovation in therapeutic approaches. The FDA has incentivized innovation by rewarding sponsors who bring NCEs forward with specific patent/marketing exclusivities under the Hatch/Waxman act.

- **Metric 2**: 300% increase in the number of clinical development candidates that enter the pipeline for autism indications that have NCE status.
VIII. GOAL # 5- IMPROVE THE HEALTH AND OUTCOMES OF ADULTS WITH AUTISM FROM A LIFETIME PERSPECTIVE

Background and Initiatives

In 2012, approximately 50,000 individuals on the autism spectrum will age out of educational services according to researcher Paul Shattuck in a recent *Pediatrics* paper. It is notable that among disabilities, Shattuck found that ASD is associated with the lowest overall rate of involvement in services and the workforce. Given the critical importance of accessible services and opportunities for adults, the transitional years after high school have the potential to make a critical difference for quality of life during the rest of the lifespan. This is of great concern considering that prevalence began a sharp increase around 20 years ago. Clearly, the numbers of affected individuals without services and productive activities will grow notably as each year passes.

In contrast to early childhood, there is a relative paucity of data on effective services, treatments and health concerns during adolescence and adulthood. Despite a strong evidence-base on effective interventions during the preschool period, research literature characterizing the middle and late childhood and adult periods of development is lacking. Few randomized clinical trials exist demonstrating the efficacy of interventions and services for elementary school age children, adolescents, and adults. Almost nothing is known about aging in autism. We do not fully understand the factors that promote the most positive health outcomes and foster independence, although it is clear that comorbidities such as anxiety, depression, heart disease, obesity, and epilepsy further reduce quality of life. A lifespan perspective is needed to identify the pivotal periods during which various interventions, supports and services are crucial for best outcomes. Identifying the factors that promote positive outcomes in adults will be a key priority in addressing what is one of the biggest and most important challenges we face in the next 5 years.

Enhancing school-based services

From the time autism was added as a distinct disability category under the Individuals with Disabilities Education Act (IDEA) in 1990, the number of children with autism receiving early intervention (Part C-Infant and Toddler, 0-36 months) and special education (Part B, 3-21 years) has increased dramatically. There remains a need for the development of novel educational interventions for school-aged children and adolescents, and Autism Speaks will support research aimed at increasing the scientific basis of educational programs. There are significant disparities in access to currently available services across population subgroups (i.e., race/ethnicity). In addition, considerable inter- and intra-state differences in the nature and quality of early intervention and special education programs for children with autism pose a challenge for developing and implementing evidence-based practices. Recognizing the scope of IDEA’s mandate and the need to promote quality education and care continuity throughout the lifespan, Autism Speaks will support collaborations among community stakeholders, district and state administrators to enhance access to and the quality of evidence-based practices for school-age children. Additionally, evaluation of existing educational programs and models will be incorporated. Activities will include building on the research presented by Autism Speaks and the Kennedy Krieger Institute at IMFAR 2011 to assess resources to address the needs of
children with autism in the school system and to disseminate effective interventions to school-age children. Additionally, Autism Speaks will explore potential partnerships with the Institute for Education Sciences and National Center for Special Education Research to develop/enhance surveillance activities (i.e., build on national, longitudinal studies), establish a set of core guidelines/best practices for the education of children with autism in the school system, and foster joint research initiatives. We anticipate that these activities will not only have implications for the education of children with autism in the United States, but also for children in other countries throughout the globe.

Adults with autism initiative

The increasing prevalence of autism underscores the need for research across the lifespan, particularly among individuals transitioning from adolescence to adulthood. Through Autism Speaks programs such as the Autism Speaks Autism Treatment Network, attention on the medical issues and approaches to care for children and adolescents has increased. However, there is still very little in the way of resources, services and healthcare for adults with ASD. As it has done for the younger population, Autism Speaks is dedicating targeted resources toward research that will ultimately lead to improve health and outcomes of adults with autism.

Looking Ahead 2013-2017

Objectives

- Characterizing the life trajectory of individuals with autism from middle childhood through late adulthood, with a focus on understanding the challenges that people with
autism face, the factors that contribute to various outcomes, and the best means to measure them, including quality of life

- Systematically identifying and targeting predictors and barriers to good health and outcomes in the adolescent and adult populations, including consideration of better community integration
- Developing and evaluating novel services and behavioral and medical treatments across a variety of settings (i.e., school, home, community, workplace) to address the core and associated symptoms of autism across the lifespan
- Developing and evaluating novel methods for improving communication in individuals who are nonverbal or minimally verbal
- Improving the knowledge base of adult practitioners to increase their capacity for providing medical and behavioral health services for adults with ASD

Strategies

- Building the research base around improving health and quality of life throughout adolescence and adulthood is a clear emphasis. Autism Speaks will support studies focused on characterizing the life trajectory of individuals and identifying the health, quality of life, employment, and other challenges faced by persons with autism during adolescence and adulthood in the following areas:
  - Easing the transition from school-based services to increasingly independent living
  - Identifying and assessing methods for addressing the barriers to good health and outcomes in the adult populations
  - Developing and evaluating novel behavioral interventions and medical treatments to address autism core and associated symptoms across the lifespan
  - Creating new devices and treatments that can promote communication in individuals who are nonverbal
- Identifying and addressing factors with the potential to reduce the mortality rate in autism
- Leveraging the expertise of the AS-ATN to expand into adult transition and health issues. The AS-ATN network of medical centers provides significant expertise on the care and management of behavioral, psychological, psychiatric and medical issues in children and adolescents with ASD. This may require cross fertilization among pediatric emphasis areas by adding a growing cadre of adult practitioners with experience managing behavioral, life skills and health issues for adults with ASD. Via the Autism Collaborative on Improving Quality Care of the AS-ATN, some of their centers will be working on developing models of integration with their primary care physicians. This effort will start with the pediatrics service providers and be expanded to reach out to the network of community physicians that are able to care for adults. AS-ATN centers will also be developing tools targeting all stages of the transition to adulthood, starting in early adolescence, and they will continue to conduct trainings and develop tools specific to the needs of adults with ASD.
- Continue to facilitate a collaborative network of investigators who are funded by Autism Speaks to conduct research on late adolescence and adulthood. This network of investigators first met on January 26th, 2012, when Autism Speaks held a research summit entitled, “Adults with Autism: Sharing Ideas, Filling the Gaps” in Chapel Hill, NC. The event was co-hosted by Extraordinary Ventures, a model employer of adults with autism. The meeting brought together many researchers studying adulthood, people
with autism, Autism Speaks staff, parents, and donors. Since that time, Autism Speaks has continued to host events that allow this network of scientists to share ideas and collaborate.

- As part of Autism Speaks Innovative Technology for Autism Initiative, support research focused on the application of technology for promoting speech and language development and communication in individuals with autism.
- Through the Autism Speaks website and Autism Speaks National Conference, provide a platform for dissemination for adult providers as effective interventions are developed.

**Metrics for measuring success**

- A solid base of information that fills the knowledge gap around autism from a lifespan perspective, especially information that can be translated into improving quality of life, such as identification of factors that promote positive outcomes
- Enhanced availability of new and more effective interventions, treatments and services for middle and late childhood and adult individuals, including the use of innovative technology for improving quality of life and facilitating communication
- Greater community awareness of adults with autism and their potential to contribute to employment and recreation settings
- An increase in the number of clinicians and practitioners who are able to readily provide behavioral and medical health care for adults with autism
- Increased employment opportunities and the supports needed for individuals with ASD to obtain jobs and succeed in the workplace
IX. INNOVATIVE TECHNOLOGY FOR AUTISM INITIATIVE

Background and Initiatives

Autism Speaks Innovative Technology for Autism Initiative (ITA) is supporting the development of therapies and assistive technologies by promoting collaboration among designers, engineers, scientists and individuals and families affected by autism.

Its primary mission is to adapt and promote the use of available technologies and spur the development of new technologies in an interdisciplinary and creative way to facilitate applied research that directly enriches quality of life for people with ASD and their families throughout the lifespan.

Technology has long been used to support the needs of people with autism and their families. In recent years, however, emerging technologies such as smartphones and tablet computers have generated unprecedented interest and excitement in the community about their potential to deliver novel solutions to address the challenges families face daily. In addition, new technologies are emerging in clinical settings poised to facilitate and enhance existing best practices in screening, diagnosis, and treatment, including evaluating clinical outcomes.

Autism Speaks plans to focus on the following technology-related priorities:

- Novel technologies for improving communication abilities of people with ASD
- Distance-learning and eHealth solutions to enhance capacity for professional training and access to treatment
- Novel technologies for early detection of ASD
- Novel technologies for assessing outcomes in clinical trials
- Social media and Internet solutions to enhance quality of life

As part of its Innovative Technology for Autism (ITA) initiative, Autism Speaks sponsored a competition in 2011 for design students called Autism Connects. The students were challenged with designing a technology concept to promote interactions and understanding between our community and society. There were 130 submissions from over 30 countries and the winners showed the diversity in potential applications:

([http://core77.com/blog/competition/autism_connects_design_challenge_competition_winners_19222.asp](http://core77.com/blog/competition/autism_connects_design_challenge_competition_winners_19222.asp)).

More recently, Autism Speaks partnered with Hewlett Packard on the Hacking Autism initiative, which has already surveyed the autism community about the types of touch-screen apps it would like to see developed. In October of 2012, teams came together to build seven new apps to provide cost-free and state-of-the-art applications to support communication, social understanding, safety, and timetabling:

Both of these activities represent a “crowd sourcing” approach to identify innovative ideas and mobilize volunteer efforts that is efficient and cost-effective. While not designed to evaluate the effectiveness of an application or device that may require a more formal regulatory path, it is very productive for developing assistive technologies that are meant to improve quality of life of persons with ASD and their families.

**Looking Ahead 2013 - 2017**

**Objectives**

- Promote the development of technologies that can improve the lives of persons with ASD through our regular grant mechanisms and new mechanisms such as grants to small businesses for research and development
- Increase opportunities for new developers of technologies to receive funding from investors
- Develop technical specifications for technologies that claim to deliver therapeutic benefits to affected individuals and families. Efforts will be made to define and enhance functional consistency across hardware and software platforms.
- Generate and disseminate evidence or data that will inform professional and lay consumer decision-making in autism-related technologies
- Leverage technology to support our goals of earlier diagnosis, access to early intervention, and development of effective interventions and supports for individuals with ASD and their families

**Strategies**

- Building on the successes of the “Autism Connects” and “Hacking Autism” projects, deploy “crowd-sourcing” processes as a cost-effective way to solicit, identify and develop novel ideas and solutions from experts as well as hobbyists. This approach can be further enhanced with an X Prize-like purse (>$500K) to attract top talents.
- Connect new developers of technologies that can improve the lives of persons with ASD with potential investors through an annual venture capital and philanthropic investor conference
- Invest in for-profit entities to develop, market, and/or evaluate effective products through a small business grant mechanism
- Revise ITA website to include consumer or community rating/feedback mechanisms as well as editorial reviews by experts
- Identify research using innovative technologies as a funding priority for recurring funding mechanisms like Trailblazer, treatment, and basic and clinical awards

**Metrics for measuring success**

- Technical specifications for technologies that claim therapeutic benefits are available
- Scientific support in helping bring to market or make broadly available new products that improve the lives of persons with ASD and their families
- Technology accelerates our ability to screen, diagnosis, and provide intervention for people with autism through direct application or web-based professional training
X. COMMUNICATING WITH OUR CONSTITUENTS

Individuals and families affected by autism will always be at the heart of Autism Speaks science. Our twin goals – to improve lives today and transform lives in the future – demand a continuing dialogue with our community. This community includes the tens of thousands of families, volunteers, donors and Autism Speaks staff members who passionately care about all those who struggle with autism.

Our community’s investment in science is now paying exponential dividends with new insights into the causes, prevention and treatment of ASD. This is tremendously exciting. However, the flood of news can prove overwhelming to families and supporters trying to interpret how specific findings apply to their daily lives, hopes and needs. It is important to provide them with clarity, context and perspective. Equally important is the creation of open channels through which our community’s questions, concerns and priorities can continually flow to our science staff and funded researchers.

Here, then, we share our internal and external science communication goals and strategies for the years ahead:

Science Communication Objectives

Objective #1: Create a welcoming online community that provides timely, relevant and reliable news and perspective on emerging autism science

What recent progress has been made? Over the course of 2011 and early 2012, the science staff has expanded and enriched the content, lay accessibility and multimedia aspects of the science-based sections of the Autism Speaks website (“Research” and “What Is Autism?”). This includes deepening our website’s content and resources to better embrace and serve adolescents and adults on the autism spectrum.

Over the last year, the science department has also increased the regularity and quality of the website’s science news and science blogs. The latter include the popular weekly “Got Questions?” column. Most recently we have added the publication of feature profiles of families and researchers involved in the studies we fund. The comment sections of these stories and blogs have become a community forum for the exchange of ideas and follow up questions.
**What will future success look like?** The above-described work is ongoing, with the goal of extending across the extensive “Research” and “What Is Autism?” sections of the Autism Speaks website. Increasingly, this enhancement will include audiovisual content such as embedded videos, slideshows and podcasts. The envisioned result is an online resource so enjoyable and informative that our families, volunteers, donors and staff members will visit its pages daily.

**Objective #2: Develop new vehicles for delivering informative and accessible content to those in our community who are hungry for news and perspective on autism research, while also opening new avenues for community feedback to guide Autism Speaks science.**

**What recent progress has been made?** In the summer of 2011, the science leadership began hosting live webchats to address community questions generated by media coverage of major research findings. The webchat regularly features invited guests who specialize in areas such as autism-related GI disorders, complementary medicine and dentistry.

Science leadership has also been increasing their engagement with the autism community through social media such as personal Twitter feeds and participation in media-sponsored Twitter Hours. These tools have proven especially useful in directing individuals and families to the rich resources available on the Autism Speaks website.

In addition to the above efforts, the science department launched its own e-newsletter, “Autism Speaks Science Digest,” which delivers science news, perspective-rich commentary and feature stories to the inboxes of subscribers on a bi-weekly basis. “Science Digest” was launched in July of 2012, and as of February 2013, the subscriber count is over 14,400.

**What will future success look like?** We are developing informative and engaging audiovisual clips for use both on our website and in staff presentations to lay audiences. These will feature science staff and funded researchers explaining the real-world importance of their work. Working with our international partners, we likewise hope to produce podcasts that provide practical information about autism. The goal is to have these translated into multiple languages for radio delivery to communities that lack Internet access.

**Objective #3: Help staff in the field to convey the importance of the science that our volunteers and donors make possible.**

While the Autism Speaks staff seeks to provide support to all departments and staff within Autism Speaks, we recognize a special relationship with the Field staff who convey our integrated missions of “Research-Awareness-Compassion” to local communities across North America. As such, the science department has a special goal of helping Field staff to convey the importance of the science that our volunteers and donors make possible – and to do so in ways that are deeply meaningful to local communities.

**What recent progress has been made?** In late 2011, the science department produced two sets of slideshows highlighting region-specific scientific research and Autism Speaks Autism Treatment Network (AS-ATN) activities. Created with lay-friendly suggested scripts, the elements of these slideshows were designed to be broken apart and used by Field leaders in
their community-specific presentations. In addition, the science department worked with Field leadership to provide science speakers for Walk Kick Offs and other major community events.

With the launch of Field’s It Takes a Village newsletter in early 2012, the science department also began delivering a weekly roundup of science news and blogs to Field staff and Walk volunteers. These projects are part of a larger melding of Science and Field communications dedicated to meet the needs of local communities.

What will future success look like? Continued close communication with staff in the field will enable the science department to respond and adapt to the evolving needs of our families and their communities. In the planning stages are a series of special science webchats for Field staff and for Walk volunteers.

Objective #4: Enhance and develop the supportive role that Autism Speaks science staff play in helping all Autism Speaks departments and staff achieve their goals for serving our families, donors and other supporters.

What recent progress has been made? The science department has increased its assistance to Major Gifts in communicating the progress and results of directed grants for scientific research, with increased emphasis on translating these results into clear and meaningful lay language.

In addition, the science department has largely taken over the production of its own web content in ways that enhance the visual appeal and informative depth of its webpages, while allowing for rapid publication and updating of science information directly meaningful to our broader community and the public at large.

What will future success look like? As capacity allows, the science department will play a greater role in translating research findings into lay-accessible content to support legislative advocacy as well as public awareness and donor services.
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