

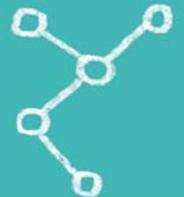
Autism Speaks Strategic Plan for Science



2009 - 2011



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It's time to listen.





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Autism Speaks 2009-11 Strategic Plan for Science

Executive Summary

Autism is one of today's most urgent public health challenges. The estimated prevalence of autism spectrum disorder is 1 in 150, greater than Type 1 Diabetes (1 in 400), childhood cancer (1 in 2000) and cystic fibrosis (1 in 3500), combined. Moreover, based on the World Health Organization's measure of burden of disease (Disability Adjusted Life Year), autism is a larger burden to society than Type 1 diabetes, childhood leukemia, and cystic fibrosis. The annual cost of autism to society is estimated to be \$35 billion, most of which is due to lifelong 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 to 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.

The purpose of the strategic plan is to help guide Autism Speaks' 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. The plan seeks to inspire synergy among each of the components of the science department, so that the department can have a unified strategy that leverages resources and expertise.

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.*” As such, the goals of the strategic plan for science must not only serve to accelerate science, 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.*** Thus, we must not be satisfied with the creation of a new screening tool for autism or the discovery of an autism susceptibility gene. The time is ripe to develop goals that seek to get the screening tools into the hands of practitioners who see individuals with ASD, and translate genetic findings into treatments and diagnostic tools.

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***; and the belief and commitment that ***parents are our partners*** in this effort. Each of these values relates to fundamental commitment at Autism Speaks to ***individuals with autism and their families.*** These families should be intimately involved in setting the direction and priorities for the science department. As we align our compass, people with autism and their families are the true north toward which we are oriented. To achieve these goals, we will utilize a core set of tactics, namely, promoting interdisciplinary collaboration, funding strategies that are highly leveraged, data-sharing, a balance between short- and long-term goals, and innovative science.



To address the need for clearly articulated goals and objectives, a framework utilized by the Gates Foundation¹ was adapted. Utilizing this framework, the Autism Speaks' science department carried out the following steps, the results of which are described in this document:

1. Two detailed analyses of the funding priorities and outcomes of past funding at Autism Speaks² were conducted, one by Autism Speaks' science staff and the other by the Washington Advisory Group, an independent consulting firm.
2. An assessment of the current status of initiatives and funding at Autism Speaks was conducted, including an assessment of the current data base resources that exist.
3. Two outside consultants were utilized in creating the plan: Fay Twersky, Director, Impact and Planning, Gates Foundation, and John Peabody, MD, PhD, FACP, Professor and Deputy Director, Institute for Global Health, University of California, San Francisco.
4. Autism Speaks solicited input from outside "thought leaders" and stakeholders on the strategic plan priorities and strategies. Six small strategic planning workgroups were convened pertaining to the following topic domains: (1) Etiology, (2) Biology, (3) Diagnosis, Phenotyping, and Epidemiology, (4) Treatment, (5) Dissemination, and (6) Bioinformatics. Each workgroup was comprised of Autism Speaks' science staff members, experts in the field, and at least one parent of a child with ASD. Each Strategic Planning Workgroup generated a document describing the highest priority goals, strategies, and metrics for measuring success for their domain. These documents were integrated into the first draft of the strategic plan and presented to the Scientific Advisory Committee for feedback.
5. Autism Speaks' science department met with the Scientific Advisory Committee (SAC) in New York City in September 2008 for a two day retreat to solicit their input on the priorities, strategies and metrics of the strategic plan. The SAC's input and feedback was integrated into the plan.
6. Additional feedback from the initial Strategic Plan workgroups was solicited.
7. The Strategic Plan was presented to the Autism Speaks Board of Directors in December of 2008 to be approved at the March 2009 meeting.

Strategic plan framework

The strategic plan framework we adopted requires defining end goals that directly involve health impact, i.e., translation of scientific results into real world outcomes and services. The process of achieving this end goal moves from *scientific discovery* to *development* and refinement of those discoveries to *dissemination*³ of results within a real world setting. Such strategic thinking depends on a "theory of change", i.e., a well-articulated plan for how change can be accomplished.

For the past several decades, the field of autism research has been primarily focused on discovery. For example, in 2007, whereas approximately \$160 million was spent on discovery research, less than \$20 million was spent on each of development and dissemination research. This is understandable given that, even a decade ago, we understood very little about autism, only a small number of committed scientists were devoted to autism, and the level of federal and private funding was extremely small. Thus, efforts have been largely focused on basic work aimed at defining and understanding the nature and causes of autism. Among the exceptions are studies in the areas of early recognition and intensive behavioral intervention. Now, in

¹ Adapted from Fay Twersky, Director, Impact and Planning, Gates Foundation.

² Note that "Autism Speaks" in this document refer collectively to the activities of Cure Autism Now, National Alliance for Autism Research, and Autism Speaks, which now have merged into one entity.

³ Note that the path from discovery to dissemination is not unidirectional. In fact, we often have new discoveries about etiology and treatment that come from dissemination and clinical practice.



large part due to the historic efforts of Cure Autism Now, the National Alliance for Autism Research, and Autism Speaks, the field is turning a corner such that a greater investment in developing, translating, and disseminating results is justified. It will be important to consider how Autism Speaks can accelerate science along this pathway from discovery to delivery by utilizing targeted funding mechanisms.

LOOKING BACK: ANALYSIS OF PAST-FUNDING PRIORITIES

Internal review of our return on investments in scientist-initiated research

The staff at Autism Speaks conducted an internal assessment of the accomplishments and return on investments based on the past decade of grant funding⁴. Autism Speaks has granted research funds for the study of autism and related disorders since 1997. The number of proposals and funding levels were initially modest but grew over time. The total funds awarded for investigator-initiated grants through 2007 were approximately \$77M. These funds were distributed among 683 research projects and 649 scientists (including 181 pre- and post-doctoral fellows, across 205 institutions), in 35 U.S. states and 17 countries. Moreover, these funds led to \$143.8 million of multi-year federal funding, and one patent. Outside of the US, funds were primarily directed toward the UK and Canada, two countries that already had a strong research base.

Field-building research grants have always been a core feature of Autism Speaks science programs. This goal has primarily been reflected in the formation of Autism Speaks' fellowship programs, where the brightest up-and-coming researchers expressing an interest in autism are rewarded with support through their training years. Our fellowship program, which supports both pre- and post-doctoral researchers, has steadily grown over the years. To determine whether Autism Speaks funding has had an impact on their career choice, we recently tracked former fellows through 2005 (103 in all) and found that 69% had remained in autism or autism-related fields in the next phase of their career. Very interestingly, further analysis shows that the retention rate of our pre-doctoral fellows within autism is 82%, indicating that they are finding positions and scientific opportunities within autism, proof that we are indeed expanding the field. Such high retention also suggests that our selection process is rigorous and that our pre-doctoral fellows are among the best.

As the knowledge base increased and theories were tested through the benefit of our awards, the information was disseminated to the public through scientific publications in peer-reviewed journals. Our grant program has directly contributed 700 scientific publications on autism research, some published in the most prestigious peer-reviewed scientific journals and highly utilized by other researchers (over 10% of these articles have been cited in at least 50 subsequent publications). The research findings in these publications have had an enormous impact on how we think about the disorder, including its causes and treatments. In this way, the grant money has been far reaching, benefiting both the researchers who are the direct recipients and the entire autism research community. Indeed, there was a dramatic increase in the number of autism publications indexed in PubMed starting in the mid-1990s, which was the point at which Autism Speaks efforts began. This likely is the product of many factors, including efforts by Autism Speaks, NIH funding of the Collaborative Program of Excellence in Autism in 1996, new technological advances

⁴ Note that this analysis focuses primarily on investigator-initiated grant funding and does not include an exhaustive analysis of our return on investments based on funding of specific research resources, such as the Autism Genetic Resource Exchange, Autism Genome Project, Autism Tissue Program, Clinical Trials Network, and many others.



(such as the sequencing of the human genome), and the increased prevalence and awareness of autism, all occurring within the same timeframe.

External review

At the request of the Chairman of the Board of Directors, Autism Speaks also contracted with the Washington Advisory Group (WAG) to conduct an independent review of the results from the grants made by NAAR and CAN during fiscal years 2004-05. Dr. Purnell Choppin, a WAG Director and President Emeritus of the Howard Hughes Medical Institute, served as Lead Director on this project. In collaboration with Drs. Dawson and Colamarino, WAG developed a set of evaluation criteria and assembled a list of potential reviewers (outside the autism research community).

The WAG team concluded that they were “very impressed with the great breadth of the areas of research being addressed by investigators, both basic and clinical.” They added, “Though there is an enormous amount yet to be learned, very significant progress is being made on many fronts.” In response to Autism Speaks’ leadership question, “Did we get our money’s worth?”, the WAG team concluded, “the answer to that question is yes.” They did recommend that grants be made for periods longer than two years, as this was noted as a problem by many of the reviewers. Furthermore, they recommended that careful attention be paid to obtaining the necessary expertise on science review panels, and to the evaluation of interim and final reports so that more information for assessing progress is available in the future.

Analysis of past and present funding priorities

An analysis of 2007 funding showed that Autism Speaks devoted more funding to studies focused on basic science research in the areas of etiology and biology than to applied science research in the areas of diagnosis and treatment. Within the Biology Portfolio, more funds were devoted to animal than human research (human research is generally more expensive, however). Within the Etiology Portfolio, more funds were directed toward studying genetic than environmental factors and very few funds were devoted to studying gene-environment interactions. Within the Treatment Portfolio, most funding was directed toward school age children and relatively lower levels of funds were directed toward adult treatments.

2007 distributions made by Autism Speaks were also examined by type of research (discovery, development, dissemination). Discovery research was defined as basic science aimed at gaining knowledge or understanding about fundamental processes, whereas development research was defined as scientific studies in which knowledge obtained from basic research with genes, cells, or animals is translated into diagnostic or therapeutic applications. Dissemination science is a newer field of study. In fact, the first NIH conference on the science of dissemination was held in 2007. The goal of dissemination science is to promote implementation of evidence-based practices by the broader community, including health providers, insurers, policy makers, and the general public. It was found that the majority of funding was devoted to discovery research. Lower levels of funding were devoted to development research and very little funds targeted dissemination research.

Funding by other organizations was also examined. The total amount of funds spent in 2007 by the U.S. on autism research, not including funds spent by Autism Speaks, is \$150,989,910. Based on NIH, CDC, and the Simons Foundation, portfolio funding distributions are: Biology (28%), Treatment (13%), Diagnosis (20%), Risk Factors (24%), and Other (15%). One striking take-home message from these data is that treatment and dissemination research are highly underfunded.



Grant and program analyses: moving forward

The utility of program evaluation is twofold: first, it measures our accomplishments against our goals, and second, it is a tool for strategic planning. Data from the evaluation of our grant program aids in our subsequent funding decisions, in expanding programs that yield returns or extending our reach into new growth territories, or even in retreating from approaches that have not produced. To move forward requires our collective scientific experience as well as concrete knowledge about our past performance. Evaluation will afford us the ability to correct ourselves and/or align our priorities, if necessary, to save valuable time and resources. To assist us in these efforts going forward, Autism Speaks' science department will be establishing an Advisory Committee on Impact and Analysis.

It is important that evaluation mechanisms be built into our grant process to provide reference for comparing our past, present and future funding decisions. Our grant program has pre- and post-grants components: "pre-grants" consisting of the submission, review, prioritization and awarding of grants, and "post-grants" consisting of the gathering of return-on-investment (ROI) data and grants analysis. Between these components lie "current grants," where interim productivity on long-term grants and the overall distribution of our grant portfolio can also be evaluated. At present our grants database software manages pre-grants and current grants adequately but has very little capacity for post-grants analysis. Upgrading our grants analysis system so that it can automatically collect and track ROI data will greatly facilitate evaluation and be a high priority for 2009-11. Examples of ROI data to be collected include publications (articles, book chapters, etc.), additional leveraged funding, inventions (patents, reagents, research tools, etc), career development, and information dissemination (news articles, posters presentations, lectures, etc.), which can be obtained from the grantees themselves, from online databases, or other sources (e.g., in-house staff, other experts, etc.). The ROI on a grant usually materializes after the funding period, so follow up data collection should take place 3-5 years beyond grant completion. Computational analysis is possible if grants data are entered into the database in machine-accessible format, i.e., they are coded. Rapid real-time evaluation can then be performed with pre-programmed queries, and the results used for strategic planning that will allow us to respond to changing funding environments and shifting scientific priorities.

What should we measure? Flexibility should be built into the system so we can evolve our evaluation criteria and data collection. As autism research matures and moves closer to treatment dissemination, new and different program goals will be set, novel evaluation questions will be asked, and, most likely, more innovative metrics will be devised. Based on a survey we recently conducted and information derived from the Health Research Alliance, it appears that we are well-aligned with other foundations in the evaluation metrics we currently collect.

In the future we will also want to collect data that will allow us to answer questions that are more directly aligned with our mission, such as: *Have we improved clinical practice and patient quality of life? Have we lowered the prevalence of autism? Do our programs provide economic benefit to families?* Therefore, our program analyses, and the system we put in place for such analyses, must be able to accommodate more mission-based goals, which are not so reliant on publications but instead measure progress in terms of real impact for families.



LOOKING FORWARD: 2009-11 STRATEGIC PLAN FOR SCIENCE

Strategic directions

Five strategic directions were identified by multiple workgroups and the Scientific Advisory Committee. Their near universal endorsement is noteworthy as they may provide insight into particularly effective common strategies that can potentially influence success in several domains. *First*, the need for *an individualized approach to diagnosis and treatment* was identified as an important common goal by four of the five strategic plan workgroups and the SAC. Specifically, the need to identify *biomarkers or clinical features that index meaningful subtypes of ASD*, point to specific etiologies, and predict response to treatment was endorsed by all of these groups. It is recognized that autism is comprised of many different diseases with different etiologies, symptom profiles, courses and prognoses, and treatment responses. Given the multiple etiologies related to autism, incorporation of more comprehensive genetic and environmental exposure testing, assessment of underlying and associated medical conditions, and eventually the identification of new biomarkers will enable clinicians to provide more individualized and more targeted and effective treatments. Progress in this area will require a multi-pronged approach, including but not limited to studies focused on identification of useful biomarkers, (e.g., electrophysiological, immunological, metabolic), examination of genetic and other biomarkers as predictors of vulnerability to environmental triggers and moderators of response to treatment, and closer collaboration between researchers and clinicians, among others.

Second, the need for *better tools and more attention focused on understanding environmental risk factors and gene-environment interactions* was highlighted throughout. Prevention and treatment of autism through alteration of potential environmental factors is now considered a fundamental goal of research. Closer collaboration between geneticists and environmental scientists will be necessary, as well as new methods for measuring exposures and analyzing their interaction with genetic factors. A wide range of environmental factors needs to be vigorously explored including but not limited to exposure to toxins, vaccines, chemicals, immune challenges, and the role of early behavioral intervention in altering the course of brain and behavioral development. Methods for identifying children who are medically vulnerable to adverse effects of environmental events need to be developed. Closely tied to this theme is the need to develop methods of early assessment of risk. The identification of infants at risk for autism will allow implementation of prevention strategies during the early postnatal and toddler period when significant changes in brain development are occurring.

A *third* strategic goal endorsed across the workgroups and SAC was the urgent *need to translate genetic and other biological findings into clinically useful tools* that can facilitate risk assessment and drug discovery. Again, multiple strategies will be required, including the development of appropriate animal models, development of preclinical assays to fast-track screening of novel treatments, practice guidelines for the communication, and use of new and sometimes poorly-understood genetic findings or exposure data within a clinical setting. It was agreed that the development of model systems that uniformly characterize the most relevant biological and behavioral abnormalities found in autism is paramount in moving the field forward. More generally, there is a need for the development of clinical standards and practice parameters for clinicians serving individuals with autism and their families. A better understanding of the factors that promote or impede acceptance of empirically-supported practices will be an important step in the dissemination of findings to the clinical community.

Fourth, in an effort to balance short and long term goals and improve the lives of persons with ASD now, the need to *develop treatments that can address the core symptoms and associated medical conditions* from which



people with ASD suffered was recognized. There is a need to identify new treatment approaches, both behavioral and medical, that are appropriate for individuals across the life span. In particular, there is a need to promote the development of a comprehensive care model that can address common medical conditions, such as GI and sleep problems, as well as depression and anxiety. Addressing such issues will require new approaches to clinical diagnosis and assessment, training of physicians and other health care providers in recognizing and treatment persons with ASD, and testing the efficacy and safety of medical and other treatments.

Fifth, the need to direct resources into *dissemination of empirically-validated treatment approaches*, such as early behavioral intervention, that could significantly alter the life trajectory and improve outcomes and quality of life for many individuals with ASD and their families today was strongly endorsed. In fact, this goal was identified as the number one priority by the Scientific Advisory Committee. This will require investing in (1) studies that demonstrate the effectiveness of feasible, exportable, and scalable early intervention programs, (2) the identification of factors that promote or impede the implementation of such programs in the community, (3) novel methods for provider training that can be accessed by the wider community (e.g. web-based technologies), (4) implementation of training programs that can build capacity of the community to provide interventions, and (5) changes in insurance benefits for early intervention and other empirically-validated treatments.

Given the rapidly expanding knowledge base pertaining to autism and related fields of inquiry and the complexity of the ASD, the *development of central information repositories* that are highly useful and flexible for scientific exploration will be vital for moving the field forward toward discovery of prevention and treatment methods. These information systems need accommodate international efforts and provide a platform for web-based training modules and wide-scale information dissemination.

Furthermore, *closer collaboration and improved communication* among scientists of different disciplines and between families and scientists, clinicians and researchers, public and private funders, and stakeholders and scientists world-wide will allow for the discovery of more effective treatments and prevention strategies and their dissemination and implementation in the broader community, so that all individuals with ASD and their families can benefit from the work we are striving to accomplish.

Other recommendations from the Scientific Advisory Committee

The SAC noted that Autism Speaks should place high priority on innovation rather than incremental research. They strongly endorsed developing a funding mechanism designed to respond quickly to opportunities and novel ideas. Autism Speaks has already implemented changes in its review criteria to reflect greater emphasis on innovation and relevance to Autism Speaks' mission. Furthermore, in 2009, following the SAC recommendation, Autism Speaks will establish the Trailblazer Awards which will be modeled after the Rapid Response Innovation Awards offered by the Michael J. Fox Foundation for Parkinson's Research. The Trailblazer Award mechanism will be a rolling application to support highly novel autism-related research that addresses significant roadblocks and can open new avenues for understanding the causes and treatments for autism spectrum disorders. No preliminary data are required, but the project needs to have the potential to substantially impact our understanding of the causes or effective treatments for autism. Awards will be made for one year at a level of \$100,000 or less.

The SAC recommended that Autism Speaks continue to explore opportunities to form strategic partnerships, including partnerships with other disease foundations that share similar goals (e.g., Epilepsy



Foundation, United Mitochondrial Disorders Foundation), government and private funding agencies in other countries (e.g., UK, Middle East), NIH, Gates Foundation, World Health Organization, pharmaceutical companies, and biotechnology companies.

Noting the high level of retention of scientists (particularly predoctoral fellows) funded through the fellowship program, the SAC strongly recommended that fellowships continue to be a core part of the funding portfolio at Autism Speaks. The possibility of providing career development awards should also be considered.

The SAC also strongly recommended that the science component of Autism Speaks' website be better designed, "meticulously curated," and better utilized to promote research and science information dissemination. Among the ideas discussed were more detailed and personal science stories that are more reader friendly for the general public, conference and other event postings, interviews with funded scientists, job postings, and others. Collaboration with the Interactive Autism Network and International Society for Autism Research on this effort was recommended.

Finally, the SAC remarked on the great usefulness of interdisciplinary workshops that focus on topics in which Autism Speaks wishes to stimulate investment. Such workshops serve to develop the needed communication among diverse types of scientists and clinicians that is needed to move in novel directions and provide translation from the bench to the bedside and vice versa.

Summary of goals and priorities for 2009-11

Table 1 provides a summary of the goals, strategies, objectives, and initiatives identified in the 2009-2011 strategic plan for science. Although many challenges exist, including the current downturn in the world economy which is certain to affect funding for autism research and services, there is reason to be optimistic about our ability to make significant discoveries, translate those discoveries into treatments and prevention strategies, and disseminate these into the wider community for the benefit of individuals with ASD and their families. The number of scientists devoted to studying autism and the amount of resources (albeit still far below what is needed) have never been higher. In large part due to Autism Speaks' efforts, the stakeholder community has developed a strong and unified voice, increasing our ability to influence policy and resources. President Obama recognizes the urgent need to investigate the causes and treatment of individuals with ASD, making federal support for autism research and policy changes that could influence access to treatment more possible now than ever before. New and exciting technological advances and bioinformatic resources are becoming available at an extremely rapid pace, making new discoveries and fast dissemination of information possible. All of these factors give us real hope that the lives of individuals with ASD and their families will be improved through our efforts. To this goal, we remain steadfastly committed.

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Table 1. Goals, Strategies, Objectives, and Initiatives

Goal	Strategies	Objectives	Initiatives
1 - Identify genetic and environmental risk factors for autism and their interaction	<ul style="list-style-type: none"> • Create and integrate large scale genetic and environmental exposure data bases • Develop analytic tools for examining gene-environment interactions • Leverage existing projects and international partnerships to enhance genetic and environmental data collection • Promote data-sharing and large scale data base integration • Enhance collaboration among geneticists, environment scientists, and clinicians 	<ol style="list-style-type: none"> 1. To enhance resources for discovery of autism susceptibility genes 2. To promote identification, collection, and evaluation environmental exposure data 3. To facilitate novel directions in the exploration of environmental factors and gene-environment interactions 	<ul style="list-style-type: none"> • Autism Genetic Resource Exchange • Autism Genome Project (AGP) • Collaborative Risk and Outcome Scientific Study (CROSS) • Gene and Environment Contributions to Risk for Autism (GECRA) • National Children's Study (NCS) Collaboration • Environmental Factors Initiative • International Autism Epidemiology Initiative • High-risk/High impact Initiative • Weatherstone Fellowships • Trailblazer Awards
2 - Identify the underlying biological mechanisms of autism	<ul style="list-style-type: none"> • Develop appropriate of animal models • Use animal models to study biological pathways, drug responses, and recovery • Develop pre-clinical assays to study effects of risk genes and environmental factors on biological pathways and fast track screening of novel treatments • Create state-of-the art tissue program, including brain, stem cell, and other tissues • Collaborate with Allen Institute for Brain Sciences to study gene expression and brain development • Develop novel brain imaging technologies to study early brain development 	<ol style="list-style-type: none"> 1. To stimulate innovative studies using animal models to understand biological mechanisms and test novel treatments 2. To develop in vitro and in vivo methods for pre-clinical testing of drugs 3. To create state-of-the art tissue bank 4. To facilitate development and application of novel brain imaging techniques 	<ul style="list-style-type: none"> • AS-MRC collaboration on Rett syndrome recovery • AS-Allen Brain Institute Collaboration on brain development • Autism Tissue Program Initiative • AS-Simon Foundation-NIH initiative to create state-of-the-art Autism Tissue Bank • High-Risk High-Impact projects on Mitochondrial Disorder and Novel approaches to brain imaging
3 - Develop improved and more efficient diagnosis and risk assessment methods	<ul style="list-style-type: none"> • Explore the validity and reliability of briefer, scalable methods of diagnosis that would allow acquisition of larger data bases • Develop consensus standards for diagnosis and phenotyping in research studies to facilitate data base integration across studies • Develop methods for screening and diagnosis for infants and toddlers, including biomarkers • Examine the utility and feasibility of genetic, medical, and metabolic assessments as part of a diagnostic work-up and as predictors of response to specific treatments • Encourage and prioritize research on adults and aging 	<ol style="list-style-type: none"> 1. To promote the development of briefer, scalable methods of diagnosis that are useful in multiple research and clinical environments 2. To reach a consensus in the field on a standard set of diagnostic and phenotype measures 3. To promote identification of reliable and valid risk/bio markers for autism 4. To assess the utility and feasibility of genetic/medical testing as part of a diagnostic workup 5. Increase knowledge on adult outcomes and aging in ASD 	<ul style="list-style-type: none"> • AGRE/NIH study exploring the use of parent questionnaires for screening and diagnosis • HR-HI IAN Studies exploring the validity of parent questionnaires for screening and diagnosis and assessment of nonverbal persons • Workgroup on Phenotyping Standards • AGRE and AGP studies on gene discovery • Baby Siblings Research Consortium • Conference on Translating Genetic Discoveries into Clinical tools • Autism Treatment Network • Prioritize research on adults and aging through pilot and basic/clinical grants



<p>4 - Identify effective treatment and prevention strategies for individuals with ASD⁵</p>	<ul style="list-style-type: none"> • Develop and test the efficacy of interventions for infants • Develop best practice guidelines for medical and behavioral interventions • Develop and test the efficacy of medical and behavioral/psychosocial treatments for school age, adult, and nonverbal individuals • Improved outcome measures for treatment studies are needed 	<ol style="list-style-type: none"> 1. To have effective, scalable interventions for infants and toddlers 2. To provide treatments that address the medical conditions associated with ASD 3. To publish practice guidelines for medical care 4. To have effective treatments for school age, adult, and nonverbal individuals 5. To develop sensitive and reliable outcomes measures for use in treatment studies 	<ul style="list-style-type: none"> • Toddler Treatment Network • Autism Treatment Network • Treatment Initiative/Grants Program • Clinical Trials Network • Innovative Technology for Autism Initiative • High-Risk High Impact Initiative • Interactive Autism Network • RFA on Treatment of GI Problems
<p>5 - Widespread dissemination of empirically-validated methods for screening, diagnosis, and treatment to the broader community worldwide</p>	<ul style="list-style-type: none"> • Convene "thought leaders" on effective dissemination and service delivery systems to discuss and develop a strategic plan for addressing the lack of dissemination of best practices in the community • Establish functional linkages to promote communication and partnership among the government and professional groups invested in dissemination of health care to prevent duplication of effort, reduce cost and effort, and increase collaboration • Work closely with Awareness, Government Relations, and Family Services components of Autism Speaks to coordinate with their efforts at policy change and dissemination • Survey existing models for dissemination of autism best practices or similar models for other diseases • Pilot dissemination model through Global Autism Public Health Initiative nationally and internationally 	<ol style="list-style-type: none"> 1. To improve communication among the government, private, and professional groups invested in dissemination of clinical practices 2. To develop a coordinated vision for dissemination of empirically-based best practices into the community both nationally and internationally 3. To pilot GAPH model of dissemination of empirically-based practices 	<ul style="list-style-type: none"> • Global Autism Public Health Initiative • Autism Treatment Network • Interactive Autism Network

⁵ Strategies, objectives and initiatives for meeting Goal 1 and 2 also are important for the development of effective treatments (See Goals 1 and 2)



PART ONE: INTRODUCTION

Autism is one of today's most urgent public health challenges. The estimated prevalence of autism spectrum disorder is 1 in 150, greater than Type 1 Diabetes (1 in 400), childhood cancer (1 in 2000) and cystic fibrosis (1 in 3500), combined. Moreover, based on the World Health Organization's measure of burden of disease (Disability Adjusted Life Year), autism is a larger burden to society than Type 1 diabetes, childhood leukemia, and cystic fibrosis. The annual cost of autism to society is estimated to be \$35 billion, most of which is due to lifelong 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 to 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' 2009-11 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. Finally, the plan seeks to inspire synergy among each of the components of the science department, so that the department can have a unified strategy that leverages resources and expertise.

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 plan described in this document reflects Autism Speaks' vision for its science program over the next 3-5 years. It is anticipated that the strategies and approaches will be constantly evolving as new data and technologies become available. Thus, the plan will be updated annually and should be considered a living document. Furthermore, we have built in flexibility to allow Autism Speaks to be a nimble, responsive organization that can rapidly respond to new opportunities.

The strategic plan for science at Autism Speaks must be fully aligned with the overall mission of the organization. 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.*" As such, the goals of the strategic plan for science must not only serve to accelerate science, 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.* Thus, we must not be satisfied with the creation of a new screening tool for autism or the discovery of an autism susceptibility gene. The time is ripe to develop goals that seek to get screening tools into the hands of practitioners who see individuals with ASD, and translate genetic findings into treatments and diagnostic tools.



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**; and the belief and commitment that **parents are our partners** in this effort. Each of these values relates to fundamental commitment at Autism Speaks to **individuals with autism and their families**. These families should be intimately involved in setting the direction and priorities for the science department. As we align our compass, people with autism and their families are the true north toward which we are oriented.

Tactics

To achieve our strategic goals, we will utilize a core set of tactics. First, we recognize that new breakthroughs will require creative *interdisciplinary collaboration*. Although, for administrative purposes, we have defined separate science portfolios which tend to align with specific scientific disciplines, 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. Indeed, although it has long been recognized that the usefulness of scientific findings rests in their translation into practice, it is increasingly recognized that the results of clinical trials and the observations of clinicians in the field often lead to critical breakthroughs and new fruitful directions.⁶ Furthermore, 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 Medical Research Council in the United Kingdom and the Shafallah Center in Qatar. Such partnerships often not only multiply our results, but also accelerate them. Fortunately, the NIH has recently developed a new strategic plan for autism research (as mandated by the Combating Autism Act), and the AS science department leadership, as well as Peter Bell from AS Family Services Programs and Alison Singer from AS Communications and Awareness, have all been involved in the development of the NIH strategic plan. The 2008 NIH strategic plan for autism research can be found at <http://iacc.hhs.gov/strategic-plan/>.

Core Values

- **Sense of urgency**
- **Scientific excellence**
- **Families as partners**
- **Persons with ASD are at the center**

⁶ Ledford, H. The Full Cycle. *Nature*, 2008, 453: 843-845.



Tactics

Interdisciplinary

Highly Leveraged

Data sharing

Balance short & long term goals

Innovation

Third, *sharing of data* across investigators and institutions worldwide will be 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 generally agreed that there exist many different “autisms” with many different causes. To parse apart this heterogeneity, large data bases are needed. Effort 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, the Autism Genetic Resource Exchange and the Autism Tissue Program, can be found at <http://www.agre.org/> and <http://www.atpportal.org/>. They are described below.

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. 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, the Brain Development Initiative, and the Autism Tissue Program. Examples of initiatives that reflect shorter term goals include (1) the Autism Treatment Network - a network of 15 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 Global Autism Public Health Initiative (GAPH) aimed at providing training in 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. The NIH does not typically provide a rapid response to highly innovative ideas. Autism Speaks distinguishes itself by funding 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 is the intended impact? What specific populations of individuals will benefit? What does success look like 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 have adopted 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.



Process and framework for formulating plan

To address the need for clearly articulated goals and objectives, a framework utilized by the Gates Foundation⁷ was adapted, as shown in the Table 1 below. Utilizing this framework, the AS science department carried out the following steps, the results of which are described in this document:

1. Two detailed analyses of the funding priorities and outcomes of past funding at Autism Speaks, CAN, and NAAR were conducted, one by AS science staff and the other by the Washington Advisory Group, an independent consulting firm.
2. An assessment of the current status of initiatives and funding at AS was conducted, including a survey of the current data base resources that exist.
3. Two outside consultants were utilized in creating the plan: Fay Twersky, Director, Impact and Planning, Gates Foundation, and John Peabody, MD, PhD, FACP, Professor and Deputy Director, Institute for Global Health, University of California, San Francisco.
4. AS solicited input from outside “thought leaders” and stakeholders on the strategic plan priorities and strategies. Six small strategic planning workgroups were convened pertaining to the following topic domains: (1) Etiology, (2) Biology, (3) Diagnosis, Phenotyping, and Epidemiology, (4) Treatment, (5) Dissemination, and (6) Bioinformatics. Each workgroup was comprised of AS science staff members, experts in the field, and at least one parent of a child with ASD. The workgroup composition is shown in Table 2 below. Each Strategic Planning Workgroup generated a document describing the highest priority goals, strategies, and metrics for measuring success for their domain. These documents were integrated into a draft strategic plan and presented to the Scientific Advisory Committee for feedback.
5. AS science department met with the Scientific Advisory Committee (SAC) in New York City in September 2008 for a two day retreat to solicit their input on the priorities, strategies and metrics of the strategic plan. The SAC’s input and feedback was integrated into the plan.
6. Additional feedback from the initial Strategic Plan workgroups was solicited.
7. The Strategic Plan was presented to the AS Board of Directors in December of 2008 to be approved at

Table 1. Strategic Plan Framework

Step 1	Defining the challenges and opportunities	<ol style="list-style-type: none"> 1. Detailed review of the current challenges 2. Consideration of how the problems can be addressed 3. Review previous strategies and their outcome 4. Gather input from “thought leaders” and stakeholders
Step 2	Choosing the strategy that informs the initiatives	<ol style="list-style-type: none"> 1. Articulate a “theory of change” to solve the problems. 2. Review major strategy assumptions 3. Propose steps of action 4. Consider AS’s unique role in implementing steps 5. Develop metrics for measuring success
Step 3	Plan for execution	<ol style="list-style-type: none"> 1. Specify implementation plan that reflects priorities, goals, and initiatives 2. Utilize strategies that will maximize success 3. Ensure that budget fits into AS overall resource plan

⁷ Adapted from Fay Twersky, Director, Impact and Planning, Gates Foundation.



the March 2009 meeting.

Table 2. Strategic Plan Workgroups

Topic	AS Staff Leader (s)	Members	Area of expertise
Etiology	Andy Shih, Ph.D. Alycia Halladay, Ph.D.	Sallie Bernard Patrick Bolton, M.D. Joachim Hallmayer, M.D. Pat Levitt Isaac Pessah, Ph.D.	Safe Minds/Parent Genetics Genetics Neuroscience Environmental Health
Biology	Sophia Colamarino, Ph.D. Leanne Chukoskie, Ph.D.	Ted Abel, Ph.D. Eric Courchesne, Ph.D. Jacqueline Crawley, Ph.D.	Neuroscience/parent Neuroscience Animal Models
Diagnosis Phenotyping	Alycia Halladay, Ph.D. Michael Rosanoff, M.P.H. Andy Shih, Ph.D.	John Constantino, M.D. Lisa Croen, Ph.D. Portia Iversen Lonnie Zwaigenbaum, M.D.	Genetics/phenotyping Epidemiology Parent Infants/diagnosis
Prevention and Treatment	Clara Lajonchere, Ph.D. Alycia Halladay, Ph.D. Peter Bell (parent)	Evdokia Anagnostou, M.D. Alice Carter, Ph.D. Richard Paylor, Ph.D. Amy Wetherby, Ph.D.	Pharmacology Early intervention Pharmacology Early intervention
Dissemination and Policy	Andy Shih, Ph.D. Peter Bell	David Mandell, Sc.D.	Dissemination Science/parent
Bioinformatics	Clara Lajonchere, Ph.D. Andy Shih, Ph.D.	Maja Bucan, Ph.D. Mark Igra, Ph.D. Paul Law, M.D.	Computational genetics Data base integration/parent Bioinformatics/parent

Framework for establishing goals and priorities

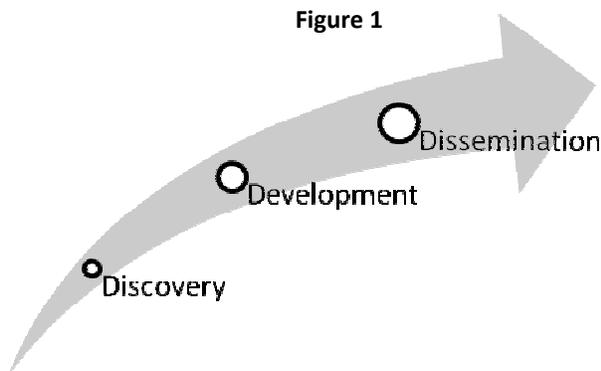
The framework we adopted requires defining end goals that directly involve health impact, i.e., translation of scientific results into real world outcomes and services. The process of achieving this end goal moves from *scientific discovery* to *development* and refinement of those discoveries to *dissemination*⁸ of results within a real world setting (Figure 1 below). Such strategic thinking depends on a “theory of change”, i.e., a well-articulated plan for how change can be accomplished⁹ For example, discovery of specific genes should lead to development of animal models, and experimental therapeutics should lead to drug trials and eventually FDA approval of an effective drug. Discovery of specific environmental factors should lead to an understanding of the mechanisms whereby the environmental factor influences the biological system, which should then lead to prevention efforts. Diverse strategies can be undertaken to achieve the end goals. Strategies to facilitate discovery include RFAs, targeted grants to talented people, development of infrastructure and resources (e.g., AGRE, ATP), research initiatives, and workshops. Strategies to facilitate refinement of discoveries into development of clinically relevant interventions include creation of assays, animal models, experimental therapeutics, and small randomized clinical trials (RCTs). Strategies to facilitate dissemination and implementation include clinical trials and treatment networks, services research, cost-benefit analyses, policy and consensus papers, training and education initiatives, and so on. There are well-developed “strategy templates” that other organizations have used to help refine and formulate their goals

⁸ Note that the path from discovery to dissemination is not unidirectional. In fact, we often have new discoveries about etiology and treatment that come from dissemination and clinical practice.

⁹ Colby, S., Stone, N., & Carter, P. (2004) Zeroing in on impact in an era of declining resources, nonprofits need to clarify their intended impact, *Stanford Social Innovation Review*. Stanford Graduate School of Business.



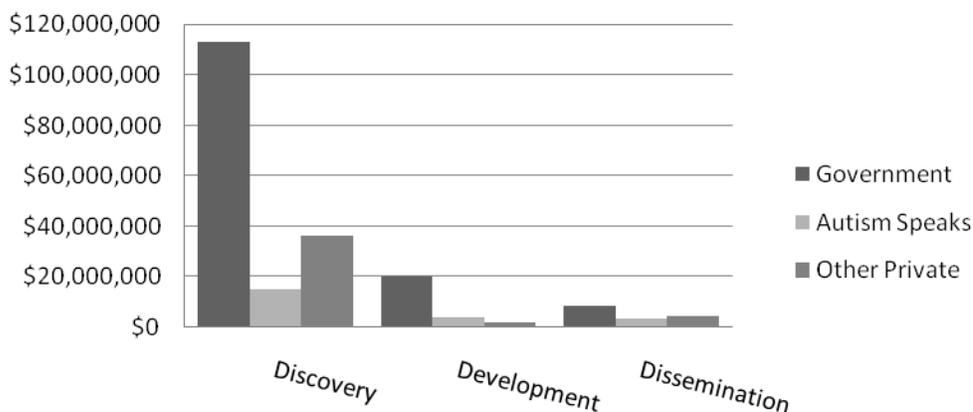
and strategies. We have primarily utilized the template developed by Fay Twersky at the Gates Foundation in consultation with suggestions provided by our consultant, Dr. John Peabody.



For the past several decades, the field of autism research has been primarily focused on discovery. As shown in Figure 2, in 2007, whereas approximately \$160 million was spent on discovery research, less than \$20 million was spent on each of development and dissemination research. This is understandable given that - even a decade ago - we understood very little about autism, only a small number of committed scientists were devoted to autism, and the level of federal and private funding was extremely small. Thus, efforts have been largely focused on basic work aimed at defining and understanding the nature and causes of autism. Among the exceptions are studies in the areas of early recognition and intensive behavioral intervention. Research in this area has not only demonstrated the remarkable effectiveness of early intensive intervention in improving outcomes of individuals with ASD, but is also now being translated into real world impact through broad training initiatives and mandated insurance coverage. Nevertheless, substantial challenges must be addressed in order to disseminate and implement early intervention programs in the wider community, including a lack of providers and insurance coverage. In 2009, Autism Speaks will be forming an advisory committee on dissemination and autism public health which will be considering how we can best move empirically-based practices into the community. The Autism Speaks Government Relations Department is spearheading the insurance benefit initiative. So, while progress is being made, Autism Speaks must keep in mind that early behavioral interventions result in highly variable outcome, and most individuals with ASD continue to face major challenges related to their disorder despite having early intervention. This underscores the critical and urgent need for continued research on causes, prevention, and treatment of autism throughout the lifespan.

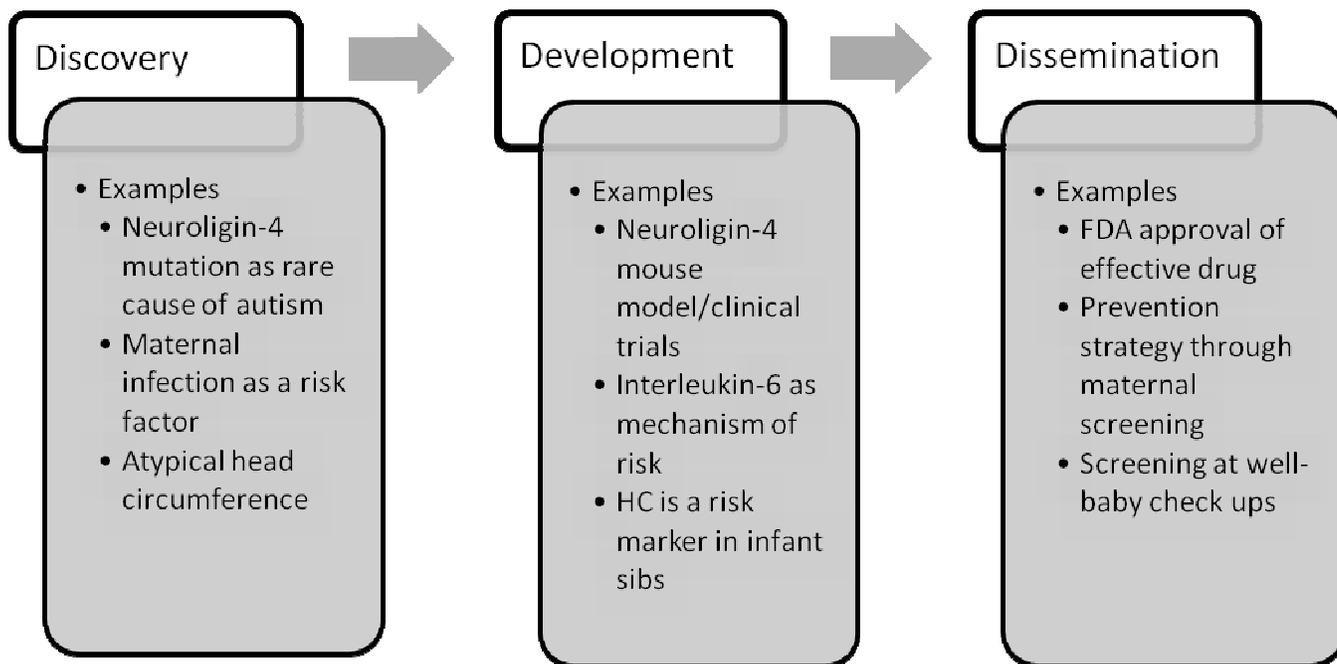


Figure 2
2007 Autism Research Funding



Now, in large part due to the historic efforts of Cure Autism Now, the National Alliance for Autism Research, and Autism Speaks, the field is turning a corner such that a greater investment in developing, translating, and disseminating results is justified. It will be important to consider how Autism Speaks can accelerate science along this pathway from discovery to delivery through targeted funding mechanisms. Examples of how basic findings might move through development to dissemination are shown in Figure 3.

Figure 3



Barriers to translational science that can bring basic findings from the bench to the bedside are significant. 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 (see “Where are the Cures?” by Sharon Begley, *Newsweek*, November 10, 2008). Scientists are ill equipped to develop the technologies that are required for translational research, and funding of such research is lower priority relative to discovery-focused research at



the NIH. Thus, an important role for Autism Speaks will be to facilitate translational research through data sharing policies, multi-disciplinary collaboration, and targeted funding on needed technological and knowledge advances that will help pave the way to treatment, prevention, and cure.

Setting Priorities. There may be several 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 in light of such priorities. 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) 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 NIH, the CDC, and the Simons Foundation. With respect to the latter, the priorities and objectives identified in the 2008 NIH Interagency Autism Coordinating Committee Strategic Plan for ASD Research represent potential areas of collaboration between the NIH and AS.



PART TWO: LOOKING BACK: ANALYSIS OF PAST FUNDING

A decade of advocacy and funding hastens the pace of autism research

Twelve years ago there were relatively few biologists, geneticists, neuroscientists, or clinical scientists who identified themselves as autism researchers. A small group of psychologists, psychiatrists, and neurologists formed the core of the autism research field. The work of these scientists was foundational – they defined the syndrome and its subtypes, developed standardized methods of screening and diagnosis, identified that genetic risk factors contribute to autism, described its association with various neurological features and autistic regression, and discovered what remains the most effective treatment for autism (applied behavioral analysis). Nevertheless, science was moving too slowly, primarily because autism was not attracting the attention and resources it deserved. Very little was known about the causes, biology, or medical treatment of autism. Moreover, this small group of scientists started their work when autism was considered a rare disorder. As the prevalence of autism increased dramatically, so did the awareness that autism is a significant public health problem that must be addressed. This increase in the prevalence of autism was accompanied by remarkable technological advances that allowed scientists to probe the human genome and brain function in ways that were not previously possible. The sequencing of the human genome in 2001 heralded a new era in the science of neurodevelopmental disorders. At about the same time, techniques such as functional magnetic resonance imaging, became more widely available, and discoveries about the inner workings of the brain became possible. Frustrated and knowing that so much more could be done, parents bonded together and formed the organizations, Cure Autism Now and the National Alliance for Autism Research. Their goal was to attract new scientists to the field and provide them with the resources to apply the new technologies to the study of autism.

In light of the recent merger among Autism Speaks, National Alliance for Autism Research (NAAR), Cure Autism Now (CAN), and the Autism Coalition for Research and Education (ACRE), there was a clear need for a well-articulated strategic plan for science at Autism Speaks that reflects the integration of each of these organizations, yet capitalizes on the unique strengths of each organization. In this section on looking back, when we refer to “Autism Speaks”, we are referring to the historical entities of CAN and NAAR, as well as the current entity of Autism Speaks. The mission of Autism Speaks is to accelerate scientific research to prevent, treat and cure autism, not just for future generations, but for this one as well. Urgency is a core value. Through rigorous scientific review, the Autism Speaks’ science program distributes funds in the form of grants and staff-driven initiatives that aim to reveal the risk factors that cause autism, the underlying biological mechanisms, unambiguously diagnose individuals with autism, investigate treatment and prevention approaches, and explore the best ways of disseminating empirically-supported treatments into the larger community. The grant programs address the necessity to stimulate novel research and entice new investigators to join the fight to understand autism. The end goal is clear: a better future for all who are affected by autism.

Looking back on the past decade or so, how do we know that the work that has been funded by Autism Speaks has helped move us closer to this goal?



What have we have accomplished? An Internal Review

The staff at Autism Speaks conducted an internal assessment of the accomplishments of the past decade of grant funding. Most of the analyses reported in this section were carried out by Dr. Romulo de Castro under the direction of Sophia Colamarino. Autism Speaks has granted research funds for the study of autism and related disorders since 1997. The number of proposals and funding levels were initially modest but grew over time (See Figure 4). The total funds awarded for investigator-initiated grants through 2007 were approximately \$77M. As shown in Figures 5 and 6, these funds were distributed among 683 research projects and 649 scientists (including pre- and post-doctoral fellows, across 205 institutions), in 35 U.S. states and 17 countries. Moreover, analyses show that outside the US, international AS funds in this first decade were primarily directed toward the UK and Canada, two countries that already had a strong research base.

Figure 4. Growth of number of grants and level of research funding from 1997-2007

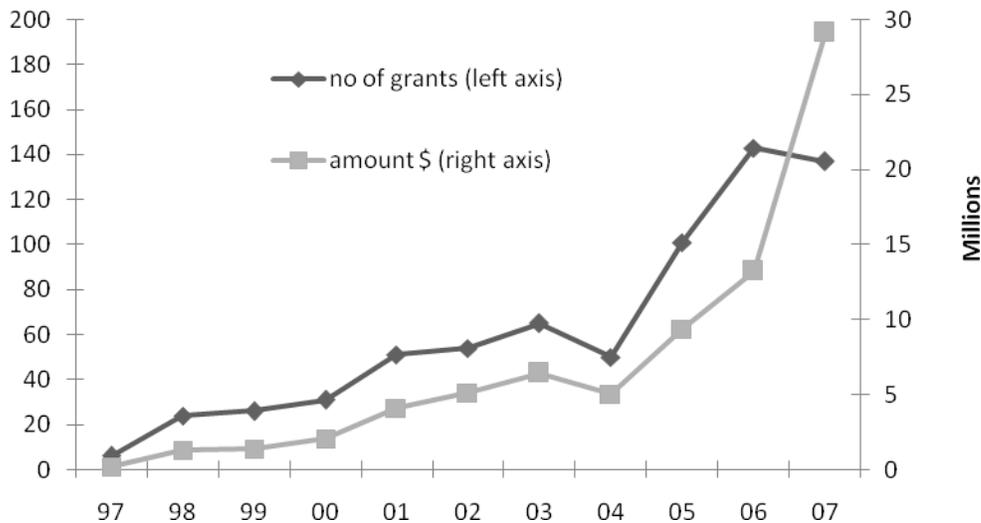
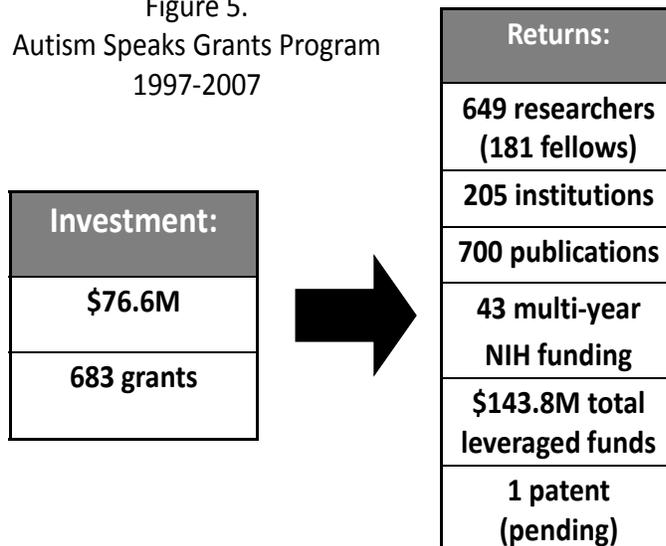


Figure 5.
Autism Speaks Grants Program
1997-2007



Perhaps the most obvious return from our investment is also one of the most important: autism is now positioned among other very important disorders such as neurodegenerative diseases (e.g., Alzheimer disease and Multiple Sclerosis), acute injuries (e.g., brain and spinal cord trauma), and other developmental disorders (e.g., Down and Fragile X syndromes) in global interest and priority. Recent events, national and international in scope, including U.S. presidential politics, support the notion that autism has become an important scientific and social undertaking. An analysis of the PubMed biomedical publication database for the overall number of autism publications during this period verifies an explosive increase in autism research relative to publications on other developmental disorders, as illustrated in Figure 7.

Figure 6. Grants awarded by Autism Speaks in the United States, 1997-2007

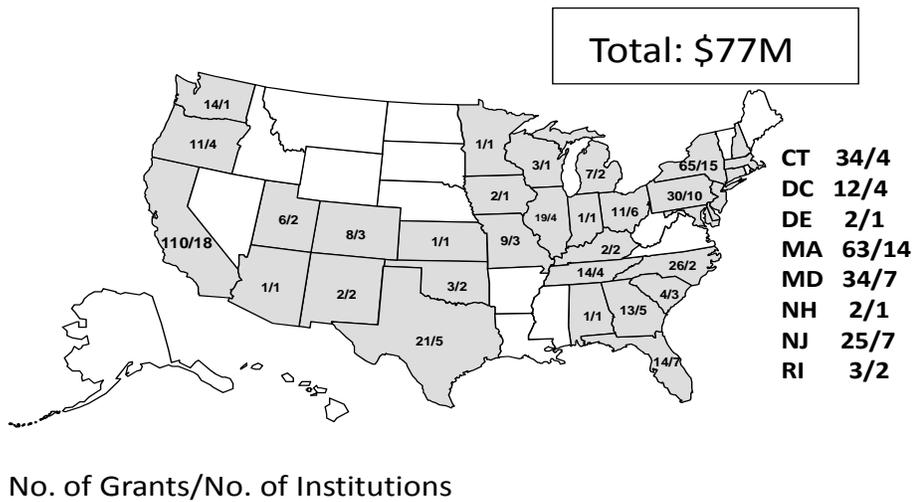
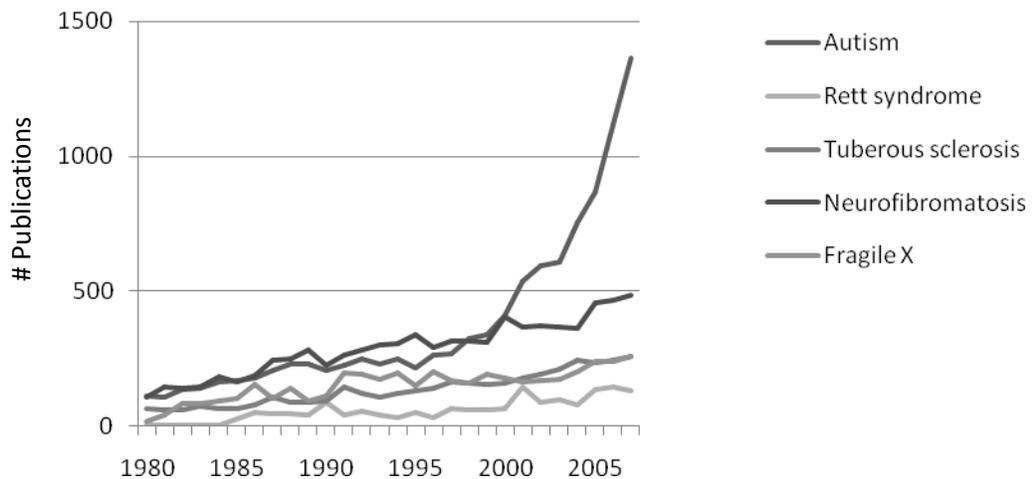


Figure 7. Rise in number of publications



Field-building research grants have always been a core feature of Autism Speaks science programs. This goal has primarily been reflected in the formation of Autism Speaks' fellowship programs, where the brightest up-and-coming researchers expressing an interest in autism are rewarded with support through their training years. Our fellowship program, which supports both pre- and post-doctoral researchers, has



steadily grown over the years. To determine whether AS funding has had an impact on their career choice, we recently tracked former fellows through 2005 (103 in all) and found that 69% had remained in autism or autism-related fields in the next phase of their career. Very interestingly, further analysis shows that the retention rate of our pre-doctoral fellows within autism is 82%, indicating that they are finding positions and scientific opportunities within autism, proof that we are indeed expanding the field (see Table 3). Such high retention also suggests that our selection process is rigorous and that our pre-doctoral fellows are among the best.

Table 3. Fellowships

Number of Fellowship	184
Total amount of funds	\$11.8M
Overall retention of fellows	69%
Predoctoral fellow retention rate	82%

Our awards led to a gain in knowledge and test of theories, and the information was disseminated to the public through peer-reviewed scientific publications. In this way, the grant money provided benefits not only to the researchers who are the direct recipients, but also to the entire autism research community. As mentioned above, the rise of autism publications indexed in PubMed

entered an accelerating phase starting in the mid-1990s, as illustrated in Figure 7. This likely is the product of many factors, including efforts by Autism Speaks, NIH funding of the Collaborative Program of Excellence in Autism in 1996, and the increased prevalence and awareness of autism, all occurring within the same timeframe.

Our grant program has contributed directly to the body of published scientific knowledge about autism with 700 research articles, some published in the most prestigious peer-reviewed scientific journals and highly utilized by other researchers. (Over 10% of these articles have been cited in at least 50 subsequent publications.) The research findings in these publications have had an enormous impact on how we think about the disorder of autism. For example, they include uncovering the first evidence for an ongoing neuroinflammatory reaction in individuals with autism, galvanizing the field to search for causes of brain inflammation. They also include pinpointing the white matter increases to regions of local brain connectivity, supporting a theory of disrupted information processing in the brains of individuals with autism. Furthermore, one of the main successes in autism research during the past decade has been to move the average age of autism diagnosis from 5 to 3 years of age through the development of methods for detecting autism in infants, allowing much more valuable time for early intervention. This could not have happened without the formation of Autism Speaks' Baby Sibling Research Consortium that focused on identifying the earliest sign of autism in an at-risk population.

Thus, together, AS publications are forming a central part of the foundation of knowledge that researchers all over the world are using to pursue a cure for autism. But the impact of Autism Speaks funding does not end with publications. Data and ideas produced through these awards can then be used to apply for money to carry out follow-up investigations, bringing even more support into a field that was so woefully underfunded when AS started. AS grantees have so far reported that as a consequence of AS funding, they have been able to bring in an additional ~\$144 million of grant support through the NIH and other granting agencies. This means that, at the very least, our initial investment has doubled in leveraged funds. Therefore, during a time when competition for biomedical disease research funding is intense, and preliminary data are required to qualify for large government funding sources, seeding innovative ideas through Autism Speaks grants has directly secured almost \$144 million more dollars for autism research.

Lastly, it is important to note that Autism Speaks' impact on science goes beyond its grant making efforts. Over the last decade, the organization has invested in sponsoring targeted research think tanks and collaborative research resources. Most notable among these efforts are Autism Speaks' Autism Genetic



Resource Exchange (AGRE) and Autism Tissue Program (ATP). The decision to create and support these open-access biomaterial databanks for autism research was visionary and created a paradigm shift towards collaboration and data sharing in the field. Each of these programs has accelerated the pace of autism research significantly by providing precious biological materials in the form of brain tissue, cell lines, and DNA as well as extensive clinical information on individuals with autism. An independent survey of these programs revealed that the AGRE and ATP have been responsible for 134 and 56 publications, respectively, some of which resulted from AS-sponsored grants.

What have we have accomplished? An External Review

At the request of the Chairman of the Board of Directors, Autism Speaks also contracted with the Washington Advisory Group (WAG) to conduct an independent review of the results from the grants made by NAAR and CAN during fiscal years 2004-05. Dr. Purnell Choppin, a WAG Director and President Emeritus of the Howard Hughes Medical Institute, served as Lead Director on this project. In collaboration with Drs. Dawson and Colamarino, WAG developed a set of evaluation criteria and assembled a list of potential reviewers (outside the autism research community). The criteria are shown in Table 4 below.

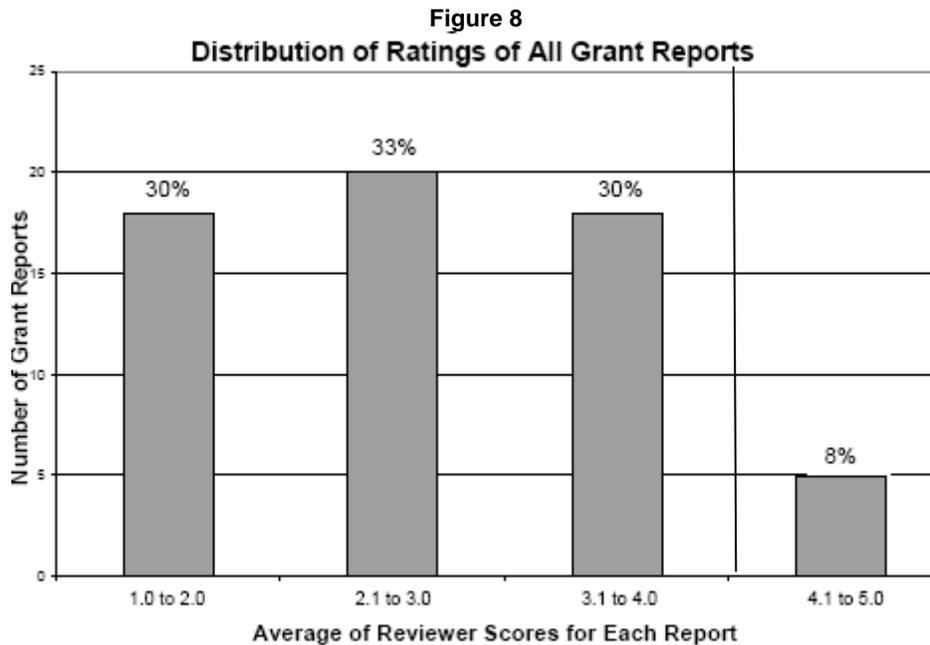
Table 4. Criteria used by WAG to rate final grants reports

Criteria	Score
The investigators met all their goals and/or produced other results that contributed substantially to the knowledge of autism. Funding of this type of research should be continued.	1.0
Although not all of the specific aims were achieved, significant knowledge was obtained to justify funding.	2.0
Although the investigators did not meet all of the goals of the project, the area is of great importance for autism and, thus, the study probably was worthwhile.	3.0
The investigators did not complete any specific aim or produce other significant results so the grant was not successful.	4.0
This grant should not have been funded because the potential for an impact on autism was minimal from the outset.	5.0

The reviews were then compiled and analyzed by WAG. In all, WAG reviewed 61 final grant reports (20 from CAN and 41 from NAAR) which had available the necessary information to provide a fair review. The reviewers were distinguished and experienced experts in a wide range of fields including neuroscience, neuroimaging, psychology, psychiatry, genetics, cell biology, immunology, biochemistry, computational biology and structural biology. Figure 8 below displays the distribution of ratings for the



grant reports. The data did not reveal a significant difference between the successes of the NAAR and CAN grants.



The WAG team concluded that they were “very impressed with the great breadth of the areas of research being addressed by investigators, both basic and clinical.” They added, “Though there is an enormous amount yet to be learned, very significant progress is being made on many fronts.” In response to Autism Speaks’ leadership question, “Did we get our money’s worth?”, the WAG team concluded, “the answer to that question is yes.” They did recommend that grants be made for periods longer than two years, as this was noted as a problem by many of the reviewers. Furthermore, they recommended that careful attention be paid to obtaining the necessary expertise on science review panels, and to the evaluation of interim and final reports so that more information for assessing progress is available in the future.

2007 Autism Speaks and NIH Science Funding

We next examined the distribution of money by funding mechanism (grants, fellowships, initiatives/programs), portfolio (etiology, biology, diagnosis, treatment), and amount of funding directed toward discovery vs. development vs. dissemination research. A breakdown of Autism Speaks and NIH 2007 funding is shown in Table 5. A more detailed breakdown of NIH funding is shown in Table 6.

Science portfolios were defined as follows:

- **Biology**
 - *Subcategories:* Clinical Neuroscience, Basic Neuroscience, and Biological Systems
- **Treatment**
 - *Subcategories:* Psychopharmacology, Biomedical, Behavioral/Psychosocial, Services Research, and Biomarkers for Treatment Response
- **Diagnosis**
 - *Subcategories:* Instrument Development, Early Identification, Characterization, Incidence/Prevalence
- **Risk Factors**
 - *Subcategories:* Genetics/Genomics, Environmental Influences and Gene x Environment Interplay, Mechanisms and Model Systems of Environmental Influences, and Psychosocial
- **Other**
 - *Subcategories:* Research Resources (e.g., data systems, repositories of biomaterials), Education and Dissemination, and Other



Table 5. 2007 AS Science Funding

ALL	Discovery	Development	Dissemination	Total
Grants	\$9,539,472	\$3,632,629	\$111,707	\$13,283,808
Fellowships	\$3,462,612	\$297,500	\$0	\$3,760,112
Initiatives/Prog	\$6,538,395	\$340,508	\$3,812,781	\$10,691,684
Total	\$19,540,479	\$4,270,637	\$3,924,488	\$27,735,604
AUTISM ONLY				
Grants	\$8,202,037	\$3,599,296	\$111,707	\$11,913,040
Fellowships	\$2,854,566	\$237,500	\$0	\$3,092,066
Initiatives/Prog	\$6,538,395	\$340,508	\$3,812,781	\$10,691,684
Total	\$17,594,998	\$4,177,304	\$3,924,488	\$25,696,790

BY PORTFOLIO

ALL	Etiology	Biology	Diagnosis	Treatment	Other	Totals
Grants	\$2,428,062	\$5,517,878	\$1,727,052	\$3,610,816	\$0	\$13,283,808
Fellowships	\$432,186	\$2,193,978	\$888,419	\$245,529	\$0	\$3,760,112
Initiatives/Prog	\$4,481,555	\$1,087,554	\$0	\$1,542,201	\$3,580,374	\$10,691,684
Total	\$7,341,803	\$8,799,410	\$2,615,471	\$5,398,546	\$3,580,374	\$27,735,604
AUTISM ONLY						
Grants	\$2,152,512	\$4,522,689	\$1,677,052	\$3,560,787	\$0	\$11,913,040
Fellowships	\$383,574	\$1,634,544	\$888,419	\$185,529	\$0	\$3,092,066
Initiatives/Prog	\$4,481,555	\$1,087,554	\$0	\$1,542,201	\$3,580,374	\$10,691,684
Total	\$7,017,641	\$7,244,787	\$2,565,471	\$5,288,517	\$3,580,374	\$25,696,790

2007 NIH Funding

ALL	Discovery	Development	Dissemination	Total
Grants	\$103,053,692	\$21,273,322	\$2,516,723	\$126,843,737
AUTISM ONLY				
Grants	\$65,840,479	\$18,012,146	\$2,516,723	\$86,369,348

BY PORTFOLIO

ALL	Etiology	Biology	Diagnosis	Treatment	Other	Totals
Grants	\$32,354,598	\$37,106,194	\$20,885,329	\$17,264,631	\$19,232,985	\$126,843,737
AUTISM ONLY						Totals
Grants	\$20,873,621	\$17,290,394	\$20,279,750	\$16,485,270	\$11,440,313	\$86,369,348



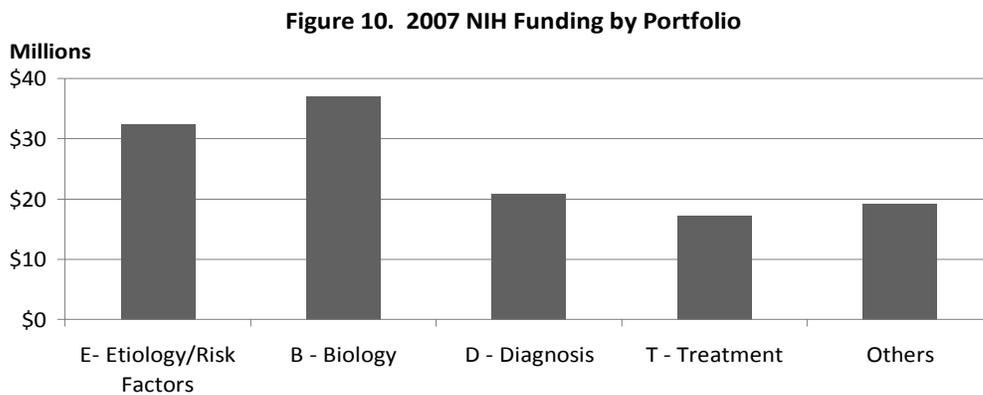
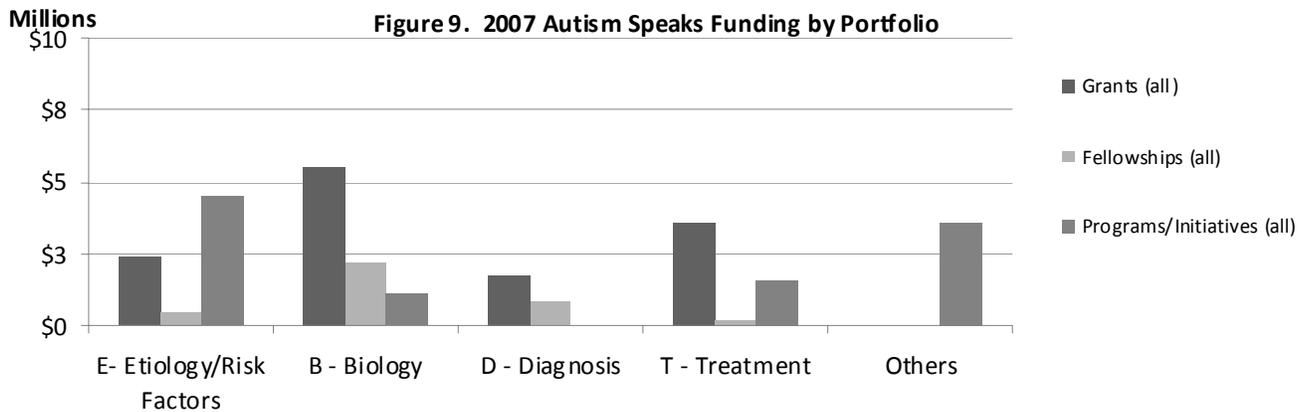
Table 6. Detailed breakdown of 2007 NIH Funding for Autism-related Research

Subcategory	Research Area					
	Biology	Treatment	Diagnosis	Risk Factors	Other	
Clinical Neuroscience	\$22,407,705					
Basic Neuroscience	\$13,517,497					
Biological Systems	\$542,423					
Biology Subtotal	\$36,467,625					
Psychopharmacology		\$4,963,704				
Biomedical		\$1,201,569				
Behavioral/Psychosocial		\$10,275,206				
Services Research		\$1,576,656				
Biomarkers for Treatment Response		\$161,869				
Treatment Subtotal		\$18,179,004				
Instrument Development			\$1,601,155			
Early Identification			\$2,507,980			
Characterization			\$15,704,246			
Incidence/Prevalence			\$1,057,328			
Diagnosis Subtotal			\$20,870,709			
Genetics/Genomics				\$20,670,059		
Environmental Influences and Gene X Environment Interplay				\$6,672,090		
Mechanisms and Model Systems of Environmental Influences				\$356,750		
Psychosocial				\$644,943		
Risk Factors Subtotal				\$28,343,842		
Research Resources					\$18,012,053	
Education and Dissemination					\$4,149,842	
Other					\$820,660	
Other Subtotal					\$22,982,555	
Grand Total	\$36,467,625	\$18,179,004	\$20,870,709	\$28,343,842	\$22,982,555	\$126,843,735

Autism Speaks further conducted an analysis of the autism research grants that comprised the close to \$127 million figure that NIH reported spent in 2007. Of interest was how many of these grants are directly related to autism versus those that may only be indirectly related. AS determined that \$86.5 million of the \$127 million was “autism-direct” research; the remainder was non-autism, though related. Of the \$86.5 million, approximately \$41 million was in new commitments made during 2007; the remainder, \$45.5 million, was for grant commitments made in prior years.



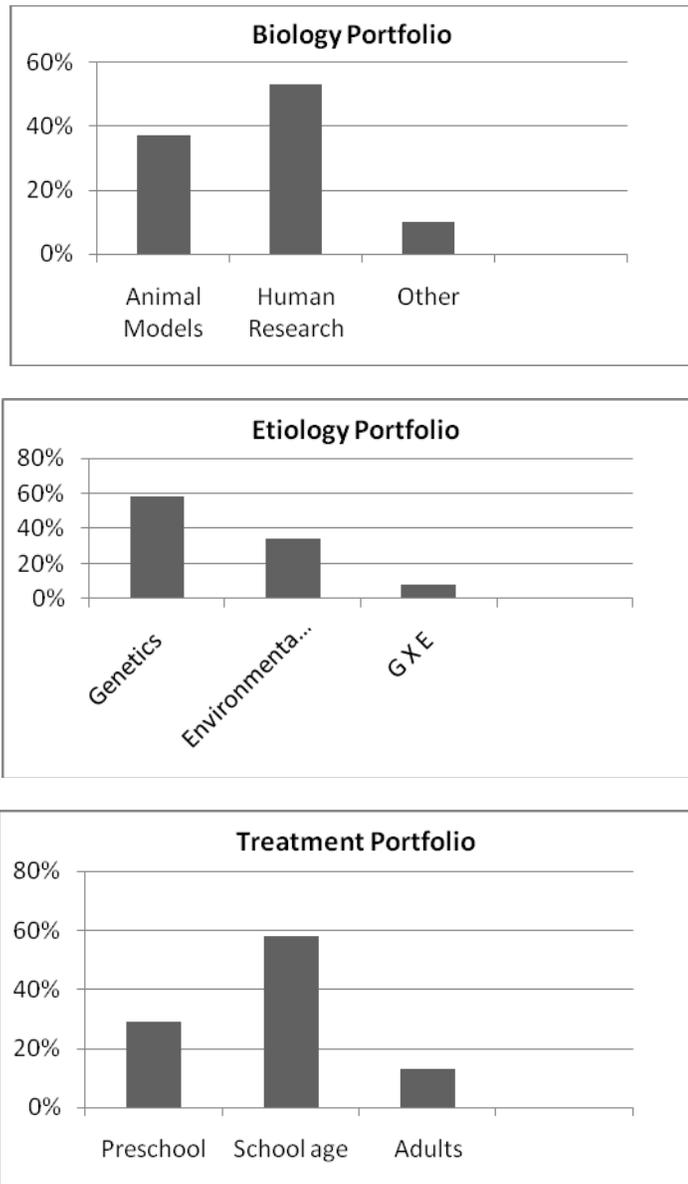
Distribution among and within research portfolios and by type of research. Distributions of 2007 Autism Speaks and NIH funds by portfolio are shown in Figures 9 and 10, respectively.



As shown in Figure 11, within the Biology Portfolio, more funds were devoted to animal than human research (human research is generally more expensive). Within the Etiology Portfolio, more funds were directed toward studying genetic than environmental factors and very few funds were devoted to studying gene-environment interactions. Within the Treatment Portfolio, most funding was directed toward school age children and relatively lower levels of funds were directed toward adult treatments.

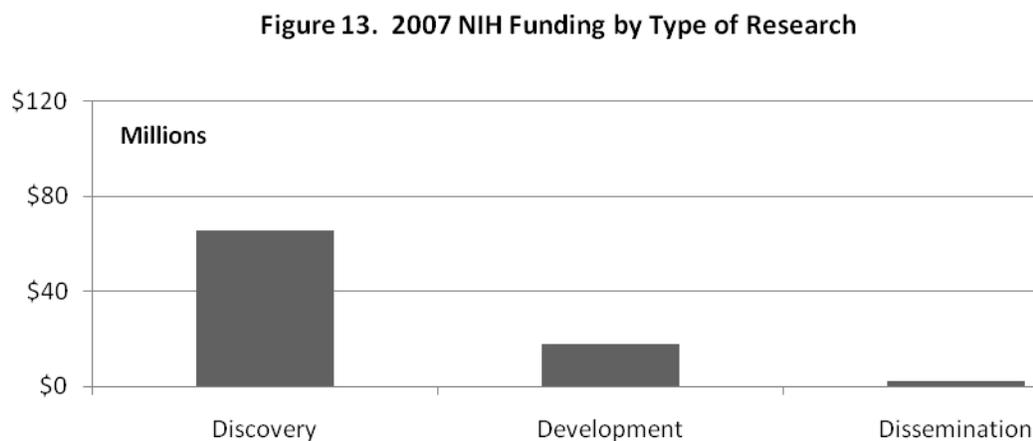
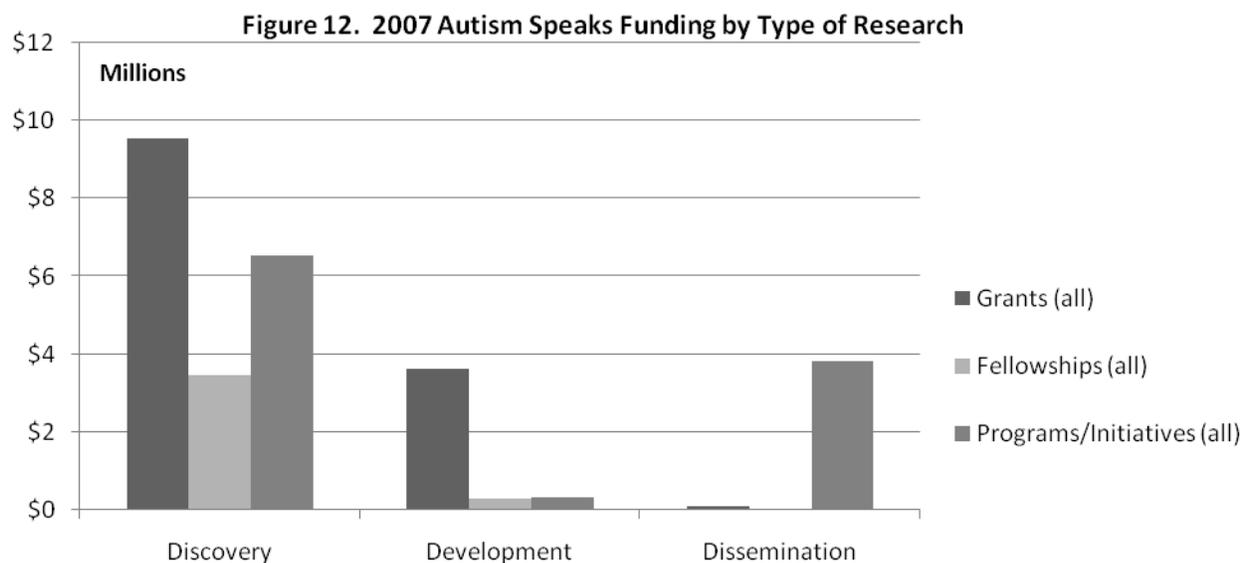


Figure 11. Distribution of Funding Within Portfolios



Distributions of 2007 Autism Speaks and NIH funds by type of research (discovery, development, dissemination) are shown in Figures 12 and 13, respectively. Discovery research was defined as basic science aimed at gaining knowledge or understanding about fundamental processes, whereas development research was defined as scientific studies in which knowledge obtained from basic research with genes, cells, or animals is translated into diagnostic or therapeutic applications. Dissemination science is a newer field of study. In fact, the first NIH conference on the science of dissemination was held in 2007. The goal of dissemination science is to promote implementation of evidence-based practices by the broader community, including health providers, insurers, policy makers, and the general public.





The total amount of funds spent in 2007 by the U.S. on autism research, not including funds spent by Autism Speaks, is \$150,989,910. Based on NIH, CDC, and the Simons Foundation, Portfolio funding distributions are: Biology (28%), Treatment (13%), Diagnosis (20%), Risk Factors (24%), and Other (15%). One striking take-home message from these data is that treatment and dissemination research are highly-underfunded.



2008 budget distributions

A review of the 2008 Autism Speaks science program budget reveals that the majority of funds (51%) are spent on the investigator-initiated grants program. Of the remaining funds, 37% is spent on research initiatives (targeted programs of research, such as the Autism Genome Project) and 12% is spent on Research Resources, such as the AGRE and ATP programs. Note, however, that these resources are heavily subsidized by NIH. Figure 14 illustrates the distribution of Autism Speaks funding among the current research initiatives. Figure 15 illustrates the distribution of funds among the clinical programs/research resources.

Figure 14 Autism Speaks Research Initiatives Budget Distribution

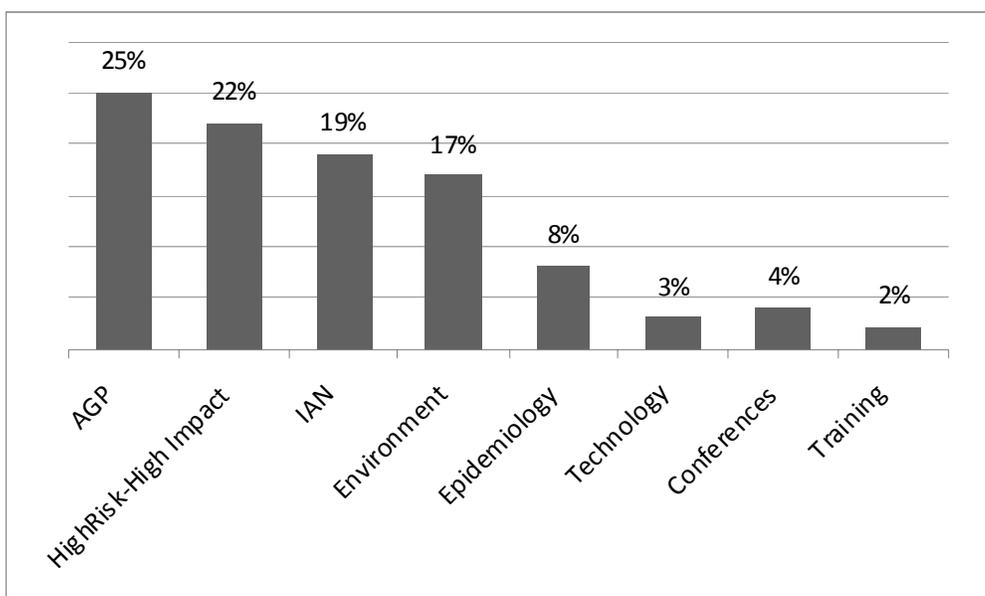
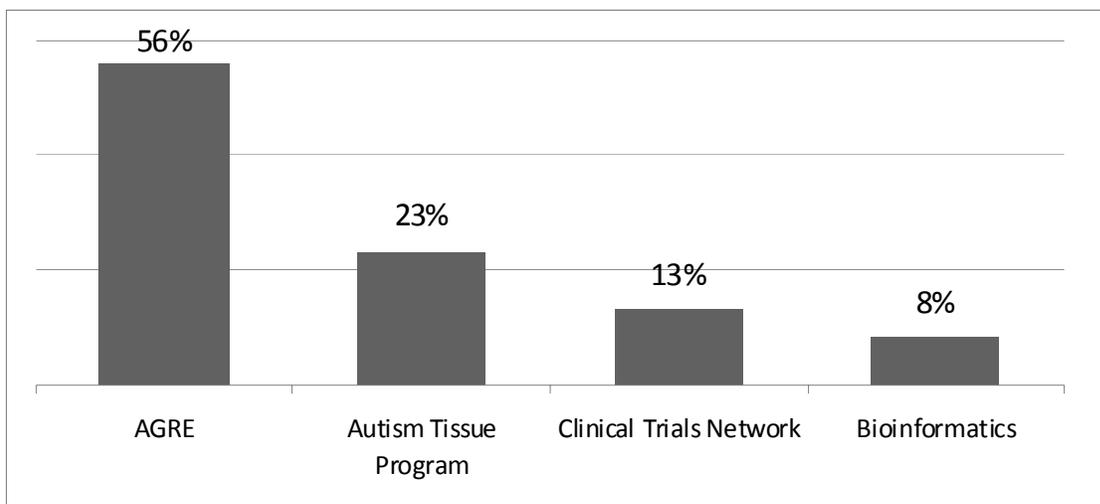


Figure 15. Autism Speaks Clinical Programs/Research Resources Budget Distribution



Grant and program analyses: moving forward

The utility of program evaluation is twofold: first, it measures our accomplishments against our goals, and second, it is a tool for strategic planning. Data from the evaluation of our grant program aids in our subsequent funding decisions, in expanding programs that yield returns or extending into new growth territories, or even in retreating from approaches that have not produced. To move forward requires our collective scientific experience as well as concrete knowledge about our past performance. Evaluation will afford us the ability to correct ourselves and/or align our priorities, if necessary, to save valuable time and resources. To assist us in these efforts going forward, Autism Speaks' science department will be establishing an Advisory Committee on Impact and Analysis.

Before we move much further, evaluation must be built into our grant process to provide reference for comparing our past, present and future funding decisions. Our grant program has pre- and post-grants components: "pre-grants" being the submission, review, prioritization and awarding of grants, and "post-grants" being the gathering of return-on-investment (ROI) data and grants analysis. Between these components lie "current grants," where interim productivity on long-term grants and the overall distribution of our grant portfolio can also be evaluated. At present our grants database manages pre-grants and current grants adequately but has very little capacity for post-grants analysis. Upgrading our grants analysis system so that it can automatically collect and track ROI data will facilitate evaluation and be a high priority for 2009-11. Examples of ROI data to be collected include not only publications (articles, book chapters, etc.) and additional leveraged federal funding, but inventions (patents, reagents, research tools, etc), career development, and information dissemination (news articles, posters presentations, lectures, etc.), which can be obtained from the grantees themselves, from online databases, or other sources (e.g., in-house staff, other experts, etc.). The ROI on a grant usually materializes after the funding period, so follow up data collection should take place 3-5 years beyond grant completion. Computational analysis is possible if grants data are entered into the database in machine-accessible format, i.e., they are coded. Rapid real-time evaluation can then be performed with pre-programmed queries, and the results used for strategic planning that will allow us to respond to changing funding environments and shifting scientific priorities.

What should we measure? Flexibility should be built into the system so we can evolve our evaluation criteria and data collection. As autism research matures and moves closer to treatment dissemination, new and different program goals will be set, novel evaluation questions will be asked, and, most likely, more innovative metrics will be devised. Based on a survey we recently conducted and information derived from the Health Research Alliance, it appears that we are well-aligned with other foundations in the evaluation metrics we currently collect (See Tables 7 and 8).

In the future we will also want to collect data to answer broad-scope questions that are more directly aligned with our mission, such as: *Have we improved clinical practice and patient quality of life? Have we lowered the prevalence of autism? Do our programs provide economic benefit to families?* Therefore, our program analyses, and the system we put in place for such analyses, must be able to accommodate more mission-based goals, which are not so reliant on publications but that instead measure progress in terms of real impact for families.



Table 7. Survey of Metrics used by other Foundations

Organization	General Metrics	Mission Specific Metrics
American Cancer Society	Publications	Generation of therapeutic targets
American Heart Association	Number	Drugs entering clinical trials
Avon Foundation	Impact	Collaborative work among scientists
Christopher & Dana Reeve Foundation*	Citations	Changes to existing treatment modalities
Damon Runyon Cancer Research Foundation*	Speed to publish	Product development
Doris Duke Charitable Foundation	Presentations	Clinical guidelines
Fragile X Association*	Abstracts	Improvement in patient quality of life
Gates Foundation*	Lectures	Prevention of disease morbidity
The Leukemia & Lymphoma Society	Leveraged funding	Continuous research activities
Myelin Repair Foundation*	Government (NIH)	Economic benefit
	Private	Program perception
	Researcher training	
	Career development/Retention	
	Patents	

*Organizations that use milestone criteria in the grant/program evaluation

Table 8. Measuring the impact of grants: a survey of program evaluation metrics by funding agency

Source	General metrics	Mission-specific metrics
Douglas Landsman, Ph.D., Christopher & Dana Reeve Foundation	1. Publications (number) 2. Further funding	1. New scientists entering the field 2. Intangibles e.g., grant stimulated a lifelong interest in the field
Yung Lie, Ph.D., Damon Runyon Cancer Research Foundation	1. Further funding (R01) 2. Time to R01 3. Publications 4. Presentations (seminars, abstracts)	
Michael Tranfaglia, Ph.D., The Fragile X Research Foundation	1. Publications (impact factor, speed to publish)	1. New scientists entering the field 2. Generation of therapeutic targets 3. Collaborations with established scientists
Marc Hurlbert, Ph.D., Avon Foundation	1. Training (publications and funding) 2. Further funding	1. Generation of new knowledge in the field 2. Therapeutic targets 3. Drug candidates going into clinical trials
Bart Kamen, Ph.D., The Leukemia & Lymphoma Society	1. Career development 2. Training (trainee publications)	1. New scientists entering/remaining in field 2. Changes to existing treatment modalities
Betsy Myers, Ph.D., Doris Duke Charitable Foundation (via email)	1. Publications 2. Career development 3. Further funding 4. Presentations 5. Training (number of trainees)	
Melanie Turner, Ph.D., The American Heart Association	1. Career development 2. Further funding 3. Publications 4. Presentations (abstracts)	
TJ Koerner, Ph.D., The American Cancer Society	1. Career development 2. Patents	
Carol Menaken, Myelin Repair Foundation	1. Patents	1. Therapeutic targets



Our vision for autism scientists is one of communication, cooperation and collaboration. Of particular use to scientists new to autism is that our staff work proactively to connect them with other researchers so that expertise can be shared. In addition to this, through the post-grants system, we hope to collect and distribute information on the tangibles of our funded grants beyond just publications and leveraged funding. ROI data on reagents (antibodies, cell lines, animal models, samples, etc) and other research tools developed (diagnostic and intervention protocols, medical and analytic devices, etc) will be collected, annotated on our web pages, and made more readily available to other researchers by virtue of including stipulations for open-access to unique research resources created with Autism Speaks' funding. At the same time, we hope to promote communication in the autism research community by allowing autism scientists to post open research positions in their laboratories on our website, and potentially even look through our list of fellows for possible candidates. By assisting our research community, this will aid retention of trained researchers in autism by facilitating the difficult and time-intensive job search. Importantly, we are expanding communication and development beyond the research community into the lay community by making it obligatory to deposit peer-reviewed research publications funded by Autism Speaks into the publicly-accessible data warehouse PubMed Central. In doing so, we hope to make biomedical research of the highest quality within reach of the entire autism community such that anyone can benefit from the information, perhaps our overall greatest ROI. We will become the first public advocacy organization in the United States to require this of our grantees.

Finally, most agree that knowing the results of a failed experiment or clinical trial will point to improvements in experimental design and lead to better hypotheses. However, negative data are almost never reported, and much less published. Consider how much effort and resources would be saved by not repeating failed experiments or pursuing already tested hypotheses. Autism Speaks will lead the field by asking for results/conclusions from grants that have failed to produce peer-reviewed publications to be made available to other autism researchers via our website.

Responsibilities for changing times

The widening economic crisis will likely affect charitable giving and attitudes toward stewardship. Donations could diminish while at the same time our donors will hold us even more accountable. Thus, our grant program must not only be effective but also efficient. Because we work under the auspices of generosity, we must always strive to waste little and maximize impact. The increasing interest shown by our stakeholders in our activities dictates responsiveness and transparency; it is because of them and through them that we do our work. In conclusion, to be effective, efficient, responsive and transparent our grant program requires periodic, if not constant, evaluation.



PART THREE: AS' SCIENCE INITIATIVES & PROGRAMS

ETIOLOGY PORTFOLIO

Genetics (Andy Shih, Ph.D., Vice President)

Autism Speaks has a well-balanced portfolio in genetics research. In addition to supporting such diverse approaches as the copy-number variation (CNV), homozygosity-mapping in special populations and “model” autism-related genetic disorders such as Fragile X and Rett, we have substantial investment in the Autism Genome Project (AGP), an international consortium of research pursuing novel strategies to integrate genome-wide association analyses (GWAS) and CNV analyses in the identification of ASD genetic risk factors.

AGP Phase One assembled the 1200 multiplex autism families, whereas AGP Phase Two is assembling a complementary sample of trios (two parents and one child with autism). Given the growing evidence that multiplex families may have a different pattern of inheritance as compared to singletons, each sample will be useful for study. Over the past few years, AGP investments have started to generate returns where several lines of converging evidence (e.g., AGP finding neurexin; Christian/Daly/Scherer on ch16p) are reshaping our thinking about the field. Enabled by the largest autism dataset currently available, the AGP is particularly well positioned to systematically explore and evaluate new genetic mechanisms and replicate/validate findings reported by other researchers. Their integrated association/CNV strategy seems likely to yield the identification of additional genetic risk factors in the next 18-24 months, which will point to new scientific opportunities and research directions, such as facilitating explorations of gene-environment interactions within the Baby Sibs Research Consortium (see below) and the development of animal models.

In the coming years, the AGP also intends to translate their findings to influence clinical practices. The development of DNA-based tests to identify at-risk individuals, for instance, would involve epidemiologic efforts to assess the frequency of risk alleles across various populations. Fortunately, the foundation for such activities had already been laid with the International Autism Epidemiology Network (see below), as well as established international partnerships in Qatar and Mexico.

Finally, since multiple genetic mechanisms are likely to result in DNA modifications and variations, including those due to environmental influences, more emphasis will be placed on exploring epigenetics, microRNA and other possibilities.

Autism Epidemiology Initiative (Michael Rosanoff, M.PH. Asst. Director)

Autism Speaks and the Centers for Disease Control (CDC) co-developed the International Autism Epidemiology Network (IAEN) to obtain credible estimates of autism prevalence worldwide through the development of epidemiological research collaborations around the world. By helping standardize epidemiologic methodology when possible, autism prevalence can be compared across territories, informing public health policy and facilitating new research opportunities. With participants from over 30 countries, this initiative and the resulting findings have the potential to significantly enhance our understanding of autism etiology and natural history by examining similarities and differences in relevant genetic and environmental factors around the world.



Divided into workgroups based on the varying levels of research and service capacity as well as public health infrastructure within different countries, IAEN is moving forward in developing three different projects. An RFA was posted in 2008 that focuses on countries that can take an epidemiologic approach involving the systematic review of medical, educational, and service records to obtain a population-based estimate of autism prevalence. We are also exploring the development of an international research consortium of developing/low-resource countries for which the most feasible approach to obtaining prevalence estimates is through widespread screening or community canvassing. A third approach, and perhaps one that is more likely to yield valuable information in the nearer term, involves countries that maintain large, population-based health registries. By the linking of these registries into a “registry of registries,” a multi-national virtual database could be formed to tackle ambitious research projects such as possible associations between pre- and peri-natal environmental factors and autism.

Environmental Factors in Autism Initiative (Alycia Halladay, Ph.D., Director)

Prior to the merger of Autism Speaks with CAN and NAAR in 2006 and 2007, each organization was funding research investigating the environmental and genetic influences in autism. However, there has been very little funding for projects which involve the interaction of genetics and environmental exposures, how genetics may predispose or sensitize a person for a later environmental exposure, and how environmental contributions may affect genetic expression, or “epigenetics.” For example, CAN conferred an “environmental innovator award” to Isaac Pessah in 2005 which provided funding to an excellent researcher to conduct cutting edge research the biological impact of environmental exposures. Likewise, NAAR invested almost \$1million in investigator initiated awards, including environmental epidemiological studies. From 1994-2007, Autism Speaks invested over \$10 million toward research on environmental factors in ASD. These applications included those that directly examined effects of toxicant exposure on behavior in animals, mechanisms related to toxicant exposure, and epidemiological studies focused on environmental factors. It also includes funding on downstream effects of potential neurotoxicant exposure, or systems-based susceptibility factors, such as immune system function and capacity of the neuron to adjust to oxidative stress. Such funding in the area of environmental factors has increased the amount of research supported, as well as the number of scientists who are interested in studying ASD. Also, because of the pilot money available to researchers in this area, many of these researchers have converted these projects into larger scale programs funded by the National Institutes of Health, including ones that were instrumental in competing for the NIH Autism Centers of Excellence Awards.

In order to facilitate research on environmental science, in 2008 a special RFA was released through AS’ Environmental Factors in Autism Initiative that targeted a wide range of environmental exposures, including, but not limited to, pre- and post-natal pharmaceutical and chemical exposures, study of vaccines in animal models and medically-vulnerable populations, and conditions during the pre- and early post-natal environments that may affect child development. The organization received 60 applications which were evaluated by peers in the scientific community. This RFA was suggested by a special environmental sciences advisory committee, comprised of Autism Speaks staff and outside scientists, which met in 2008 for the purpose of developing a strategy for promoting 2008 research on environmental factors in ASD. In September of 2008, it was announced that 12 grants were funded for at total of \$3.6 million. They focused on epigenetics, the immune system, oxidative stress, the gene-environment interactions related to effects of vaccines, as well as gene x environment interactions examining novel exposures. This number is not included in the \$10 million mentioned above.



In addition to funding projects and workshops, a goal of the Environmental Factors in Autism Initiative is to explore partnership opportunities, particularly the use of existing cohorts to study gene-environment interactions in autism, and to encourage meetings of experts to develop strategies for studying gene-environment interactions. By building on expertise in other areas of research, scientists who do not study autism directly may participate and share their ideas in an informal setting. As a result, a special “meetings and workgroups” mechanism was set up. As a result of support for symposium and meeting support, a workshop was hosted October 2008 at the 25th Annual Neurotoxicology Meeting in Rochester, NY. The focus was the use of animal models to study gene x environment interactions to isolate mechanism of action of different toxicants. Because over 200 neurotoxicologists were present for the 3 day meeting, this was an opportunity to gain access to their expertise as well as provide a venue for them to share their findings with a larger audience. The meeting symposium will be documented in a future issue of the journal *Neurotoxicology*.

Autism Speaks possesses the unique ability to bring together researchers with similar research interests and support collaborative projects. This was evident in the example of the Autism Genome Project. Likewise, since 2003, Autism Speaks has been actively managing and supporting the collaborative activities of the High Risk Baby Siblings Research Consortium (BSRC; more details provided later in the document). While NIH is very active in fostering individual ideas, Autism Speaks has historically encouraged these groups to work together to help solve problems where smaller groups provide non-definitive answers. Using past successes, as well as a memorandum of agreement signed by investigators regarding how to work together collaboratively, the BSRC serves as an important resource. One way in particular is through the utilization of their extensive clinical expertise to collaborate with outside researchers to identify potential genetic and environmental mediators of disease onset and severity. Such collaborations will be important, but because of their complexity, need for outside advisors, and nature of labor-intensive data coordination, such endeavors may require AS investment to ensure their success and provide incentive for timely project completion.

Genetic and Environmental Contributions to Risk for Autism Project (GECRA). In 2007, Autism Speaks solicited a proposal to study genetic and environmental contributions to risk for autism from the BSRC (to be discussed below), a group of 22 investigators at 19 research sites that have been collecting data on high-risk infants for over a decade. To date, together, the BSRC has recruited and evaluated close to 2000 high-risk sibs and expects to recruit about another 500 per year for the next five years. In 2008 the “GECRA” project– “Genetic and Environmental Contributions to the Risk of Autism” – was established, with a Steering Committee comprised of Lonnie Zwaigenbaum, Helen Tager Flusberg and Ezra Susser. After a feasibility study and successful meeting in June of 2008, the group identified several timely hypotheses that could be feasibly addressed within the BSRC. These will become part of a larger Autism Speaks proposal to study genetic and environmental contributions to ASD risk. Potential risk indices that have been proposed for study include the following: Chromosomal and genetic mutations, copy number variants, common SNP variants, mitochondrial mutations, vaccine uptake, maternal immune dysfunction, maternal and paternal age, gender of infant, low birth weight, gestational age, environmental exposures, pre- and peri-natal risk factors, accelerated head growth, and specific early behavioral/motor signs. The goal is to determine the factors which are best identified through a high-risk cohort where early and intense phenotyping from birth to age 3-4 years can be most effectively correlated or linked with environmental or biological data. While the baby sibs consortium is uniquely poised to answer some of these questions (i.e. vaccinations and pre- and peri-natal risk factors), it also has the advantage of continued access to the families to provide information dissemination to those involved, and as a group, can share the challenges and successes of working in a multi-disciplinary environment.



IBIS-EARLI Collaborative Study. The IBIS-EARLI Collaborative Study, funded by a generous donation from the Gund Foundation, is a collaboration of seven US research institutions representing two major NIH-funded autism centers for excellence networks. The IBIS (Infant Brain Imaging Study) network is led by Dr. Joseph Piven at the University of North Carolina and is focused on brain development using imaging techniques in high-risk siblings as well as low-risk sibs. High risk infant sibs are recruited at 6 months and screened using standard instruments. They are brought back for additional assessment and imaging at 12 and 24 months of age. The EARLI network (Early Autism Risk Longitudinal Investigation), led by Dr. Craig Newschaffer of Drexel University, is recruiting and tracking women with one child affected with autism through their subsequent pregnancies to identify genetic and environmental contributions, interactions, and correlations of the two in a prospective design. Collectively, the networks hope to recruit 1750 children and expect 1500 to complete their studies. The focus of this collaboration will be examining gene-environment interactions and genetic and environmental factors related to developmental trajectory, including trajectory of brain development in ASD. In April of 2008, the principal investigators of the two component networks, along with representatives from Autism Speaks, NICHD and NIEHS, gathered in Washington, DC to discuss the design and logistics of this collaborative study.

Each of these networks receives federal support to prospectively study infants with an older sibling affected with autism. The Gordon and Laura Gund Foundation leveraged the NIH-funded infrastructure to provide a unique and ground-breaking collaborative effort to address genetic and environmental risk factors for autism. This effort will entail (1) combining the two large NIH-funded infant sibling networks to create a sample of 1700 (with an attrition estimate at 1500) at-risk and low-risk infants, (2) adding genetic and environmental exposure measures to the data collection, and (3) ensuring that both sites are collecting information in a parallel manner at congruous time points. The generous gift from the Gund Foundation will support collection of the additional measures and data coordination across the centers, improve the power of the findings, and allow the researchers to conduct interim and final analyses which include endpoints not previously possible.

BIOLOGY PORTFOLIO (Sophia Colamarino, Ph.D., Vice President)

With the exception of the 10-20% of cases in which a specific genetic etiology is known, autism is a biological disorder that is currently defined in terms of a specific behavioral profile. Many advances have been made in characterizing the particular behaviors that define autism, but the underlying pathobiology resulting in those behaviors is still poorly understood. In order to design the most targeted treatments, we need to understand the biological bases of autism. In fact, regardless of the different causes of autism, knowledge of the disrupted biochemical pathways will be what ultimately allows scientists to design specific treatments to overcome them. Moreover, any attempt to explain the underlying biology of autism must also take into account that, in some individuals, autism is not necessarily just a brain disorder. A systems approach is needed to study the overall body physiology.

The Biology Portfolio is designed to encompass grants and initiatives in the areas of neurosciences, physiology and molecular biology, among others, and is intended to understand the underlying biological mechanisms that generate the features of autism. The portfolio promotes research that characterizes *all* levels of impairment, from behavioral to cellular to molecular. Current initiatives in this portfolio include the Brain Development Initiative (which also utilizes Autism Speaks' Autism Tissue Program), two of our High Risk-High Impact Initiative projects, and the many biology research conferences being organized or sponsored by Autism Speaks.



Brain Development Initiative (BDI)

Neuropathology and Brain Development. As a direct result of our Brain Development Initiative and feedback from scientists at our 2005 White Matter Think Tank, in 2006 Autism Speaks formed a collaborative neuropathology workgroup to look more directly at how the brains of individuals with autism develop.

The Neuropathology Workgroup is a collaborative effort that combines unbiased stereology with modern molecular neuropathology to directly examine the frontal lobes of individuals with autism. The goal is to reveal what accounts for the structural and functional abnormalities, including the brain enlargement and white matter volume increases that have been observed by so many previous brain imaging studies. The workgroup, led by Dr. Eric Courchesne, Ph.D., University of California, San Diego, represents a partnership across multiple institutes/organizations, bringing together researchers with different expertise, many of whom have never worked together before. The workgroup will be cohesively characterizing several parameters, including neuron numbers and the presence of abnormalities in laminar patterns, minicolumns, neuroinflammatory cells, and axonal characteristics. The Autism Tissue Program, overseen by Drs. Jane Pickett and Daniel Lightfoot, provides critical resources for this collaboration.

Gene Expression and Brain Development. In Spring 2008, Autism Speaks expanded its neuropathology efforts by providing additional support through the BDI to allow Dr. Courchesne and the Allen Institute for Brain Science in Seattle, Washington, to carry out a screen of molecular markers to characterize the development of the frontal lobe in individuals with autism. Autism Speaks believes that leveraging the technologies of others is key to rapid progress in understanding the biology of autism, and this collaboration, organized by Autism Speaks, represents the first time the Allen Institute is applying its expertise to any particular disease population. An initial panel of 25 genes has been selected for their ability to demarcate laminar organization of specific cell populations in the human frontal lobe and the first hybridization runs are scheduled for Winter 2009 after the brain samples pass quality control.

Targeted Research Conferences

Beyond funding individual research projects, another major activity of the Biology Portfolio is to promote collaboration through scientific meetings. They provide the venue for exchange of ideas and collaborative thought. Such meetings energize research efforts by encouraging sharing, expanding the research community, and ensuring scientists regularly gain knowledge of autism. A selection of the most recent Biology Portfolio organized or sponsored meetings includes: The Autism and Immunology Workshop (the first of its kind), The Shared Neurobiology of Autism and Related Disorders Conference (co-sponsored with FraX, RSF and other advocacy organizations), a conference on Neurocognitive Development and Autism: The Mirror Neuron Hypothesis (co-sponsored with NSF), a weeklong Workshop on Autism Spectrum Disorders (held at Cold Spring Harbor Laboratories), a conference on Cortical Modularity in Autism (co-organized by the Autism Tissue Program), Mouse Behavior Workshop in Baltimore, and an international meeting on the Neurobiology of Autism (co-sponsored by the Wellcome Trust). A full listing of scientific conferences can be found at <http://www.autismspeaks.org/science/scientificmeetings/index.php>



DIAGNOSIS AND PHENOTYPING PORTFOLIO (Alycia Halladay, Ph.D., Director)

The high risk baby siblings research consortium (BSRC) was established in 2003 as a collaboration between NICHD and NAAR, and has flourished for many years due to the productivity of the individual members, strong leadership, and recognition that groups “at risk” for autism provide one of the best ways to study early precursors of behavior, biological risk markers, and methods for improving developmental outcomes. In 2007 the group published over 53 articles in peer reviewed journals and obtained 26 grants outside Autism Speaks to support their research. Autism Speaks provides the opportunity for these investigators to maintain regular contact through teleconferences, meetings and supports collaborative studies which bring together data and intellectual power from all consortium members.

The researchers recruit families with siblings as young as 1 month of age and some follow the children to 7-8 years old. As mentioned earlier, this group is comprised of 22 researchers at 19 institutions across the US, Canada and Israel, with a parallel group forming in the UK. This group has made significant accomplishments since its inception, including a multi-site study of atypical head circumference as a risk factor for ASD. These results will be published and the implications for utilizing this biological marker in diagnosis will be highlighted. Preliminary results on the head circumference project were presented at IMFAR this year.

In addition, in the last 2 years, the BSRC has published 2 articles in the *Journal of Autism and Developmental Disorders* regarding methodological issues involved in high risk ASD samples, and has edited a special issue of this journal, which provided an overview of the research these sites are undertaking (from behavioral, to biological, to intervention and treatment). Finally, as a follow up to the 2007 *Pediatrics* paper which outlined recommendations to clinicians for identifying and managing children with autism, the BSRC published a paper focused on recommendations for monitoring, evaluation, and treatment of high risk infants. It is expected this will make a major impact on standards of care and practice guidelines for infants at risk for ASD.

Currently, the group has just undertaken a consortium wide effort to examine variables that affect developmental trajectory and outcome. One of the central goals of research investigating infant siblings of probands with ASD is to understand the range of outcomes they experience (e.g., ASDs, speech and language delays, other developmental conditions). Infant and family factors may influence the range of developmental outcomes. At present, the best data about developmental outcomes of later born siblings are derived from family genetic studies, most of which were conducted in the 1980s and early 1990s. However, given recent shifts in the epidemiology of autism and related ASDs, these relative risk figures may have changed significantly. It is important to examine how specific risk factors - including proband and infant sibling sex, number of affected family members, and functioning level of the proband - influence the range of developmental outcomes in the infant siblings. Because most sites did not collect community-based epidemiological samples and self-selection and other ascertainment biases are likely, the data cannot be used to estimate recurrence risk. However, the BSRC will examine how factors such as age of the infant sibling at enrollment and age of onset of symptoms impact developmental outcome rates.

It is important to note that while individual research projects have been funded by NIH, the investment in the consortium by AS has been small and most of the work completed has been done voluntarily or with minimal investment. This group of researchers is extremely efficient in their use of time and resources, and the collaborative projects completed or in progress would not be possible without both



outside funding from Autism Speaks, and the dedication of these researchers to work together enthusiastically and productively, to design projects which will answer many questions that are of importance to both families and progress in research.

NIH National Children's Study Partnership

The National Children's Study (NCS) is a project which was authorized in 2000 but did not receive ample funding until 2006 to set up over 105 study centers across the US. The main goal of the project is to investigate the influences of environmental and genetic factors on the health and neurodevelopment of more than 100,000 children in the U.S. followed prospectively from pregnancy through age 18. Autism Speaks sought to capitalize on this study to examine factors related to risk and outcome in ASD. Using the intellectual strengths of scientists involved with Autism Speaks and their intense knowledge on issues related to phenotyping, early identification, and methodology, we have assembled an expert working group to advise the National Children's Study in helping determine the best and most cost effective methods to diagnose autism within a screen positive group or subgroups of individuals at each site which screen positive and negative. This is only an example of the many possibilities that will be discussed with the initial teleconference of the advisory group in mid November 2008. Because of the design of the NCS and the wide array of biological, psychological, developmental and environmental exposure variables collected via both urban and rural study sites, there are a multitude of opportunities that exist by partnering with this ongoing NICHD/CDC/EPA funded project. The initial goals of the workgroup are to 1) introduce the NCS leadership and several ASD experts, 2) integrate experts in epidemiology and biomaterial collection to assist in how the intense biological assessment may enhance autism diagnosis, and 3) potentially use this study as a way to examine autism behavior in a population based epidemiological design. Autism Speaks has invited epidemiologists and leaders of NCS study centers with familiarity in autism research to help guide this initiative, with the ultimate goal of improving the study protocol for the NCS to include autism as a reliable endpoint and to use the NCS as a platform for other autism-specific studies.

PREVENTION AND TREATMENT PORTFOLIO (Clara Lajonchere, Ph.D., Vice President)

Clinical Trials Network (CTN) (Nancy Jones, Ph.D., Director)

The CTN was created as part of ongoing efforts to accelerate autism research. The CTN is comprised of clinical and research centers collaborating on multi-site, single protocol clinical trials, which enable researchers to reach recruitment goals in a much shorter amount of time. This leads to faster results for the autism community, including the ability to expedite FDA approval of drugs with indications for the core symptoms of autism.

The CTN was established in 2005 through a Treatment Initiative grant to bring together leading experts in clinical trials and autism. From its conception, the CTN assembled a collaborative group of experts both from large, NIH-funded academic institutions, and community-based clinics with significant outreach and service to the community.

The CTN contributes to the mission of the science department by providing a vehicle for translational research. The CTN provides infrastructure and expertise for large scale studies (17 sites or more), which increases our ability to rapidly and rigorously evaluate current treatments including off-label medications and nutritional supplements currently taken for ASD. The participating members' expertise



with both autism and clinical trials also provides an opportunity to test combined therapies of behavioral interventions with pharmaceuticals/nutraceuticals. The CTN's major advantage is that it can serve as a platform for companies interested in testing novel compounds, which provides a motivation for these companies to become involved with autism trials.

Current Trials. The memantine trial is a randomized, placebo-controlled trial evaluating the effects of memantine on motor planning and expressive language in children with autism. While this FDA approved Alzheimer drug is used "off-label" for autism, its use in autism has not been systematically and rigorously examined. The study involves eight of the participating CTN member sites and will include 60 children with autism ages 6-12. As with all studies of memantine, the study is currently on clinical hold by the FDA while additional safety data are gathered from the manufacturer, Forest Laboratories.

The Study of Fluoxetine in Autism (SOFIA) is the first industry-sponsored trial with specialty pharmaceutical company, Neuropharm. Fluoxetine (Prozac) is a well-known SSRI used for depression, Obsessive-compulsive disorder and other Central Nervous System disorders. The study will evaluate the efficacy of Neuropharm's specialty formulation for reducing stereotyped and repetitive behaviors in 128 children and adolescents with autism ages 5-17. The study also provides an 18-month open label extension where families will have access to the study drug before it goes on the market. The study is significant in that the study sponsor is seeking an FDA indication for Autistic Disorder thereby providing one of the first medications to be FDA-approved to target core symptoms of autism.

The CTN can be a vital component of a robust pharmacology portfolio. To fully accelerate the development of therapeutics for autism, research must be focused on both the pre-clinical and clinical stages of the drug pipeline. Pre-clinical research collaborations can be developed through pilot and clinical grant mechanisms. Smaller investigator-initiated, multi-site trials can be supported through special Treatment RFAs. The CTN complements the grant portfolio by providing a mechanism for large scale studies particularly pivotal Phase III and Phase IV studies seeking FDA indications.

An important current short term goal for the CTN is to ensure the success of the first two clinical trials. Measures of success in three to five years would include the successful completion of the memantine study, and the leveraging of the initial grant investment for large scale government funding. The most impactful outcome from the current trials would be FDA approval of fluoxetine for the treatment of repetitive behaviors in autism.

The current goals for the CTN include developing new collaborations with pharmaceutical and nutraceutical companies to promote research of novel compounds for autism and the development of CAM treatments. To maximize the advantages of the CTN, it would be strategic to partner with companies who have drugs in Phase II or Phase III of clinical development. Another approach is to interest pharmaceutical companies in pursuing autism indications for existing FDA-approved drugs or to develop new formulations for their existing compounds. Companies who have expressed interest in working with autism or Autism Speaks include Abbot, Targacept, Pfizer, Eli Lilly, and Martek.

Autism Treatment Network (ATN) (Nancy Jones, Program Director)

The ATN is a collaboration of clinicians at major hospitals and medical centers dedicated to providing comprehensive medical care for children and adolescents with autism. The mission of the ATN is improving medical care and creating clinical consensus standards for care of those individuals. Bringing



together a network of experts at major medical facilities also provides the platform for externally-based clinical research that directly supports the ATN mission by providing evidence for the clinical care consensus standards and rigorously testing treatment protocols. The goals of the ATN are: (1) to develop a common protocol for multidisciplinary assessment and follow-up of children with autism – with common domains and measures, (2) to characterize the autism population and to track care and outcomes, (3) to create a patient registry, and 4) to develop and disseminate evidence-based practice parameters for physicians and other health care providers nationwide. The ATN is comprised of fifteen medical centers across the United States and in Canada. Oversight and program management is provided by the Autism Speaks program staff.

The Clinical Coordinating Center (CCC), currently hosted at Massachusetts General Hospital, provides the medical leadership for the participating members and includes the Director of the CCC, the Medical Director and the CCC Coordinator. The Data Coordinating Center is the EMMES Corporation, which provides statistical analyses and administrative support. It also hosts the enrollment systems and the databases for ATN custom forms through its propriety system, Advantage EDC. The EMMES Corporation works cooperatively with the Autism Speaks ISAAC staff, responsible for managing the ISAAC database which is used to collect data from copyrighted assessments.

The fifteen participating sites have institutional commitment to support a multidisciplinary care model. All sites must minimally have a collaborative team including pediatricians, psychologists, pediatric neurologists, gastroenterologists, sleep specialists, genetic/metabolic specialists, and access to ancillary care services. All sites also have access to other specialized services such as immunology, pain management, and dentistry. The key component of the ATN model is that access to care is managed and coordinated for the family.

Patient Registry. The patient registry includes de-identified data collected on clinical assessments required in the ATN battery for children and adolescents ages 3-17. Data are collected at baseline and for all subsequent clinical visits with the lead clinician responsible for managing the child's care. For sites that do not currently have regular follow up, data are collected minimally for an annual follow up. Data on specialty referrals are also captured in the database. The data are collected through two systems. Enrollment and ATN custom forms are collected via the Advantage EDC system hosted by EMMES. Copyrighted assessments are collected via ISAAC. Data collected via ISAAC are transferred to EMMES for data quality checking and analysis.

Current Goals. The Autism Treatment Network (ATN) is part of the portfolio of Research Resources and Clinical Programs. The goals for the network include four major areas: network growth, access to services, standard setting, and outreach/training. A core goal for the network is the development of clinical consensus standards in each of the ATN specialty areas: overall management of care for autism, GI, sleep, neurology, and behavioral sciences. As part of their network activity, the participating specialist will develop toolkits, and standards for referrals and for treating specific issues based in part on their own clinical experience and information from the registry. To provide rigorous support for these standards, the participating researchers will also be encouraged to develop externally funded clinical and treatment research projects. This component of the ATN will be overseen by the Chief Science Officer with advisory oversight of the SAC. A major goal for the network is to maximize the treatment portfolio by developing RFAs to provide opportunities for ATN-based research.

In 2008, the ATN received a \$12M grant from the Health Resources and Services Administration (HRSA) to develop an Autism Intervention Research Network for Physical Care (AIR-P) using the ATN



platform over the course of 3 years. The successful development of a functional network comprised of leaders in research and clinical care for children with ASD allows the ATN to serve as a platform for translational research. The AIR-P award will help support the development of collaborative research projects across the network in the areas of sleep, diet and nutrition, and will also leverage the collective expertise to develop standards of care and practice guidelines for the medical community.

There are two major goals for the bioinformatics component of the ATN. The first medium-term goal is to bring the Data Coordinating Center completely in-house at Autism Speaks. This goal requires: (1) staffing improvements, including more staff for data management and staff with expertise in biostatistics and (2) improvements in the data system to meet the needs of collecting data on long, potentially complex medical forms. The third longer term goal, is to integrate and coordinate the ATN database with other data management systems for a unified approach for all science programs.

Toddler Treatment Network (Alycia Halladay, Ph.D. Associate Director)

In addition to medical and pharmacological studies to improve treatment strategies for those affected with autism, Autism Speaks has invested in examining the efficacy of early intervention – prior to diagnosis, for those “at risk” for developing the disorder. Most of these paradigms involve manualized intervention strategies targeting early social and communication development that can be implemented in the clinic and at home and that teach parents skills to be used in all settings to improve functioning. In 2006, Autism Speaks issued an RFA which invited applications to study different intervention paradigms from age 12-24 months. Out of these projects that were funded (7 projects at \$6.1 million), the Toddler Treatment Network was born. This network consists of over 26 PIs and CO-PIs at 17 research institutions nationwide. In March of 2006 and February of 2007, these groups convened to discuss how they could best work together in light of disparate projects and funding sources. At these meetings, it was recognized that there are common baseline and outcome measures that groups are using, and it was agreed that such network activity could lead to further understanding in this order. In addition, all studies are using a parent-mediated intervention tool to minimize cost, provide training to the parent for use in a more comprehensive setting, and reduce burdensome treatment time. The goals of this network are to: (1) improve the methodology for improving outcomes for children and their families; (2) define best practices for designing and implanting parent-delivered interventions; (3) improve research design and analytic approaches; (4) facilitate young researchers to develop programs; and (5) disseminate these findings and best practices to the community where they can be utilized on a larger scale by school systems, other research studies, state and local government agencies, psychologists, physicians, educators, occupational therapists, and speech-language therapists. The role of AS in the development of this program has been twofold: first, to fund investigator-initiated, peer-reviewed applications through an RFA mechanism, then to ensure communication among the participants to solve problems, standardize measures, and set up the projects for collaborative analyses at a later date.

Innovative Technology for Autism Initiative (Sophia Colamarino, Ph.D., Vice President)

Improving the lives of individuals *currently* affected by autism is a priority for Autism Speaks. Autism Speaks’ Innovative Technology for Autism (ITA) Initiative facilitates the development of technology that can assist individuals with autism, their families and their caregivers. Its primary mission is to encourage applied research that adapts the use of available technologies or spurs the development of new ones, for the benefit of the autism community. ITA supports interdisciplinary project teams by encouraging



collaboration among technology design teams and clinical researchers. ITA activities include funding internship programs, classes, and interdisciplinary conferences to motivate talented R & D engineers and computing experts to begin investigating and designing more specifically for the needs of people affected by autism.

Current ITA funded projects involve development of tools to help individuals with autism live more independently by, for instance, providing structured reminders of daily tasks, or promoting personal care and household task management for teens with autism transitioning out of school. ITA is also committed to enabling new interventions that utilize technology. While most ITA projects focus on treatment and assistance with daily living, ITA also funds projects that enable earlier and more accurate diagnosis of autism by developing innovative technologies that may automatically detect characteristic speech patterns or capture nuances in behavior that are too subtle or complex for human observers to document.

HIGH RISK - HIGH IMPACT INITIATIVE (Sophia Colamarino, Ph. D., Vice President; Leanne Chukoskie, Program Director)

For any research organization, diversification along several dimensions, including discipline and modes of support, is essential to avoid reliance on any one decision-making strategy. The inherent uncertainties of scientific discovery suggest that a program may do best by creating a balanced and varied portfolio of project types, including both mainstream and higher risk or understudies areas of research. Therefore, to support unusual or higher risk investments with the potential to produce major scientific breakthroughs, Autism Speaks currently supports a High Risk-High Impact Initiative (HRHI).

The HRHI Initiative, currently headed by Dr. Sophia Colamarino, is being designed to proactively organize and support projects that have a potential for high reward if placed on a "fast track" and given a high level of financial commitment through formation of collaborative research workgroups. This initiative aims to support cutting edge research in areas that are under-investigated or could benefit substantially by bringing in outside experts to elevate quality and, most importantly, progress.

High impact areas were identified by an AS-appointed HRHI Steering Committee, an advisory committee that includes outside experts, stakeholders, and AS science staff. The areas recommended by the HRHI committee in 2008 included (1) investigating the poorly-understood but special cognitive abilities of individuals who do not use spoken language, (2) early intervention for non-verbal children with ASD, (3) mitochondrial dysfunction, (4) methods for rapid acquisition of functional neuroimaging data, and (5) methods to rapidly increase sample sizes for genetic studies. Summit meetings of a small number of researchers, both in and out of the field of autism, took place in the first half of 2008 to discuss the state of research in each area. Following these initial meetings, promising areas of research and appropriate, interested investigators were identified to carry forward projects. Research proposals were then generated by the investigators for internal and external review. The proposals were subsequently evaluated by the AS Scientific Review Panel which made final recommendations for funding to the Board of Directors. In 2009, it is anticipated that additional areas of study will be identified by the HRHI committee for consideration.

CLINICAL PROGRAMS (Clara Lajonchere, Ph.D., Vice President)

AGRE and the ATP are two key programs that support and accelerate basic science research by providing critical biomaterials (DNA, cell lines, plasma, serum, brain tissue), and genetic and phenotype data



to qualified researchers to support their investigations in autism. These programs have yielded 135 and 55 peer-reviewed papers, respectively, and together support over 200 researchers worldwide.

Autism Genetic Resource Exchange (AGRE)

The AGRE program was founded in 1997 by parents, scientists, and clinicians who felt that in order to facilitate more rapid progress in the identification of the genetic underpinnings of autism spectrum disorders, they needed to collect critical phenotypic and genetic information from families with autism and make these data available to the scientific community. AGRE is a DNA repository and family registry, housing a database of genotypic and phenotypic information that is available to autism researchers worldwide. To date, AGRE has enrolled 1,720 families into the program, over 92% multiplex. Of these families, 1,020 are available for researcher use. This complements efforts of other large scale research programs (i.e. Simons Simplex Collection) that focus on families with only one affected child. The program is participating in several NIH-funded studies, all of which serve to increase the depth and breadth of data made available to researchers. AGRE also serves as a mechanism for collaborations with other academic investigators through co-recruitment efforts or to obtain additional data points on existing families. The fact that families indicate a willingness to be re-contacted for other projects offers researchers across a variety of disciplines a vehicle to re-canvass well-characterized families for additional information or to acquire additional specimens.

Over the next 5 years, through a large multidisciplinary collaboration, AGRE will be doubling the number of families in the resource and will be collecting data on environmental exposure, quantitative craniofacial morphometry, air pollution, imaging and finer-grained genetic analyses. In addition, AGRE will boast the largest collection of well-characterized autism twin pairs, both concordant and discordant for autism, ever used in research. Using an expanded phenotype battery, AGRE hopes to meet the emerging needs of science by offering more information on unaffected family members (parents and siblings) to better understand the broader autism phenotype. With the increase in the number of genetic findings in the last few years, it is important to understand the clinical implications of recent genetic findings. AGRE hopes to work collaboratively with experts across a variety of disciplines (clinical genetics, medicine, neuroscience) to develop potential screening and treatment guidelines for families.

Autism Tissue Program (ATP) (Jane Pickett, Ph.D., Director, Brain Resources and Data; Daniel Lightfoot, Ph.D., Program Director)

Similarly, the ATP continues to provide high quality brain tissue to many qualified researchers worldwide who are seeking to understand how and why the brain is different in individuals with autism. Since its inception in 1998, more than 130 families have donated brain tissue and over 80 research projects are now underway that would not have been possible without this resource. The ATP works to increase awareness about the importance of brain donation worldwide. Using brain tissue, scientists can go far beyond the constraints of other technologies and study autism on both a cellular and molecular level. The ATP maintains a website and donor hotline, coordinates tissue donation and distribution to researchers, and maintains a web-based portal for data and information.

There are over 6,000 families currently registered with the ATP, and Autism Speaks' national reach increases awareness among our constituents. The ATP currently maintains an inventory of 101 brains, 90 autism brains (includes relatives), 7 brains from families with chromosome 15q duplications, 3 control brains, and 1 autism brain in the UK. The ATP just recently expanded to the UK where it received permission from its Medical Research Council to start collecting autism brains in partnership with researchers at Oxford University. Over the last 10 years, the ATP has engaged researchers from Germany



and the US to develop a brain atlas of age and sex-matched cases and controls to perform deep phenotyping (including imaging, histology, and stereology) on brains in the collection. In December 2007, Dr. Steve Scherer from the Hospital for Sick Kids in Toronto, Canada was funded to genotype all the tissue in the collection. All these data will be made available to the broader community of ATP approved researchers.

Internet System for Assessing Autistic Children (ISAAC)

ISAAC is a web-based data management system developed in 1998 as a tool for scientists that contains a library of over 200 standardized forms most widely used in autism research. ISAAC is currently in use by over 400 researchers worldwide and is the portal that approved researchers use to access phenotype data from the AGRE program. The system offers researchers a mechanism for data sharing, real-time updates of study status, and data downloads using a secure internet connection. The system is used by researchers at leading universities, medical centers, and government agencies who are conducting their own investigations into autism and are in need of a study and data management tool to store phenotype data. The staff has obtained permission from key publishers to use scoring algorithms for copyrighted materials. ISAAC's easy to use layout allows study personnel a fast, easy and secure method for entering and validating (double data entry) study information and exporting to a favorite database application or analysis tool.

ISAAC uses a proprietary form management system, called DEFE (Database of Electronic Form Elements), which simplifies the process of developing data entry, data validation, and data edit forms/templates. Adding new templates and modifying existing templates is a data entry process. No programming is required. ISAAC controls version management, so during the course of a study, when paper collection forms change, it is simple to keep data entry screens synchronized.

Online System for Clinical Research (OSCR):

OSCR is currently being developed in partnership with MDLogix to facilitate family participation in research by offering families a way to complete study questionnaires online using a secure internet connection. Research relies on our ability to gather a lot of information about children and families with autism. However, one of the obstacles has always been the amount of time it takes to gather these data. OSCR will allow the study team to get information to scientists quickly through a series of online questionnaires that will be continually updated in an effort to accelerate the pace of autism research.

The system is being developed with two goals in mind. The first concerns the wait time between research/clinical visits and the ability to start the research process. By completing parts of the evaluations online, it will help to speed up the process and also reduce data entry. Second, the system was also designed to ease the burden on families participating in research. The need for more and more data collection creates a demand on families that can be daunting. Our hope is not only that OSCR will allow them to remain connected, but will also offer them the opportunity to work at their own pace.

Interactive Autism Network (IAN)

The Interactive Autism Network (IAN) was one of the first web communities supported by Autism Speaks. At the time, parents were reporting a desire to participate in research while researchers were struggling to recruit families for their studies. IAN was developed in partnership with the Kennedy Krieger Institute to bring together families and researchers to accelerate scientific progress. In some ways, IAN serves as a patient registry of sorts since it offers families a web-based mechanism to fill out questionnaires about themselves and their children. It has become one of the largest online research databases available to researchers with a registry of over 25,000 families. The technology offers the research community an



opportunity to survey the community on various issues allowing them to get a family perspective on some of the critical issues facing their children.

IAN allows researchers to take the pulse of the autism community in a very timely fashion and offers them a platform for large-scale initiatives. IAN has advanced the field by offering researchers the sample sizes that they've needed to move their research forward, and in doing so, has been able to support more innovative studies that would have been too costly and resource intensive to do on a smaller scale. The IAN community was designed to create a virtual space for families to learn more about research, including the latest scientific findings, and IAN exchange offers researchers online tools for networking and collaboration. This cadre of web-based environments has had an impact on the field, and integrating IAN into the overall bioinformatics plan will yield a significant return on investment. Ensuring that information is disseminated to clinicians, researchers, and families in a timely fashion is critical to the mission of Autism Speaks. Therefore, any informatics plan must support web-based services in order to serve the needs of the broader community of physicians, psychologists, educators, and other health care providers, as well as researchers and parents.

IAN also has collaborated in genetic research that relies on "light phenotyping", i.e. large data sets with phenotype characterization collected in a more limited but less labor-intensive manner. The goal of this approach is to maximize signal via larger samples with tolerable error rates.

GRANTS AND FELLOWSHIPS (Anita Miller Sostek, Ph.D., Vice President)

Through its Basic/Clinical Grants, Pilot Grants, Treatment Grants, and Fellowships, Autism Speaks seeks to identify and support promising research with the hope that results from these efforts will produce significant findings that will be reported in peer-reviewed journals, and which ultimately will lead to treatments for autism. These grants often lead to additional research support from government or other funding agencies.

Autism Speaks grants and fellowships generally include:

Pilot Studies. Grants for Pilot Studies are intended to draw new investigators into the field of autism research and to allow researchers to collect preliminary data to show the plausibility of an innovative area of exploration.

Basic and Clinical Grants. Basic and Clinical Grants fund a broad range of areas, providing researchers the opportunity to pursue leads that have shown promise in pilot studies and offering larger awards over a longer period of time.

Treatment Grants. Treatment 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, biomedical and technological interventions.

RFAs on Special Topics. These are Targeted Requests for Applications focused on areas of research that Autism Speaks wishes to stimulate. Examples in 2008 include the *Environmental Sciences RFA*, the *Epidemiology Research RFA*, and the *Treatment of GI Conditions RFA*.

Fellowships. Fellowships provide the necessary resources to support and encourage the development of young scientists who benefit from the mentorship of prominent researchers. We believe the investment in autism research training will grow exponentially as many of our fellows later assume teaching roles and join departments (many of which currently have no representation in autism research) around the country and the world.



AUTISM SPEAKS UNITED KINGDOM (Andy Shih, Ph.D., VP; Simon Wallace, Ph.D., UK and European Science Director)

Autism Speaks in the UK is an independent “sister organization” with its own board, funding, development strategy and priorities. Constituted as a company limited by guarantee it is also a registered charity. Its aims are: “To raise funds to accelerate biomedical research to determine and understand the causes and biological basis of autism spectrum disorders and through that understanding to discover and promote new ways of improving the quality of life of all those affected.” Funds are primarily raised in the UK (largely from private individuals and trusts and foundations) and directed towards research programs and projects in the UK some of which are linked to the scientific programs of Autism Speaks Inc. Autism Speaks in the UK follows the same model as many other UK research charities in raising funds and making research grants, rather than developing or managing research programs directly. Its advocacy activities are directed towards persuading other public and private research funders such as the Medical Research Council (MRC) and Wellcome Trust to give greater priority to autism research.

To ensure that program management of linked portfolios is well coordinated, Autism Speaks provides support and supervises one full-time science staff member in the UK (Dr. Simon Wallace) who manages day-to-day program activities, identifies and helps develop new opportunities in the UK and Europe, and serves as a liaison with the Wellcome Trust and the Medical Research Council, with whom we have already occasionally partnered on select grants and activities. In addition to responsibilities with Autism Speaks UK, Dr. Wallace more broadly oversees Autism Speaks broader portfolio of research activities throughout Europe.

Currently, Autism Speaks in the UK is the principal funder of the British Autism Study of Infant Siblings (BASIS) network, developed as a result of a pilot project funded by Autism Speaks. The BASIS network is modeled on the Baby Siblings Research Consortium (BSRC) but aims to pursue scientific opportunities unique to the UK infant research community as well as complementary or synergistic with those of the BSRC. While many investigators are involved, Dr. Mark Johnson of Birkbeck College, University of London, is the principal organizer and administrator for the network. BASIS is also supported by a grant from the MRC. The Brain Bank for Autism and Related Developmental Research (BBA) works collaboratively with Autism Speaks’ Autism Tissue Program. The Brain Bank for Autism was formed to take advantage of the existing UK brain-banking expertise and infrastructure, and the high population density relative to the US, in the hope that it would allow more donations of high quality post-mortem brains for research. The program has multiple collection sites throughout the UK, with Professor Margaret Esiri at Oxford University serving as consultant and coordinator of the program. The program received its ethical approval recently and is now operational, with five brains received in the first three months of operation.

As it was alluded to earlier, Autism Speaks in both the US and UK has existing relationships with both the MRC and the Wellcome Trust. Autism Speaks has partnered with the MRC on several efforts, both indirectly (e.g., BASIS) and directly (e.g., Autism Genome Project and the recently approved Adrian Bird grant on Rett Syndrome). Representatives from both organizations participated in the MRC Autism Forward Look January 2009 meeting, where autism research priorities for the coming years were considered. Autism Speaks partnered with the Wellcome Trust in January of 2008 to support a focused symposium entitled “Frontiers in the Neurobiology of Autism,” where leading international autism researchers presented latest findings and discussed scientific opportunities and priorities. We are currently continuing to explore partnership opportunities with the Wellcome Trust.



PART FOUR: LOOKING FORWARD: 2009-11 STRATEGIC PLAN FOR SCIENCE

ETIOLOGY PORTFOLIO

Autism is a complex biological disorder characterized by a broad spectrum of behavioral and medical symptoms, which is caused by a combination of genetic and environmental factors. Similar to asthma, diabetes, cancer, and other complex diseases, interactions between genetic susceptibility and environmental factors contribute to disease risk, clinical presentation and trajectory, and outcome. The identification and characterization of autism risk factors will allow early detection of at-risk individuals, elucidate disease mechanisms that can guide treatment, and lead to prevention strategies.

Genetic factors. The past several years have marked a dramatic increase in our understanding of autism genetics. Driven largely by new technologies and larger-scale studies, several autism susceptibility genes have been identified which are beginning to point to a common biochemical pathway at the synapse. Furthermore, the emerging significance of copy number variants (CNV) in autism has reshuffled research priorities and hinted at new avenues of investigation, including translational opportunities. We are in the early stages of understanding how autism risk is associated with these genetic variants. For example, the well-replicated CNV finding at ch16p11 was associated, in addition to autism, with bipolar disorder, mental retardation and ADHD, albeit at much lower frequency. Some CNVs are found in affected individuals but not their parents or close relatives. Environmental factors are among the suggested sources of these “*de novo*” events. Alternatively, influences of some environmental factors are thought to be mediated by epigenetic mechanisms, where changes in gene expression occur without alteration of DNA coding sequence

The most pressing challenge is to identify specific genetic risk factors and their influence on biological development so that a clear understanding of how autism risk is associated with these variants can emerge. A better understanding of genetic risk factors will allow us to flesh out the relevant biological pathways and elucidate possible disease mechanisms. This can speed the development of risk assessment tools and provide potential targets for drug development. Given our mission, a key short term goal is to deliver DNA-based risk assessment tools to the clinical community.

Environmental factors. Autism’s heritability does not preclude the influence of non-genetic factors in the cause, severity, or onset of the disorder. In the past few decades, the prevalence of autism has increased dramatically. Although broader and better diagnosis is certain to account for some of this increase, the scale of the increase suggests that environmental factors should be vigorously explored. If environmental factors that contribute to risk for ASD can be identified, prevention and treatment strategies should be possible. A wide range of factors needs to be explored, including those potentially influencing prenatal development (such as maternal infection), and those potentially influencing postnatal development (such as diet, pesticides, nutrition, and so on). A comprehensive review of the state of autism environmental sciences can be found in Altevogt, Hanson, and Leshner (2008) *Autism and the Environment: Challenges and Opportunities for Research, Pediatrics, 121: 1225-1229*. Evidence suggests that autism is associated with indices of oxidative stress and neuroinflammation. The role of genetic and environmental factors in oxidative stress and inflammation will be important for identifying causes and treatment of autism. There is



also a need to understand protective moderators of the effects of environmental factors, such as the microbiome, diet, and enriched early environment.

It is clear that there has been less progress in autism environmental sciences research than in disciplines like neuroscience and genetics. Environmental risk factors research is currently limited by methodology, technology and capacity. A more systematic and strategic approach is needed to accelerate the development of the field. The identification of environmental risk factors could readily lead to changes in public health priorities. The confirmation and subsequent elimination of even one environmental risk factor could potentially have immediate impact on susceptible individuals, underscoring its importance and urgency. Given that gene-environment interactions likely underlie risk for autism, the fields of genetics and environmental sciences will benefit from more integration and interaction.

Goals and theories of change

Goal #1 Within the next three years, several autism susceptibility genes and their influence on signaling pathways and risk for ASD are recognized and understood. A high priority goal continues to be the identification of autism susceptibility genes using the latest technological, statistical, and bioinformatics strategies. Autism gene discovery is expected to translate into improved methods for early detection and medical intervention. Strategies include high resolution genetic scans (including copy number variation), reverse phenotyping, investigating known genetic mutations, studying families with specific genetic characteristics (e.g.,16p), exploring ASD differences in gene expression in brain tissue, investigation of known diseases that have phenotypic similarities to autism or display autism as a co-morbidity (Down syndrome, fragile X, Rett syndrome, tuberous sclerosis), and exploring gene-environmental interactions. The integration of the fields of genetics, environmental sciences, and neuroscience will broaden the research framework and generate additional insights through correlation of otherwise independent data (see Goal # 3 below).

Both large sample and targeted biological approaches are likely to inform how best to attribute disease risk to genetic and environmental events. For instance, a better understanding of the distribution and architecture of benign and pathogenic CNV in various populations around the world would help confirm those CNVs that contribute to pathology and the associated risks either individually, or more likely, in conjunction with other genetic and/or environmental factors. Biological consequences of these variations could be mined for additional clues. Current genetic evidence suggests involvement of tens if not hundreds of loci and multiple possible mechanisms acting on biologically convergent pathways. Research using animal models, especially those mimicking well-replicated genetic variants, could help elucidate these molecular interconnections and how they contribute to the translation of genetic risks into phenotype. Furthermore, these animal models, including those with multiple autism-related variants, could be used to explore epistasis and the mechanisms of gene-environment interactions and how they relate to autism.

There is very encouraging work already occurring in the study of model disorders like Fragile X, Rett syndrome, and Tuberous Sclerosis. Working with animal models of these single-gene disorders that have autistic features, investigators have been able to better understand disease mechanism and, surprisingly, use the new insights to “recover” the animal by reversing the disease. Continued investment in this approach is likely to yield further insight and guide similar, future research involving autism susceptibility genes.

Goal # 2 Within the next five years, biomarkers or clinical features are identified that index meaningful subtypes of ASD, identify individuals vulnerable to the effects of specific environmental



factors, predict response to treatment, and reduce heterogeneity in genetic studies.¹⁰ This goal is closely related to Goal # 1 in that heterogeneity remains a major obstacle that needs to be addressed to improve both genetic research and clinical care. Biomarkers (e.g., enlarged brain) or clinical features (e.g., regression) that can reliably identify genetic subgroups are badly needed because heterogeneity in current study samples can reduce the power to detect genetic linkages and associations. The following three strategies are likely to be useful:

First, in order to develop a personalized medical approach to autism, *phenotyping efforts need to go well beyond a description of behavioral symptoms* to include genetic, environmental, and co-morbid and causative medical conditions, gender differences and developmental trajectory across the lifespan (from infancy to adulthood). It is believed that the concept of equifinality applies to ASD, i.e., the behavioral phenotype of ASD can result from different initial risk environmental and genetic risk factors that combine in many different ways. Effective treatments likely will require identification of these underlying diverse conditions, such as was required in diseases such as cancer and epilepsy. Methods or approaches for identifying biomarkers or clinical features that identify subgroups of individuals with ASD that have different etiologies, courses, and responses to treatment would accelerate gene discovery and offer opportunities for more targeted and effective treatments. At the same time, there may be common final biochemical pathways resulting from different etiologies. The identification of such common pathways may also lead to the discovery of effective treatments.

A second way to address the heterogeneity challenge is with *larger datasets*. Population based studies have the advantage of having large sample sizes in order to minimize bias and increase power. As an example of another population-based study that successfully impacted public health, the Framingham Heart Study and longitudinal cancer studies that follow individuals and their families for the lifespan have yielded research findings which have impacted detection of risk factors, intervention, treatment, and survival. Genetic studies of other complex diseases (e.g., diabetes) suggest an optimum dataset of approximately 20,000 to better assess heterogeneity and allow more unfettered analysis. There are many approaches to increasing sample size. Collecting and pooling DNA samples, for instance, from other studies and programs like BSRC or ATN may be one cost-effective way of doing so. Such studies would provide insights into genetic factors that predict variation in developmental trajectory and outcome. Another strategy would involve the emerging science of Internet-mediated research where large patient registries, such as the Autism Speaks-funded IAN project, are used to help recruit subjects and collect data. While many scientific and process issues remain to be addressed to confirm the feasibility of the latter approach, it nevertheless represents an exciting avenue to explore. Large databases such as AGRE may additionally be used to draw correlations between the autism phenotype and genotypes, but this should be expanded to include biological knowledge about the function of unusual genes, mode of action of environmental triggers, timing of environmental exposures, neurochemicals, brain anatomy, etc. in any identified subtype. Finally, analyses of this inherently multimodal data must employ advanced bioinformatics and biostatistical methods capable of identifying developmental profiles or "signatures" of biological subtypes of autism.

Third, *the use of genetically more homogeneous populations* can help to reduce heterogeneity-related complications. As a recent report by the Walsh group indicates, homozygosity-mapping using larger pedigrees from regions like the Middle East where consanguineous marriages are common is a productive approach to susceptibility gene identification. While that study was limited by the lack of validated diagnostic instruments, Autism Speaks-facilitated instrument translation currently in progress and the collaboration between the AGP and the Shafallah Center for Children with Special Needs in Qatar should

¹⁰ Note that this goal was also identified by the biology and treatment strategic plan working groups. It will only be listed here but it is worth noting that this goal was strongly endorsed by more than one workgroup.



greatly expand the range of opportunities and scientific productivity in the region in the coming years. Similarly, large-scale twin studies offer an experimental paradigm where genetic heterogeneity is better controlled to allow exploration of environmental factors and CNV in autism risk and phenotypic discordance.

Goal #3 Within the next five years, the mechanism of action of at least a subset of environmental factors that significantly contribute to risk for autism and their interaction with genetic factors is identified and understood. This will require developing an effective strategy for identifying and evaluating multiple environmental risk factors, including technologies to collect and evaluate environmental exposure data. Given the universe of possible environmental factors in autism, a deliberate, systematic approach to identifying relevant risks would greatly advance the field. The development of high throughput technologies and a corresponding assessment paradigm is an essential component of this approach.

To date, environmental exposures are typically evaluated one at a time and rarely in the context of interaction of multiple factors working with genetic susceptibility. In addition, exposure monitoring, if it occurs at all, often takes place at the time of diagnosis rather than during prenatal and postnatal exposure periods, when previous research has shown that exposure has the greatest impact. Psychosocial, nutritional, and other non-toxic chemical exposures also have been largely ignored due to the complexity of isolating one as a contributing factor. A more deliberate and comprehensive experimental approach would allow studies to be consistent with our current knowledge about ASD and environmental influences on development. It will be important to apply new technologies and corresponding assessment paradigms in autism environmental sciences. Better agreement on biomarkers of exposure (direct or downstream effects and their interpretation) will enable us to screen suspect exposures for relevant biological impact. The following strategies for identification of environmental risk factors are proposed:

First, a strategic approach is to study exposures in populations more vulnerable to developing autism, such as siblings of affected children who are already genetically at risk, e.g., infant siblings. Autism Speaks has made such an investment through a gift from the GUND Foundation in the NIH-funded EARLI and IBIS infant sibling studies. By facilitating collaboration among existing high-risk cohort studies and providing resources for enhancing data collection to include genetic and environmental risk factor data in such studies, we can leverage the initial NIH investments made in such high-risk cohort studies. We also are currently leveraging Autism Speaks' biobanking infrastructure (AGRE, ATP) to expand into collection of biomaterials potentially useful for environmental sciences research.

Second, a complementary approach is to build upon on-going population-based epidemiological samples, such as the NIH National Children's Study, that can reduce potential selection bias that exist in high-risk samples. Autism Speaks currently is collaborating with the NIH National Children's Study to develop effective strategies for discovering risk factors related to ASD outcome in this longitudinal study of 100,000 children. Such large data base/sample studies, in which a wide range of factors can be examined across geographic locations, ethnicities, and age cohorts, will be especially useful. An exposure assessment algorithm consistent within the research frameworks proposed above should be developed, integrating new technologies when appropriate and available. Existing cohorts of children followed longitudinally from pregnancy, such as those included in studies funded through the Children's Center of Environmental Health, have obtained a wealth of developmental and biological data at multiple time points. Limitations exist in expanding protocols to include expansive phenotyping efforts which identify subtypes. However, because exposure assessments have been completed, analyzed, and standardized across sites, a short, translated, and easy to administer instrument may provide a useful first step at identifying cases.



Third, inclusion of biomaterials collection in AS-funded international research projects when possible would enhance the scientific value of the repository and provide opportunities to explore environmental exposures that might be unique or concentrated in regions outside the US. Integration of environmental sciences into international epidemiology efforts that foster comparison across genetic backgrounds (e.g., genetically more homogeneous populations) and diverse exposures can help identify candidate factors and determine the specificity and sensitivity of proxies of exposure (e.g., thyroid function, oxidative stress, changes in metabolism, porphyrin). Alternatively, pooling data from existing health registries will enable systematic exposure assessment across territories to identify common, shared risks or reveal territory-specific factors. In general, because of the costs of conducting large scale data sets, building upon existing large scale US and international epidemiology studies or registries to enhance environmental and/or genetic components represents a cost-effective way to gain insight and possible clues for future research within a relatively short period of time.

Fourth, development of (1) new technologies facilitating exposure assessment, including high-throughput platforms and methodologies, (2) robust biorepositories, and (3) new data analytic approaches will be needed for progress to be made. The establishment of robust virtual, or actual, biorepositories will be essential for environmental sciences research. Such biorepositories will be needed for storing and sharing high-quality prenatal and neonatal samples, as well for the development of in-vitro models of exposure in novel biological matrices (fibroblasts, hair, etc.). A distributed (i.e. virtual) international biobanking model should be explored, since laws in some territories bar prohibit export of locally collected biomaterials. Bioinformatic approaches to facilitate exposure assessment or modeling should be encouraged and integrated into the research framework. Bioinformatics could be a power tool in this integrated approach, where connections and opportunities not otherwise obvious could be highlighted and explored, laying the groundwork for experimental verification.

Fifth, to better understand gene-environment interactions, animal and tissue culture models harboring known genetic risk factors offer opportunities for incorporating environmental sciences into studies focusing on biological mechanisms and a platform for identifying possible environmental risk factors by exploring potential gene-environment interactions. In addition, a large-scale twin study offers a unique opportunity to investigate non-shared environmental factors (e.g., obstetric complications) and gene-environment interactions. Studying concordant versus discordant identical twins would also yield a better understanding of the role of CNVs in autism.

Goal #4 Within the next three years, clinically useful biologically-based methods for assessing autism risk are available and used in clinical settings. An important goal is translation of genetics and/or environmental science findings to biomarker-based clinical applications that could help assess autism risk in at least a subgroup of individuals. Such risk assessment tools and their application in a clinical setting will require careful consideration of a wide range of clinical and ethical issues, however. Unlike single gene disorders where a biomarker-driven diagnosis could be categorical, risk assessment in common diseases like autism is an emerging science and subject to modification and refinement with advancing technology and insight. Misinterpretation of findings implicating risk factors, such as the 16p11 CNV or pesticides, could lead to significant negative health consequences for individuals and families. Therefore, the development and application of clinical tools to assess risk from genetic and non-genetic factors must be dictated by the latest research and *comprehensive and well-considered guidelines* that standardize procedure and interpretation across all application settings to maximize benefits to the autism community and public health in general.



Who will benefit?

Identification of new genetic and environmental risk factors and how they confer risk or protection will ultimately benefit individuals with autism, their families, and the larger public as new knowledge translates into early detection, prevention, and treatment approaches. In the shorter term, translation of genetic and environmental findings into a clinical risk assessment tools, for instance, will benefit the individuals with ASD and their families by enabling earlier early detection and intervention and point toward effective treatment strategies throughout the lifespan. This strategy could lead to mitigation of symptoms and possibly prevention of the full blown syndrome of ASD. The clinical community also benefits by having a much needed biomarker-based tool to supplement existing clinical screening and diagnostic tools and enhance the quality of care.

Innovations in exposure assessment algorithm and technologies, for instance, will help accelerate pace of discovery and, like high-throughput genotyping did for genetics, revolutionize how environmental sciences research is done. Ultimately, this will lead to fresh perspective and novel insights, and facilitate the identification of environmental risk factors for autism. Such findings can lead to public health policy that mitigates risk or severity of autism from environmental exposures, as well as clinical solutions for managing and possibly treating exposures or adding protective interventions that might prevent harmful effects from exposures.

Implementation: What should Autism Speaks do?

- Prioritize funding in the following areas for investigator initiated awards:
 - Large scale studies using state of the art technologies for autism susceptibility gene discovery
 - Epidemiological and laboratory based studies of a wide range of environmental risk factors
 - Population-based epidemiological studies on the frequency and distribution of genetic risk alleles
 - High risk/medically vulnerable samples to investigate the role of vaccines as a risk factor for autism
 - Reverse phenotyping approaches
 - Studies of families with specific genetic characteristics (e.g.,16p)
 - Studies using genetically more homogeneous populations to enhance gene discovery
 - Twin studies focused on genetic and environmental factors
 - Longitudinal studies of high-risk cohorts (e.g., infant siblings) that examine genetic and environmental risk factors
 - Longitudinal population-based studies that examine genetic and environmental risk factors
 - Known genetic diseases that overlap with autism (e.g., Fragile X)
 - Animal models exploring genetic and environmental risk factors and their interaction
 - Research that follows up on recent work demonstrating recovery in animal models
 - Interdisciplinary approaches (e.g., genetics, environmental science, neuroscience)
 - Role of specific risk factors for specific behavioral outcome or subtype
 - Translation of risk factor findings into clinical benefits such as risk assessment tools (e.g., genetic screening, screening for high risk exposures; metabolic indices of oxidative stress)
 - New technologies for exposure assessment
 - Bioinformatic or computational biology approaches to explore genetic and/or environmental influences



- Sponsor workshops on the following topics:
 - Interdisciplinary collaboration (e.g., geneticists and environmental scientists; clinicians and neuroscientists)
 - Best practices in methodology of studying analysis gene-environment interactions as they relate to disease
 - Ethical, clinical, scientific, policy, and financial issues involved in genetic and environmental risk assessment in clinical settings

- Support approaches/opportunities that potentially will accelerate discovery:
 - Explore feasibility of gathering genetic and “light” phenotyping data on very large family samples through the Interactive Autism Network.
 - Continued funding of large genetic data set projects, such as AGRE, the Autism Genome Project, and large scale twins studies, with emphasis on use of high resolution genetic scans, including CNVs.
 - Enhance and expand biobanking-related activities, both domestically and internationally, in conjunction with data and biomaterials sharing and dissemination.
 - Ensure that AS projects such as AGRE and AGP as well as other large-scale efforts, especially those with a genetic component, include an environmental component, either through banking of additional biomaterials (blood, serum, saliva, urine, etc.) or adding questionnaires to collect environmental exposure histories.
 - Leverage existing high risk infant samples, including the Baby Sibs Research Consortium and the IBIS-EARLI collaboration by funding collection of both DNA and systematic, comprehensive, longitudinal environmental exposure data from these high-risk infants and their families. Help fund bio-banking of genetic and environmental exposure data on these high-risk samples. Such studies will allow investigation of genetic factors that relate to variability in developmental trajectory and outcome, which will provide important clues regarding meaningful autism subtypes.

- Partnerships that can facilitate discovery and dissemination of clinically relevant findings:
 - Partner with other countries, such as Saudi Arabia, Qatar and others, to conduct studies on special populations that may be strategic for gene discovery (see Morrow et al. 2008 Identifying autism loci and genes by tracing recent shared ancestry, *Science*, 321: 218-23.) as well as to explore variations in prevalence of autism and their relationship to variability in genetic and/or environmental exposures.
 - Help establish policy and best practices for their use through sponsored workshops on the ethics, cost-benefit analysis, and practice of use of risk assessments in clinical practice and through policy-related activities through the ATN and in collaboration with the American Academy of Pediatrics.
 - Help establish policy and best practices for use in (1) sponsored workshops on the ethics and practice of the use of risk assessments in clinical practice and (2) policy-related activities through the ATN and in collaboration with the American Academy of Pediatrics.
 - Form collaborations with ongoing large scale epidemiological studies, including the National Children’s Study, which will be collecting genetic and environmental information in a population –based design.



Metrics: What does success look like?

Shorter term (within 5 years)

- Identification and prioritization of environmental risk factors for assessment and launch of studies to investigate some of these factors
- Questions concerning the role of vaccines as a risk factor in subgroup of individuals with ASD have been addressed and parental confidence in the safety of vaccines is increased.
- Identification of new genetic risk factors, their mechanism of action and interaction with environmental factors
- Development of a DNA-based clinical risk-assessment tool and clinical guidelines that standardize its use and interpretation across all settings
- Development of new animal models based on known etiological risk factors
- Progress in developing exposure assessment algorithm that integrates genetics
- Incorporation of environmental and genetic components into at least two large-scale studies
- Integration of environmental data, such as exposure history, into AGRE program

Longer term (within 5-10 years)

- Broad dissemination of FDA-approved DNA, environmental, and/or metabolic-based clinical risk assessment tools
- Integration of DNA, environmental, and/or metabolic-based clinical risk assessment tools into official AAP clinical guidelines
- Routine use of clinical risk assessment tools in at least 50% of AAP members who care for children with autism
- Identification of genetic and non-genetic modifiers of risk, presentation and outcome
- Identification of biomarkers of subtypes of autism that predict course and response to specific treatments that are being used in clinical assessment
- Identification and confirmation of environmental risk factor(s) for autism and integration of that knowledge into clinical practice.
- Discovery of drugs or other medical interventions that can alter the course of autism



BIOLOGY PORTFOLIO

Research into the biology of autism will define the biological mechanisms that underlie autism, leading to more effective treatments. Although many advances have been made in characterizing the behavioral symptoms that define autism, the underlying biological abnormalities resulting in those behaviors remain poorly understood.

Research on the neurobiology of autism has just begun to yield considerable results due in large part to the technical and diagnostic advances of the last decade. As mentioned above, the concept of equifinality likely applies to ASD, i.e., the autism behavioral phenotype and brain systems that are affected in ASD can result from different initial environmental and genetic risk factors that combine in many different ways. The wide range of genetic and environmental factors that may contribute to risk for autism may ultimately converge on similar brain systems that are affected. That commonality may well lie in the alterations in synaptic functioning and neural plasticity. Functional imaging studies in adults reveal underactivation of areas of higher-order association cortices and normal-to-overactivation of more primary cortices. In addition, these studies reveal abnormal functional connectivity, characterized by a pattern of reduced long-range connectivity and enhanced short-range connectivity with brain regions. Measurement of the coordination of brain activity between regions suggests that brain regions that should normally be synchronized with each other are not, and that the prefrontal cortex may be especially disconnected with other brain regions. This has led to an “abnormal connectivity” theory of autism, which hypothesizes that brain regions are not properly linked to each other, causing them to be functionally out-of-sync. This suggests that the deficits in autism may not be found in any single brain structure but rather in the wiring of the neural networks that connect the different parts of the brain together. This is consistent with genetic evidence which implicates molecules located at the synapse, which could provide a molecular mechanism for the connectivity deficits.

One of the most reproducible findings in autism is an unusual spurt in brain growth beginning in the first year of life, perhaps paralleling or preceding symptom emergence. Interestingly, overgrowth appears to be most pronounced in the areas of the brain associated with high cognitive, language, and social skills. The phase of accelerated growth is followed by a second pattern of atypical brain development, in which brain growth tapers off and ultimately becomes slower than that of other children such that, although larger in toddlerhood in both the gray and white matter compartments, by adolescence the brains of individuals with autism may not be larger than their typically-developing peers. These unexplained differences in brain growth trajectory no doubt influence subsequent development of the intricate circuitry of the brain, and are thus consistent with the alterations in functional brain connectivity that have been noted in adults with autism.

Beyond these early brain growth trajectories, much of what we currently know about how the brain and body are affected by autism is from older individuals, well after autism has presented itself. Although much attention has been given to defining the behavioral (neurocognitive, motor, attentional, affective, and social) characteristics of autism at these early time periods, the developmental window in which these critical behavioral changes take place has been less studied from a biological perspective. The precise alterations in biochemical pathways, the cellular and molecular dysfunctions that underlie the abnormal growth pattern and subsequent development of altered brain circuitry, remain to be discovered. Equally important, the biochemical changes in other body systems (immune, GI, metabolic) that accompany or predict the behavioral changes are also poorly understood.



Identification of the altered biochemical pathways, whether brain or body, remains a vital hole to fill with regards to treatment. Recent discoveries in several developmental disorders related to autism have made very clear the therapeutic importance of identifying the biochemical alterations that underlie behavioral symptoms. By targeting disrupted molecular pathways, mouse models of Fragile X, Rett syndrome and Tuberous Sclerosis were unexpectedly “rescued” well after the mice had become disabled, heralding the possibility that developmental disorders such as autism may be treatable into adolescence or even adulthood. Moreover, phenotype reversal need not require genetic manipulation, as pharmacological targeting of biochemical signaling pathways downstream of the genetic lesions has also been effective. These results have made novel drug discovery for developmental disorders a reality, and imply that such therapeutics hold promise for individuals who already have the disorder. The arduous path from discovery of a biochemical pathway and animal model to an effective drug treatment has already been discussed and suggests that nurturing progress along this pathway will be essential.

Development of the “rescue” strategies was aided in large part by the existence of appropriate model systems of these disorders. For instance, in just four years, the field of Fragile X has managed to move from complicated behavioral symptoms, to plausible molecular underpinnings, to the potential of therapeutic intervention, based primarily on to the availability of animal models for the disorder. Although autism, in most cases, is not caused by an identifiable genetic disorder, such as Fragile X, identification of these less common genetic causes of autism has allowed generation of the first etiologically-valid model systems for careful study of downstream biological pathology. The development of such autism models will accelerate rapidly with the discovery of new genes and environmental risk factors upon which to base them, and they will become an essential part of the drug discovery process because measurement of changes in their biology can be used as surrogate markers for preclinical evaluation of new therapeutics. Unfortunately, any current autism animal models that have been validated behaviorally have yet to be linked to what little is known about the clinical pathobiology of autism (for instance, the recently described presence of neuroinflammation, or the enlargement of white matter volume).

Because the behavioral symptoms of autism can arise from different etiological and biological mechanisms, identifying the different biological profiles found in individuals with ASD will be required before targeted, individualize treatments can be provided. Subgroups of individuals with ASD may show different biological profiles, such as mutations in specific developmental genes and differences in neuroanatomy, neurophysiology, neurochemistry, and neuroimmunology. Characterizing subtypes will lead to more effective therapies tailored to the correct biological underpinnings of each profile. In addition, defining a “biology of improvement,” i.e., identification of biological markers that co-vary with behavioral improvement, will offer a demonstrable index by which treatment progress can be assessed. Moreover, targeting specific early interventions for amenable biological subtypes could reduce the overall prevalence of autism. This, in turn, would also measurably decrease autism’s burden to society. Because autism is manifest early in life, treatment of autism will also be greatly aided by characterizing the early biology of autism. Discovering autism’s earliest biological signs will allow faster, more accurate risk assessment and the opportunity to tailor treatments at young ages that can prevent the syndrome or lessen its severity.

Goals and theories of change

Autism prevalence is high and, while the urgency to best help those affected is great, too little is understood about the biology of autism to be able to predict which individual infants and children will likely improve or be significantly benefited from current treatments. Though autism is a biological disorder,



biological information has not yet had a significant impact on either the selection of appropriate early interventions or prognoses for overall clinical outcome. This absence of prognostic information impacts the child, parents, professionals and the cost of treatment.

One central problem faces families affected by autism: *a dearth of effective biologically-based therapeutics, especially treatments tailored to an individual's specific set of symptoms*. A high priority is to *develop effective means of treatment for everyone*. Achievement of the following three major biological goals would lead to either an improvement in the application of existing treatments or the development of novel effective treatments. Taken together, these three goals encompass a wide range of biological approaches, and have the potential to reduce the overall prevalence of autism by identifying and treating subgroups of autism at very early stages.

Goal #1 Within the next five to seven years, at least one efficacious biological treatment is made available that can significantly influence the core symptoms of autism. The currently available *behavioral* treatments for autism are effective for significantly reducing autism symptoms and increasing cognitive and language abilities, but these treatments are not equally effective for all children. Knowledge of the biological underpinnings of autism will be the key to allowing scientists to design rationally-based biological treatments that may have broader clinical effectiveness. *Clinical efforts that can directly lead to identification of the disrupted biological pathways should be prioritized*. For instance, molecular-based postmortem approaches may be the most direct method to identify key brain pathology at the level of cells, provide additional information about the underlying pathobiology upon which to build model systems, and reveal potential molecular targets. However, availability of postmortem brain tissue is rate limiting, so concomitant strategies for identifying pathophysiological markers of autism should be considered by utilizing more accessible clinical samples including saliva, urine, blood etc. Novel approaches to characterizing the biology of immune, gastrointestinal, metabolic systems should be considered. For instance, metabolic screens that have already proved useful in other clinical research populations may be applied. Finally, clinical anomalies in autism, such as the fever effect, should be exploited for developing assays that can uncover the functional biology, and hopefully the molecular pathways, that underlie them.

On-going longitudinal studies of large sample sizes that are collecting behavioral measures should begin gathering biological data. Choice of biological measures should be based on existent information in the ASD literature, but novel measures should be included (as above). Longitudinal designs must target early developmental ages, when the greatest changes are taking place and compensatory processes have not yet set in, and about which we know little biology. Biomarkers discovered through such screens should be incorporated in future clinical trials to determine if any correlate with treatment efficacy (see below).

Recent evidence, primarily from genetic studies, converges upon the centrality of pathways subserving synaptic function and plasticity. This provides another strategic entry point for identifying the affected biochemical pathways. More generally speaking, continued pursuit of genetic studies (see Etiology Portfolio above), whether rare or common variants, changes in nucleotide sequence or copy number polymorphisms, inherited or sporadic, will provide direct insight into the biochemical pathways that can provide targets for therapeutics. Identification of biochemical pathways will also immediately lead to discovery of the environmental factors that impinge upon them, revealing candidate environmental triggers for autism and directing prevention strategies.

Finally, evidence of effective treatments can directly inform us about aspects of the underlying biology of autism, and the workgroup felt that this is one extremely important avenue which has yet to be exploited. By studying the impact of early interventions on brain and behavioral functioning in young children with autism, we will not only understand more about the neural systems underlying autism, we will



be able to identify biomarkers of clinical progression. This will identify biological features or profiles that are predictive of treatment responsiveness and clinical outcome, even if no behavioral changes have yet occurred, and also point to improved treatment opportunities that can now be aimed at maximizing biomarker normalization. Thus, treatment studies should include measurement of biological features prior to treatment onset and following at least one year of treatment. Importantly, methods need to be established to conduct behavioral tests and assess biomarkers (molecular or physiological) at regular intervals during treatment to correlate changes with treatment progression.

Goal # 2 Within the next five years, biomarkers are identified that index meaningful subtypes of ASD and predict response to treatment (see Goal #2, Etiology Portfolio).

Identification of subtypes of autism that are biologically-based will allow clinicians to tailor treatments to those subtypes using biomarkers and/or clinical markers as a guide. Because ASD represents an extremely heterogeneous group of disorders that differ in cause, course, response to treatment, and outcome, a better understanding of biological processes that operate in the context of treatment and prevention studies will lead to more targeted intervention approaches that are designed for specific subtypes of autism. Although even current treatments may work for certain subpopulations, we cannot identify a priori those subtypes that can be treated with high probability, especially at the earliest ages. *Knowledge of the biological basis of autism will help identify the meaningful subtypes of autism and potentially reveal the range of treatment options for any given individual.*

To identify subtypes of ASD, studies need to obtain comprehensive clinical, behavioral, dysmorphology and biological measures from, for example, infants and toddlers at-risk for ASD or relevant contrasting disorders as well as typical infants and toddlers. Biological commonalities in co-morbidities, many of which reduce the quality of life for individuals with autism and their families, should also be analyzed. For example, variable symptoms not present in all individuals such as seizures, GI conditions, psychiatric co-morbidities, mental retardation, hypersensitivity to sensory stimuli, sleep disruptions, irritability, aggression, etc. may be useful to define subtypes.

Goal #3 Within the next three years, pre-clinical assays/model systems to study effects of risk genes and environmental factors on biological pathways and fast-track the screening of novel treatment interventions are developed and used in research on drug discovery. Families do not want their loved ones to wait to receive help, nor are they ready to give up hope of treatments for those who may have already passed toddlerhood. Therefore, as treatments require model systems in which to test them, there is an urgent need to prioritize their development. Exciting new discoveries using model systems from other developmental disorders (Fragile X, Rett syndrome, Tuberous Sclerosis) have given hope that novel therapeutics may be capable of reversing symptoms in older individuals. Therefore, once the affected biological pathways are identified for autism, model systems will be needed to rapidly screen for novel treatment strategies that normalize the appropriate molecular and behavioral targets. This must include knowing what endophenotypes to focus on and how to bring them to bear on treatment design.

In vitro models represent one new approach to be pursued, while animal models have traditionally represented the major strategy for developing models of diseases. Model systems may be selected that are either relevant to suspected etiologies or relevant to endophenotypes or biological profiles of individuals with autism spectrum disorders. Searches of the scientific literature can assemble the many current hypotheses about the biological causes of autism (either the triggers such as genes and environmental factors, or the many proposed biological underpinnings of autism, such as, neuroanatomy, neurophysiology, neurochemistry, immunology), and the analogous dysfunction can be generated in model organisms or *in*



in vitro systems. For example, candidate gene mutations can be introduced into the mouse genome, or rodents may be exposed to an environmental toxin, and the outcomes evaluated with assays relevant to the symptoms of autism. Besides behavioral assays, these may include unusual synaptic neurophysiology, aberrant neuroanatomy, high reactivity to stressors, and altered immune responses. Cell-based model systems will require re-capitulating aberrant molecular mechanisms *in vitro*. These may be arrived at either by culturing tissue from suitable animal models or possibly using the newest induced-pluripotent stem cell technologies.

No animal model will fully recapitulate all components of the human disorder. Methods to uniformly characterize the most relevant subset of biological and behavioral abnormalities should be paramount in defining model systems. Interactive discussions between clinical experts and animal model experts are needed to exchange information about subtypes of autistic individuals and animal models in order to determine the most useful endophenotypes upon which to focus. The goal is to reach a consensus for a set of highly relevant, well-validated measures of autism-related behavioral and biological markers. A consortium of animal model experts should be formed who hold regular meetings, share information, and establish a set of guidelines to define autistic behaviors in experimental rodent models. Because an autism diagnosis requires a deficit in three behavioral domains (social behavior, communication, and insistence on sameness), a standard battery of behavioral tests that addresses *each* of the core features of autism would finally allow a more consistent evaluation and comparison of autism models. This will provide a much valued tool required for subsequent development and screening of clinical therapeutics for autism.

Once established, model organisms and assays must be used to test treatments for their ability to normalize biological pathways and reduce developmental symptoms. Application of the consensus assays in each of the relevant types of animal models can evaluate proposed treatment efficacy and safety. For example, a mutant mouse model of a candidate gene for autism that may display impaired synaptic connections would be utilized to test a drug treatment for normalization of synaptic transmission. Studies should include adults along with early developmental stages given the new data suggesting that older individuals may also be beneficiaries of such therapeutics.

Costs may be minimized if laboratories with expertise in the relevant subtypes of animal model assays are responsible for conducting high-throughput screening of different treatment regimes. For example, a class of drugs that increases synaptic connections might be more helpful in improving cognitive abilities, while another class of drugs might work best in reducing irritability in a mouse model with high repetitive behaviors, and yet another class of drugs might reduce upset to change. Standardizing such testing paradigms will make progress go faster and also potentially attract the attention of pharmaceutical and biotechnology companies that appear to be interested in testing therapeutics for autism but refrain from doing so due to the lack of suitable animal models and surrogate endpoints for evaluating treatment success.

Who will benefit?

By intentionally choosing to focus on the development of effective means of treatment for *all* individuals with autism, the goals identified within the biology portfolio seek to have an impact on *everyone touched by the disorder, especially those directly affected by ASD*. This includes individuals with autism (young and old), their families, their caretakers, their physicians, psychologists, educators, and behavioral health workers, as well as their larger community. If preventative or treatment approaches are successfully identified for even a few of the most amenable biological subtypes of autism, the impact could be registered as a decrease



in the prevalence of autism, which would even diminish the overall burden to society as a whole (socially and financially).

In prioritizing the use of biology to parse the subtypes of autism, it will be important to acknowledge that forcing autism into a single entity has caused the needs of many to be overlooked, especially those of low-functioning individuals (who have different symptom profiles and would therefore be expected to benefit from different types of therapies) and those who suffer from a range of medical conditions, such as GI disorders. Moreover, the workgroup recognized that while it will take time to design the novel biological or behavioral therapeutic strategies required for treatment of some subgroups, treatments, such as early intensive behavioral interventions among others, already exist that would benefit other subgroups immediately. Thus, attention must be paid to defining the subgroups that would benefit not just from future treatment development but from the various biomedical and behavioral intervention strategies that we currently have.

Implementation: What should Autism Speaks do?

- Prioritize investigator-initiated funding in the following areas:
 - Projects that include efforts to subtype through biomarkers
 - Projects focused on the development of biomarkers of treatment progression
 - Impact of treatments on behavior, brain, and other biological endpoints
 - Clinical studies for defining pathophysiology in autism, including novel approaches to characterizing the biology of immune, GI, and metabolic systems
 - Methodology to identify metabolic indices of oxidative stress/damage, mechanisms by which they occur, and how they relate to environmental exposures, autism symptoms, and etiology
 - Mechanisms and indices of inflammation as it relates to ASD
 - Collaborative investments in a state-of-the art autism tissue program
 - Use of brain tissue to further explore nature of biological brain abnormalities
 - Use of induced-pluripotent stem cell technologies to advance understanding of neural abnormalities in autism
 - Projects characterizing the biology of very early development (prenatal, infancy)
 - Development and application of model systems and bioassays
 - Standardization of methods for evaluating animal models of ASD
 - High-throughput testing of treatments for their ability to biologically normalize pathophysiology in model systems
 - Animal models to study genetic and environmental risk factors and their interaction

- Sponsor workshops on the following topics:
 - Development of consensus on high priority common phenotyping assessments that may be useful for subtyping, for example: low IQ, delayed language, seizures, gastrointestinal distress, sleep disruption, immune dysfunctions, large brain size
 - Clinical and basic researchers reach a consensus set of highly relevant, well-validated measures of autism-related behavioral and biological markers (clinical investigators explain the behavioral and biological symptoms of autism, and animal model experts explain the available and emerging assays)



- *Animal model consortium.* Enlist investigators with established expertise to conduct well-validated assays using the strongest model systems. Ensure that mutant mouse models and/or *in vitro* assays are routinely shared across laboratories
- Support novel approaches/opportunities that potentially will accelerate discovery:
 - Fellowships for young investigators to learn methods for conducting the endorsed animal model assays
 - Interdisciplinary fellowships
- Partnerships that can facilitate discovery and dissemination of clinically relevant findings:
 - Provide leadership role and financial support for collaborative autism tissue bank initiative involving Autism Speaks, Simon Foundation, and NIH

Metrics: What does success look like?

Shorter term (within 5 years)

- Development has begun for a risk assessment test based on biological markers that can be used in infants
- Prevention of autism and/or reduction of severity of symptoms in significant subgroup through early detection and intervention
- Identification of biomarker(s) associated with response to different treatment modalities (behavioral, medical)
- Trials of treatment modalities for separate subtypes are launched
- Identification of common biochemical pathways involved in ASD. In particular, a detailed investigation of synaptic pathophysiology will be carried out and used to motivate design of novel therapeutics.
- Consensus on a set of biological and behavioral assays to be used in animal models that incorporate face validity to the core and associated symptoms of autism
- Model systems relevant to the biological causes of autism are validated and replicated and screening for novel therapeutics has begun
- Data collected on efficacy of treatments in the model systems, including drug treatments and behavioral interventions

Longer term (within 5-10 years)

- Pediatricians, nurses, educators, and psychologists working in community settings will routinely screen infants for risk of ASD and refer at-risk infants and toddlers for standardized bio-behavioral assays that will determine whether an individual infant or toddler fits a known subtype. Parents will be informed of the results and their implications so they will better understand the diagnosis, prognosis and treatment implications for their child.



- Individuals in subtypes most amenable to known treatments will receive those treatments, and such treatments will have been optimized through research to maximally benefit individuals. In this way, early and effective treatment for these subtypes will markedly improve developmental outcome, including near normalization of a percentage of individuals.
- Parents of individuals in subtypes not amenable to known treatments will be informed of that and offered treatment options, including participation in novel treatment trials as well as standard treatments.
- Understanding mechanisms of increased risk through environmental factors will lead to prevention strategies.
- Through early and effective intervention and better outcome, the total monetary and personnel costs of treatment for some subtypes of autism will markedly decrease, resulting in greater resources becoming available to search for effective treatments for other ASD subtypes. Expectations based on biological and treatment knowledge will lead to greater parental satisfaction that their individual child is receiving the best care possible. Through these efforts we would also expect to observe a reduction of the current 1:150 prevalence due to early identification and intervention for known subtypes.

DIAGNOSIS AND PHENOTYPING PORTFOLIO

The overarching goal of the Diagnosis and Phenotyping Portfolio is to define both behavioral and biological methods which can be used to determine who has autism and what types of interventions are most likely to be effective for that individual. Such efforts will have impact in all areas of Autism Speaks' mission: finding the causes of autism, facilitating enhanced treatment and intervention techniques and paradigms, and ultimately finding prevention strategies and cures for autism spectrum disorders.

The Diagnosis and Phenotyping Portfolio focuses on diagnosis and assessment of co-morbid conditions through the lifespan and prediction of risk of developing these, detection of conditions as early as possible so that treatment can be instituted, and ensuring professional recognition that such conditions are present in autism so they will be treated and paid for by insurance. It is also concerned with developing methods to screen adolescents and adults who may have been missed in childhood. There is a need to better understand autism throughout the lifespan including later adulthood and aging.

The challenge of providing clinically useful diagnostic instruments that also can be feasibly used in a research environment has plagued researchers and service providers for many years. The gold standard methods for diagnosis, the Autism Diagnostic Observation Scale (ADOS) and the Autism Diagnostic Interview (ADI-R), are well-validated diagnostic tools and are used worldwide in many languages for diagnosis of autism. Other instruments, such as the Autism Observation Scale for Infants (AOSI) and the Toddler Version of the ADOS are being developed to assess risk for autism in the earliest stages (6-18 months of age). In addition to these instruments, researchers and clinicians have access to many autism screening checklists and questionnaires. There are differences in these instruments with regard to their sensitivity and specificity, the time it takes to administer them, the cost, whether the measure is quantitative or qualitative, and what areas of functioning are targeted. Among the challenges associated with many existing diagnostic measures are the time and effort involved in their implementation. Furthermore, most of these tools yield a qualitative diagnosis that is specific to the developmental level of the child, making them



less than optimal for measuring outcome in treatment studies, although recent efforts are underway to address this problem.

The existing screening and diagnostic tools are beginning to be used in wider clinical settings. In an effort to improve knowledge to health care providers, in 2007, the AAP published an algorithm for screening using the Modified Checklist for Autism in Toddlers (MCHAT) that can indicate referral to a multidisciplinary team for diagnosis and intervention. This publication represented an important milestone to communicate the needs of proper screening and diagnosis to pediatricians and other health care providers, such as psychologists, nurses, and educators who may not otherwise recognize and understand the early signs. However, the impact of this publication and utility by providers is not yet fully evident. Research that identifies the factors that promote or impede the use of these guidelines in the community and best approaches for dissemination of knowledge to practitioners is needed.

Our understanding of the epidemiology of autism is dependent on how well autism is characterized through current methods of screening and diagnosis. Evidence suggests that autism exists in all countries and cultures. There is increasing appreciation for the influences of socio-cultural and/or geographic factors on the diagnosis and care of ASD. To address questions regarding the causes of autism, exploration in international autism epidemiology should focus on autism etiology in special populations (e.g., those that are genetically more homogeneous) and populations with differing types and levels of environmental exposures. At the same time as such studies are conducted, epidemiologic research can help increase awareness about autism and help government agencies develop informed policies regarding the availability of basic services needs for children and families with autism and other developmental disorders within their country. Differences across territories in terms of awareness and understanding of autism must be overcome to better understand the etiology of autism and better develop specific training and service plans in areas around the world. A “universal” screening or diagnosis method would help reduce variability across territories, cultures, and languages to allow better estimates of the prevalence, improve knowledge of the etiology, and build specific treatment models conducive to the particular environment involved.

The ADOS has been translated into 12 languages, including Spanish, Icelandic, Norwegian, French and Finnish. The ADOS and the ADI are excellent, although labor-intensive, research tools in countries with high infrastructure, and training is available to psychologists, physicians, and researchers. However, it has been noted that cultural differences in response, as well as the situations posed during the ADOS, may not translate effectively and could possibly prevent an accurate score from being assigned. Therefore, it is important that these tools be adjusted for cultural norms. This includes normal parent/child interactions, societal preconceptions about autism, and family and social dynamics. Efforts to design more efficient and culturally sensitive screening and diagnosis methods both here and abroad include adaptation and translation of currently recognized “gold standard” diagnostic instruments. While many researchers have found these translated versions very helpful and valid in calculating prevalence, other investigators find these instruments very expensive, costly, and a burden on families. A simpler and more cost-effective tool needs to be developed. Such a tool could first be piloted in the US and then be adapted to fit the cultural norms as well as needs and limitations of international territories.

Since 2003, Autism Speaks has maintained a strong commitment to early risk detection, screening, diagnosis, and assessment through the High Risk Baby Sibling Research Consortium (BSRC, described in detail above). This group, with 22 current members from 19 research institutions, has focused on methods for early detection and early intervention in infants and toddlers at risk for autism and on describing factors related to variation in early developmental trajectory among high-risk infants. While the BSRC is interested in early diagnosis (prior to 24 months of age), success has been seen with regard to early signs which may be



non-specific but considered “red flags” (such as atypical head growth and failure to respond to name). Many of the sites are currently including genetic or biomarker variables. Clearly, support of early identification and diagnosis should continue to be an important part of our overall scientific priority and strategy in the years ahead. A biomarkers initiative should be integrated into various aspects of the diagnosis portfolio, both with respect to early diagnosis and diagnosis confirmation. This may include genetic screens, identification of immune markers, neurobiological “signatures” (such as ERP) or other biomarkers.

Furthermore, it is recognized that the current methods of diagnosis which rely on careful behavioral observation and clinical interview have important utility in allowing the individual to access existing services. These methods, however, are often underutilized in the full range of ethnic and cultural settings, both in the US and abroad. *We need to improve system capacity and models of care* based on individual needs of each community. In order to ensure these needs, the following goals should be targeted:

Goals and theories of change

Goal #1: Within the next five years, biomarkers or clinical features are identified that index meaningful subtypes of ASD and predict response to treatment (see Goal #2, Etiology Portfolio).

Goal #2: Within the next five years, diagnostic tools that are less time and effort-intensive are developed and validated. Such tools should be shorter, cheaper, and more accessible to a wide variety of individuals, including clinicians, physicians, psychologists, teachers, health care providers, autism researchers and the community at large. These tools would be extremely useful in large scale epidemiology studies. A *population-based study* or other large sample study will be needed as a starting point to develop a shorter, streamlined, more accessible clinical instrument. One approach would be to examine the specificity and sensitivity of combining available screening instruments, such as the Social Reciprocity Scale and the Social Communication Questionnaire, for diagnosing autism. Another approach would be to validate the use of a shorter version of existing measures (e.g., short version of ADI-R which only assesses algorithm items) for diagnosing autism.

Goal #3: Within the next five to seven years, improved screening, diagnosis, and assessment methods are made available for individuals (a) across the lifespan and (b) across diverse and under-represented community populations. Specific age-groups of focus include those at risk and at young ages (prior to 24 months) when early diagnosis and intervention can alter developmental trajectory. Investigators studying “at risk” populations are just beginning to understand what the most effective early screening and detection models are, and further supporting their expansion and dissemination would have a huge impact on later research practices and translation to the clinic. The aim would be to lower the age of diagnosis to ensure earlier intervention. In addition, methods for better screening and diagnosis of high functioning and older individuals are needed. Aging adults with autism represent an area in which very little research has been conducted. In summary, the aim is to ensure that everyone at all ages has been correctly diagnosed, including diagnosis of co-morbid conditions across the lifespan so they can access appropriate support services. Finally, validated methods for screening and diagnosis in community populations that are under-represented in current samples and have increased ethnic, socioeconomic, and racial diversity are needed.

Goal #4: Within the next five years, consensus standards for diagnosis and phenotyping in research studies and clinical settings are developed, including both briefer assessments that will be



appropriate for larger scale studies and more comprehensive assessments which expand behavioral diagnosis to include markers of subtypes and biological measures. With respect to the comprehensive assessments, measures such as associated medical conditions, head circumference, genetic factors, neurophysiological, neuroanatomical or other biological manifestations should be considered. In addition to cytogenetic abnormalities, an inexpensive genetic analysis testing for particular mutations of genes or more general copy number variations may provide confirmation of existing diagnoses or early identification in an at-risk population. In a clinical setting, obtaining biological markers, including blood, urine, imaging data or other neurobiological information should be considered. Research projects currently underway collect biological data as part of their existing protocols, and efforts should be encouraged to expand the utility of these markers, in scope, amount or number.

In an effort to establish guidelines for clinical researchers interested in submitting treatment grants in autism, a taskforce comprised of a diverse group of psychologists, physicians, clinicians and clinical researchers was convened in 2004 and a white paper was published in CNS Spectrums. All individuals interested in applying for treatment grants were encouraged to adhere to the measures outlined in that paper. While that document served as a guide for new researchers, many of the NIH funded networks, such as the CPEA and STAART networks, had a clinical core that served to come up with a list of common measures required to answer their specific research questions. Large scale efforts such as AGRE, AGP, ATN, and the Simons Simplex Collection have independently convened their own groups of experts to generate a list of common measures relevant to their studies. Researchers are now realizing that in order to pool data across diverse data sets, it is critical that a consensus is reached and standards for common measures are evaluated.

Phenotyping is costly, resource-intensive, and there is a limited workforce with the required skill set. One rate-limiting step is that there are few agreed upon measures beyond the ADI-R and ADOS, which have limited utility beyond diagnostic classification, and each research project presents with its own unique set of limitations. For international researchers, the availability of trained personnel and of certain measures in other populations/ethnicities is limited, so the battery that is chosen may often reflect those limitations. Given the state of the field, it is extremely important that new guidelines for clinical research are established and that they re-examine the evidence base to bring the field to consensus to select common measures across each domain of functioning. To this end, Autism Speaks should convene a workgroup to achieve consensus on standards for phenotype assessment across the broad range of disciplines. This group comprised of clinicians and clinical researchers should identify common outcome measures for the field that maximize positive effects. These measures could then be incorporated into a data system that will support the data management needs of all grantees. One of the goals of NDAR is to develop the ontology for the field. It would be important for AS and NDAR to partner in these efforts to ensure ontology that is comprehensive and would serve the needs of researchers across a diversity of disciplines.

Consensus standards for diagnosis and phenotyping in research settings will facilitate integration of data which will allow meaningful analysis and understanding of the tremendous heterogeneity of ASD. Large data sets are critical for identifying subtypes and biomarkers of subtypes. Phenotyping efforts to categorize comorbid conditions and identify subtypes should be made in conjunction with development and utilization of research-reliable tools which can be made useful in a variety of clinical settings.

Goal #5: Within the next three years, models and guidelines are developed for effective dissemination of screening and diagnostic instruments both nationally and internationally. Models for effective dissemination of screening and diagnostic instruments to a wide range of communities within the US, as well as countries outside the US, are needed. This will be a first important step toward funding



global research on autism and addressing the needs of individuals with autism worldwide. If prevalence estimates are found to vary by geographic regions, this could lead to a better understanding of the etiology of autism, including genetic and environmental contributions.

Under-represented or sub-populations in the US and abroad should have access to relevant screening and diagnostic tools to facilitate better accuracy of the epidemiology of autism as well as service delivery. Models that are sensitive to differences in culture, values, and resources need to be developed. Cultural differences can influence how autism is diagnosed and treated and the impact of autism on the family and larger community. While a general model for dissemination can be development, the approach taken for each community should allow for individualization based on resources, priorities, and values. For example, some countries find that a ‘bottom down’ approach is more effective – translating and validating current diagnostic instruments and using the parent-led communities to drive changes in practices is the most effective. Other efforts have focused on larger organizations and thought leaders to identify strategies that will reach as many families and children as possible. *Any strategy for diagnosing autism should ensure that measures can be implemented effectively and that the diagnosis is delivered appropriately and sensitively within each culture.*

Recently, Autism Speaks has developed the Global Autism Public Health (GAPH) Initiative to address the needs of individuals with ASD and their families worldwide. The initiative has three components: (1) Facilitating awareness and recognition by offering awareness campaign materials and strategies that have been developed by Autism Speaks to other territories; (2) Building research infrastructure and collaborations through the Autism Speaks International Autism Epidemiological Network and targeted epidemiological studies in international territories; and (3) Proposing a model of service training that involves identification of national training teams which can provide assistance in development of region-specific strategic plans for training, on-site technical assistance to the training team in best practices for diagnosis and treatment, and on-going remote assistance as the training team moves toward independence in training other professionals in their country. In order to fully implement GAPH, it will be necessary to support leadership within Autism Speaks for the GAPH initiative, look for partners interested in funding the efforts that will be required for implementation of GAPH, and identify interested experts in the field that can help steer and implement GAPH.

Goal #6: Within the next five years, factors and best systems that will allow better access to diagnosis and treatment by individuals with autism are identified and informing policy. Whereas previous efforts at developing diagnostic methods have focused on their use in research settings, less effort has been given to translating this work into clinical and educational settings where individuals with autism typically are served. Thus, it is important that a more community-based approach be taken in assessing the efficacy of diagnostic methods. This strategy takes into account the clinical and educational settings in which a diagnostic instrument is used in practice. Many times, there is the assumption that what is studied in a research environment trickles down to the clinic. However, the methods used in research may not readily translate into clinical and educational settings in diverse regions with more limited resources and training. Therefore, a systems approach should be taken to ensure that successes in the lab are translated into standard clinical and educational practice. In addition, capacity building will depend on both training and information dissemination. Promotion of early detection and diagnosis should be paired with providing individualized service.

Among the many factors that need to be addressed is how to best develop a broader provider base for effective assessment and intervention. Without such a base, people with autism will not have access to diagnosis and intervention. Currently, the average age of diagnosis for autism ranges from 3-6 years, and individuals from minority backgrounds have an even later average age of diagnosis. Many parents report as



long as a 2 year waiting period to either receive a formal diagnosis or receive intervention services at local service providers. The capacity of systems designed to serve those affected with autism should be both studied and evaluated. In addition, we need to understand the financial disincentives that are preventing implementation of best practices. A better understanding is needed to examine how different systems succeed or where the gaps need to be filled. This can be achieved by studying different “models” of care rather than solely studying individual diagnostic and treatment protocols.

Collaborative networks of providers, such as found in the Autism Treatment Network and the American Academic of Pediatrics, will greatly facilitate dissemination and development of appropriate models for training and dissemination. Leveraging these networks to develop consensus and empirically-based policy statements and professional training programs will be an important strategy.

Who will benefit?

Accurate, efficient, and meaningful diagnostic methods, as well as the ability to diagnose different forms or subtypes of ASD which are predictive of an individual’s course and response to treatment, will have a large impact on how clinical care is provided to individuals with autism. The availability of more efficient diagnostic methods will allow more accurate estimates of the prevalence of autism globally, which will be critical for advocating for services and will form the basis for epidemiological studies that can elucidate genetic and environmental risk factors. Improvements and wider dissemination of diagnostic methods will allow all individuals affected by ASD to be identified and referred to the most effective treatments available, thereby affecting families, the general public, service providers, legislators, and government officials seeking solutions on how individuals with autism should be identified and treated.

Implementation: What should Autism Speaks do?

- Prioritize funding in the following areas:
 - Autism screening instruments for infants
 - Studies on more efficient, empirically valid diagnostic methods, such as a shortened version of the ADI
 - Studies focused on screening, diagnosis, and assessment of ASD in higher functioning and older individuals, including aging adults
 - Studies that link biological and phenotypic data, either through informatics efforts or data repositories
 - Studies that identify subtypes of ASD linked to etiology, course, and/or response to treatment
 - Studies that improve screening, diagnosis, and treatment of underrepresented and underserved populations
 - Studies that examine systems-based approaches to care in order to better understand gaps in the system of care and improve best practices through training and information dissemination. These studies should include those that identify factors that will allow better access to diagnosis and treatment of individuals with ASD.
 - Studies that focus on development of systems for building expertise through training that can be implemented broadly, such as “train the trainer” models and use of web-based methodologies
- Sponsor workshops/think tanks on the following topics:



- Consensus standards for diagnosis and phenotyping in research studies and clinical settings
- State of the science: Models and factors related to dissemination of best practices in autism
- Support novel approaches/opportunities that potentially will accelerate discovery:
 - Utilization of existing population-based studies to examine prevalence and risk factors, such as population-based registry data available only in certain territories, the ALSPAC study, the National Survey of Children’s Health, or the National Children’s Study (NCS). There were many strategies for collaborating with the NCS including a nationwide standard for screening and later diagnosis and isolating particular study sites with the proper training to collect individual data (from cases and non-affected controls) at the same sites.
 - Facilitate population-based research by providing seed money or partnering with larger scale studies to refine diagnostic instruments
 - Encourage the cooperation and data-sharing activities of research projects which share similar goals. Support opportunities for researchers to collaborate, share data, or interact using existing data.
 - Enhance clinical diagnosis with genetic screening or collection of genetic data in epidemiological studies for customized and accurate genetic diagnostic tools to enhance (but not replace) behavioral phenotyping in the future
- Partnerships that can facilitate discovery and dissemination of clinically relevant findings:
 - Partner with National Children’s Study to facilitate research on environmental risk factors and early screening and diagnosis
 - Through the GAPH initiative, partner with NIH and other government and professional agencies both in the US and from other countries to implement awareness, research and training efforts
 - Facilitate partnerships through the International Autism International Epidemiological Network , a network of epidemiologists focused on autism research, in order to build research capacity in other countries that will allow studies of prevalence and risk factors
 - Partner with the American Academy of Pediatrics, leveraging efforts focused on training and dissemination both nationally and internationally, policy and standards for diagnosis, and research on screening and diagnosis
 - Continue to support the Baby Sibs Research Consortium, a collaborative effort that will facilitate development of methods for very early risk assessment and diagnosis
 - Continue to support Autism Treatment Network, a collaboration among clinical autism centers focused on the development of a common clinical assessment protocol, detection and assessment of associated medical conditions, policy and standards for medical assessment, and training and dissemination of standard of care

Metrics: What does success look like?

- Improved tools that are used by a wider group of individuals, including a tool used by both clinicians and researchers



- Integration of genetic risk marker analysis or an additional biomarker into standard screening or diagnostic practice
- Initiation of a natural history study to describe the phenotype across the lifespan, even in a preliminary study, to examine differences at different age ranges
- Translation of gold standard instruments into three new territories, including validation; this may include utility of a more cost effective and efficient method of screening into an international setting
- Reduction in age of diagnosis
- Uniform standard for screening and diagnosis in young children
- Identification of relevant subtypes
- Enhance capacity of service providers, including the knowledge base, through an increased number of newly trained clinicians
- Change in professional practice and standardized use of diagnostic instruments by clinicians and researchers
- Development of a prospective study or partnership with current epidemiological research which can help incorporate refinement of research tools in clinical settings
- Identification and partnership with organizations that can help Autism Speaks facilitate the above missions and goals
- Employ new technologies for screens of associated conditions, such as 24 hr EEGs, sleep monitors, blood/urine tests for mitochondria dysfunction
- Identify the comorbid conditions present across lifespan and screen for these in clinical practice, such as depression, GI, sleep, immune, and attention impairment
- Methods for broad dissemination of knowledge and clinical training are developed that can be utilized both nationally and internationally

PREVENTION AND TREATMENT PORTFOLIO

Translating scientific discoveries into clinical practices is a central goal for improving the lives of approximately 1.5 million Americans currently struggling with autism. Basic science researchers need to work collaboratively with clinicians in order to develop more patient-driven and targeted therapeutics that solve real-world problems in patient care. Many families report that they are dissatisfied with their medical care; they report that their physician is lacking in adequate knowledge and expertise and unresponsive to the complex needs of their family member with autism. Many such families turn to unproven methods that have not been empirically validated in an attempt to improve the lives of their children with ASD.

In order for all individuals with autism to receive consistent quality care, the field needs to better understand the needs of individuals with ASD, develop more effective treatments, and establish standards and guidelines for biomedical and behavioral treatments *across the lifespan*. Furthermore, it is important to determine whether treatments that work under ideal conditions in controlled laboratory environments will also work under real-world conditions where providers may be parents and patient compliance is more difficult. Another major challenge is the lack of adequate numbers of trained professionals to deliver the available treatments. Thus, even when effective treatments are known, families may not have access to them. Finally, insurance coverage of autism treatment is poor, making available treatments expensive for families.

Biomedical treatments. While most compounds in use today target associated symptoms, few target the core symptoms of autism. Although we are beginning to have a better understanding of the biological basis



of autism, effective biomedical treatments that can reliably reduce autism symptoms are not available. Instead, many parents are using untested treatments that have variable efficacy based on anecdotal evidence.

The challenge in developing effective treatments is great. A tremendous amount of time and effort is required to translate pre-clinical data from biomedical research into a clinical setting¹¹. The development of animal models, a necessary step in testing experimental therapeutics, has posed a particularly difficult challenge to researchers given the heterogeneity of the disorder, the scarcity of biological markers, and the complexity of autism genetics and environmental factors. Moreover, scientists are not well equipped to develop the technologies that are required for translational research, and clinical research proposals tend to score poorly in peer-reviews compared to basic research proposals. The lack of access to large cohorts of well-characterized patients is another barrier. Multi-site networks are critical for identifying large cohorts of patients, decreasing the time it takes to move drugs through the pipeline. Autism Speaks' Clinical Trials Network (CTN) is designed to identify and fast-track the evaluation of medical treatments using a network of researchers with expertise in clinical trials and autism. The Autism Treatment Network (ATN) also offers a platform for testing medications and other treatments. The availability of these networks has attracted the attention of both specialty pharmaceutical and nutraceutical companies who wish to use them as a platform to test the efficacy of medications. Researchers have found that evaluating medications used in psychiatry to treat symptoms such as anxiety and repetitive behaviors has proven effective for some individuals with ASD. For example, Risperidol, a medication used to reduce aggression in children, has received a clinical indication for autism from the FDA based on efficacy data. Getting more drugs through the FDA with clinical indications for autism will enable insurance providers to reimburse families for costly medical interventions. Finally, the discovery of environmental risk factors, a nascent field of study in autism, holds promise for developing prevention and treatment strategies by eliminating or minimizing the impact of these environmental factors.

The modal number of simultaneous treatments that parents who responded to an IAN survey reported using is 5 (see http://www.iancommunity.org/cs/ian_research_reports/treatment_report). Individuals with ASD commonly struggle with significant co-morbid conditions, anxiety, ADHD, irritability, aggression, self-injurious behavior, and several medical conditions (discussed below). These conditions and behaviors often prevent them from benefiting from behavioral, educational, and psychosocial therapies which can be of great benefit. Indeed, autism is increasingly recognized as a disorder that affects the whole body, not just the brain. Individuals with autism suffer from a range of medical conditions, including gastrointestinal problems, seizures, sleep difficulties, allergies, and metabolic abnormalities. Many times, physicians, educators, and psychologists serving an individual with ASD will attribute challenging behaviors, such as irritability, aggression, and apathy, to core autism rather than exploring the possibility of an underlying medical condition. The general lack of information about the presence and treatment of these conditions and the poor communication skills of many individuals with ASD compound the problem further. The etiological significance of many of these medical conditions is poorly understood, but their negative impact on health and quality of life is clear. Children with poor sleep and pain are unable to take advantage of the behavioral/educational programs that have been found to be effective. Treatment of underlying medical conditions such as metabolic conditions and seizures also could result in improvement of core symptoms. To address these difficulties, many parents are seeking biomedical treatments that have not been well-evaluated. Anecdotal reports indicate that some of these treatments may be effective in reducing symptoms of autism and improving quality of life. It is imperative that better communication takes place between practitioners offering these untested treatments and the

¹¹ See Begley, Sharon, "Endless red tape and paternalism toward study volunteers is having a stifling effect on clinical research." *Newsweek*, August 9, 2008, <http://www.newsweek.com/id/151756>.



clinical scientists who can carefully test their efficacy. Parents need to know what is effective so that valuable resources can be spent wisely.

Autism Speaks' Autism Treatment Network (ATN) has been a pioneer in trying to establish evidence-based medical practice guidelines to address the medical issues of children with autism. The ATN team identified concerns critical to improving children's medical care that can be addressed through multi-site research networks. The first is the identification of common comorbid conditions affecting children with ASD, both in terms of their characterization and treatment. Conditions identified as of particular concern included GI dysfunction, sleep disorders, nutritional/feeding issues including food allergies and limited food preferences, metabolic disorders, seizure disorders, hormonal imbalances, and co-morbid psychiatric disorders. There remain questions regarding the prevalence of these conditions in ASD and their relationship to etiology, course, behavioral symptomatology, and outcome. Thus, more research in this area is clearly needed.

Complementary and Alternative Medicine (CAM). Surveys suggest that 9 out of 10 parents treat their children with complementary and alternative therapies (CAM) that range from chelation to vitamin supplementation. However, there is a lack of adequate efficacy and safety data on such therapies. Autism Speaks and other funders of biomedical research in autism have recently targeted research in this area. One trial recently funded by Autism Speaks is a randomized double blind placebo controlled study of omega 3 fatty acids in children with autism. Omega 3's are one of the most widely used supplements for children with autism thought to improve cognition, mood and behavior but its effectiveness has never been rigorously evaluated in ASD populations. One of the challenges that exist with respect to research on CAM is that the clinicians who are using such approaches with reports of success often do not have the time, expertise, or resources to conduct well-designed research studies. Thus, collaboration between such clinicians and clinical researchers will be necessary to move the field forward.

Behavioral treatments. Whereas autism previously was considered a disorder with an extremely poor prognosis with only 50% of individuals developing spoken language, it has now been demonstrated that 75-95% of children who receive early intensive behavioral intervention develop useful speech by age 5. Three separate groups have now reported that a significant proportion of children receiving intensive behavioral intervention early in life make outstanding progress, with autism symptoms diminishing and developmental outcomes improving such that some of these children no longer have evidence of disability. For the first time, prevention of ASD in a subgroup of at risk children is plausible. Prevention will entail detecting infants at risk before the full syndrome is present and implementing treatments designed to alter the course of early behavioral and brain development.

Research on typical brain development has shown that the development of brain circuitry - its acquisition, organization, and function - results in part from the interaction between the infant's brain and his or her environment. Altered interactions between the infant and his/her environment resulting from autism likely represent a "second hit" influencing atypical brain and behavioral development in autism. Such altered interactions might further influence gene expression. Such gene-environment interactions have been demonstrated in animal studies. Animal models of developmental and degenerative disorders have demonstrated the role of early stimulation in mitigating the effects of genetic risk and environmental injury. This raises the possibility that early interventions aimed at stimulating infants and toddlers at risk for ASD can substantially change the course of both behavioral and brain development, allowing *prevention of the full syndrome in some cases.*



Early identification of children as young as 18 months of age has offered new avenues for clinicians to alter the developmental trajectory of children potentially at risk of developing autism. However, the notion that one size does not fit all recognizes the need for interventions that are individualized for each child. Until recently, little, if anything, was known about the ability of early intervention programs to prevent symptoms of autism from emerging or which components of those interventions (e.g., duration, frequency) were most critical. Given that these treatments are comprehensive, intensive, and require a substantial investment over a long period of time, it is important to understand which therapies are most effective and for whom these interventions yield the greatest outcome. Autism Speaks' Toddler Treatment Network (TTN) and the Baby Sibs Research Consortium (BSRC) are two programs that have made significant advances in early identification and early interventions for autism. Researchers agree that larger scale studies and the use of multi-site networks are necessary to determine which components of a behavioral intervention program are most effective.

Multi-site research networks. The members of the workgroup identified the importance of multi-site research networks such as the CTN, ATN, BSRC, and TTN in advancing the treatment field. The advantages of multi-site research studies are well recognized, particularly in developing treatments through randomized clinical trials as stated above. Multi-site studies provide a number of advantages: (1) access to larger study samples with more diversity in clinical and sociodemographic characteristics than typically found in single site studies, (2) expedited recruitment, (3) greater statistical power, and (4) enhanced external validity. Research *networks*, where multisite researchers not only collaborate on a single study, but develop ongoing collaborative relationships with administrative support, allow even greater ability to consistently define research populations for better cross-study comparability and to develop uniform assessment batteries and data collection procedures.

Prevention through discovery of environmental risk factors. As detailed in the Etiology section above, the identification of environmental risk factors could inform changes in public health priorities. The huge increase in prevalence of autism in the last decade suggests the real possibility of environmental contributions to the etiology of ASD. The confirmation and subsequent elimination of even one environmental risk factor, for example, could have immediate impact on improving outcomes of susceptible individuals and potentially reduce the prevalence of autism. Research on environmental factors could affect public policy and governmental regulations on chemicals and other toxic exposures and also inform recommendations on prevention and treatment. Thus, research in this under-explored area is urgent.

Goals and theories of change

While autism is more prevalent than cystic fibrosis, pediatric HIV, and juvenile diabetes, standards of care for individuals with autism are lagging behind. Early identification of infants at risk for autism presents unique opportunities for early intervention but more research is needed to understand which treatments and interventions will yield the greatest outcomes. Given the average number of therapies that individuals with autism receive, it is important to develop methodological approaches to systematically evaluate them. Studies of adults will be critical to the evaluation of long-term outcome for individuals across the lifespan.

Several challenges exist across the continuum from discovery to dissemination that represent unique opportunities for Autism Speaks to affect positive change towards the development of targeted and effective therapeutics. Ultimately, families need access to evidence-based treatments that can be implemented at home and in their communities. We need to engage researchers, clinicians, and care



providers to deliver high quality, individualized care and engage parents as partners in the research process. To this end, the following goals are priorities that would have great impact on families and on the broader scientific community.

Goal #1 Within the next 5 years, at least one efficacious biological treatment is available that can significantly influence the core symptoms of autism (See Goal #1, Biology Portfolio).

Medical interventions that reliably address the core symptoms of autism are not yet available. The development of such treatments will require investment in research focused on the biological and etiological basis of autism, the development of animal models, and the development of the technologies that are required for translational research. A separate review panel for treatment research should continue to be used by Autism Speaks to ensure that adequate funds are directed toward treatment research. Continued support for multi-site networks, such as CTN and ATN, will also be critical for identifying large cohorts of patients, decreasing the time it takes to move drugs through the pipeline.

Goal #2 Within the next three years, pre-clinical assays/model systems to study effects of risk genes and environmental factors on biological pathways and fast-track the screening of novel treatment interventions are developed and used in research on drug discovery (see Goal # 3, Biology Portfolio).

Goal #3: Within the next five years, biomarkers or clinical features are identified that index meaningful subtypes of ASD and predict response to treatment (see Goal #2, Etiology Portfolio).

There is a need to develop more individualized approaches to treatment for individuals across the lifespan. We need to move away from “one size fits all” models and focus on a multidisciplinary and personalized approach to care. This includes, where possible, incorporating biological and behavioral markers in evaluation to predict treatment response. Well-identified individual differences will have significant effects on outcome and specific implications for treatment choice. Understanding both the individual and group differences between responders and non-responders to specific treatments will help determine which therapies work best for which types of individuals.

To determine the responsiveness of individuals from identified subtypes to different treatment modalities, more comprehensive genotype and phenotype information should be used to characterize individuals in ongoing clinical trials in order to retrospectively examine the relation between these variables and treatment response. To prospectively create targeted interventions for subtypes, short-duration modification/observation cycles can be conducted to obtain a tailored approach for each subtype. Individual subgroups can be moved through treatment regimes quickly, choosing the next step on the basis of past results. Research on dynamic treatment regimes (i.e. SMART research trial design – re-randomizing responders versus non-responders at each stage) can help identify what components of therapies are due to naturally-occurring developmental processes and which are due to the treatment benefits for that subgroup, *per se*.

It would be useful to establish a data base of treatments commonly used in autism and their effectiveness (or ineffectiveness) on both core and associated symptoms. This data base would be ‘reviewed’ to help ensure that there is moderate agreement among the clinical community regarding treatment effectiveness. It is equally important to include those treatments that appear to be of no, or minimal efficacy. It is understood that there is variability in treatment effectiveness, and the optimized data base could have estimation of the percentage of individuals affected positively/negatively.



Research that integrates biological and behavioral markers into long-term treatment outcome will shed light on the underlying neurobiological correlates that can be influenced by treatment. For example, early intervention is thought to influence synaptic plasticity by rewiring aberrant connections and strengthening neural networks in the brain. By stimulating these brain changes, early intervention could alter the developmental trajectory of infants and potentially mitigate the downstream effects that manifest as autism. It is important to incorporate biological measures into both behavioral and biomedical intervention studies, both in terms of predictive biomarkers that can direct treatment choice, as well as biologically-based outcome measures. Including biologic endpoints into treatment outcome research will help the basic scientists develop animal models to inform treatment.

Goal #4 Within the next five years, the mechanism of action of at least a subset of environmental factors that significantly contribute to risk for autism and their interaction with genetic factors is identified and understood (See Goal # 3 Etiology Portfolio).

Goal #5 Within the next three years, exportable, manualized, scalable early behavioral interventions appropriate for infants through preschool age are available. Given the evidence that early behavioral interventions are highly effective for many children with autism and that insurance coverage for such interventions is becoming more common (in large part due to Autism Speaks' advocacy), very high priorities will be (1) discovering the most effective early intervention methods for infants-preschool age, (2) developing methods that are scalable and exportable to a wide range of communities, including other countries, and (3) identifying the moderators and mediators of response to early intervention. In addition, studies that examine the efficacy of combined medical and behavioral interventions for children who are not responding well to behavioral interventions alone will help address the needs of children who are not making fast progress in their early behavioral intervention programs. Although best practice for young children diagnosed with ASD is to implement early behavioral intervention, there is little known about what is the best course of action when a child is making very slow progress in such programs. For example, little is known about the best strategies for addressing the needs of children who are nonverbal despite having participated in traditional early behavioral intervention programs.

Goal #6 Within the next five years, medical and behavioral/psychosocial treatments that address the needs of school age, adolescent, and adult individuals with ASD are developed. There is a great need to understand how best to sustain improvements in outcome that are made during the preschool period and how best to help children with ASD adapt to the social and academic demands of later school programs. Treatments aimed at the needs of older children and adults need to be developed, tested for efficacy, and exported and tested in community settings. Such treatments need to address social and academic functioning, such as social isolation and bullying, and co-morbid medical conditions, such as anxiety and depression, which commonly manifest during adolescence and adulthood. Very little is known about the needs of individuals with ASD as they enter later adulthood and old age. Research focused on approaches to facilitate transition to adulthood, success in college, vocations and jobs, adult relationship and social functioning, and conditions associated with aging is needed.

Goal #7 Within the next five years, best practice guidelines for biomedical and behavioral interventions and a standard for training healthcare professionals and care providers are established. In order for all individuals with autism to receive consistent quality care, the field needs to move towards establishing practice parameters and guidelines for treatment. A growing concern among families affected by autism is the availability of trained professionals to address the vast medical, mental health, and behavioral concerns of children and adults with autism. Any effective treatments must include a mechanism to train care providers to administer that treatment.



Children with chronic disorders such as cancer, cystic fibrosis, or diabetes can go to one of the specialty clinics at their local children's hospitals and receive comprehensive standardized evaluations. Individual profiles of children determine the right course of treatment. Unfortunately, these standards and practices do not exist for biomedical or behavioral treatment of children with autism, and there is a scarcity of personnel trained to administer the few treatments that have been found to be effective. It is imperative that the field move towards *establishing evidence-based guidelines and standards of comprehensive quality clinical care* for all individuals across the lifespan.

Many of the NIH-funded multi-site networks such as the STAART and ACE networks have treatment components that include outcome research. It is critical and timely that a workgroup be convened to develop consensus standards based on the judgments of the experts in the field for the delivery of behavioral treatments and interventions. Once these standards are agreed upon, researchers must design randomized controlled trials to build the evidence-base to support these standards. Standards of medical care for all individuals with autism are being addressed by the ATN. The ATN is working with the National Initiative for Children's Healthcare Quality to develop standards and practice guidelines for the treating physicians and other health care providers and to support the broad adoption of proven clinical interventions. Similar standards need to be developed for psychologists, educators, speech-language therapists, and occupational therapists who work closely with physicians to provide coordinated care.

Most insurance companies will not reimburse families for therapies and interventions that are not proven or for which there aren't standards. Once the field starts generating standards of care, insurance companies will have to change their policies to reimburse for therapies these children need.

One barrier to care for children with autism is that there are many more affected individuals than there are trained professionals to deliver comprehensive care. There is much to be gained by creating a paradigm shift among institutions of higher learning towards supporting training opportunities for professionals interested in working in the field of autism. By providing paid internships/fellowships at leading academic institutions with autism treatment centers and training programs, more young professionals will be encouraged to apply. Partnering with the federally-funded Leadership Education for Children with Neurodevelopmental and Related Disabilities (LEND) programs nationwide will help provide interdisciplinary training to improve the clinical expertise and leadership skills of health professionals who treat children with disabilities. LEND programs provide long-term, graduate level interdisciplinary training as well as interdisciplinary services and care. There are 37 LEND programs in 27 states nationwide that form a network of professionals invested in training the leaders of the future. The development of training opportunities developed through partnerships such as these would increase the workforce, reduce the clinician burden, and increase access to quality healthcare.

Goal #8 Within the next three years, outcome measures and clinical endpoints for basic and clinical research that maximize positive effects to determine safety and efficacy are identified and accelerate progress in the field. Consistency among outcome measures in drug trials, whether they be open label trials or RCT, is lacking in the field. Furthermore, sensitive quantitative measures of change do not exist for either behavioral or biological measures. Many pharmaceutical companies launch large-scale trials of repackaged compounds without a good understanding of the population characteristics potentially compromising the perceived efficacy of the compound and generalizability for individuals with different biological or behavioral profile subtypes. Behavioral and pharmacological interventions need sensitive measures of change that are agreed upon that can be established for different age groups to determine



effectiveness. Standards for study design and data collection will help investigators better target the intended outcome and will help scientists develop model systems that can be replicated.

Reaching agreement on standard outcomes for clinical trials in individuals with ASD is important in enabling researchers and clinicians to compare, contrast, and combine the findings of these trials. Agreement on these standards should also help reduce the possibility of biased reporting. If researchers have a choice of outcomes, they might be tempted to report selectively, emphasizing those that give them the results they find most attractive and/or omitting those that do not support their hypotheses. When there is a standard set of outcomes and outcome measures, researchers interested in replicating findings in other trials should be cautious of any trials that do not report all of these outcomes.

There are several initiatives that addressed the importance of standardizing outcome measures for adult disorders including those from the fields of osteoarthritis and ulcerative colitis. The initiatives that were successful in establishing these standards used a data-driven, iterative consensus process to derive standard outcome measures. For the autism field, a thorough review of the literature on clinical trials should be conducted by an expert working group to create a list of outcomes measures used in those studies. Next, a group of key thought leaders representing a range of approaches should be convened to review the list and develop consensus on the outcome measures and clinical endpoints that would be most important to maximize results and increase sensitivity. These outcome measures should be used in the design of clinical studies to determine their effectiveness in measuring treatment outcome. If these should prove effective, then a core set of outcomes measures can be established and reviewed annually to serve as an international standard for future trials and cross comparison analyses.

Who will benefit?

The development of effective treatments will benefit individuals living with ASD now. Advances in treatment research will also have an enormous impact on the quality of life of families, which often experience high levels of stress, depression, anxiety, and divorce. The development of targeted and effective therapies and parent-based interventions will empower families to implement care in partnership with primary care providers, ultimately giving way towards better outcomes. Early identification of infants and toddlers at risk for autism can lead to targeted behavioral and biomedical interventions that can alter the developmental trajectory of these children.

A key complaint among families affected by autism is access to care. The limited availability of trained professionals makes it difficult for the 1.5 million Americans living with autism to receive adequate services to address their needs. Training programs for service providers will increase the workforce and will draw specialists to the field. Evidence-based practice guidelines will also empower the primary care providers to deliver the best quality of care within a multidisciplinary care model.

Parents of children with special health care needs have significant life stressors that can have deleterious consequences. The availability of targeted therapeutics and interventions will ultimately positively impact their quality of life. As effective and safe treatments are discovered and made available to the public, there should be a push on the state and national level to make these treatments more accessible to families. Government entities that appropriate funds to improve quality of care in the school systems should ensure that these practices are integrated into well-baby clinics, schools, and adult care facilities.



Implementation: What should Autism Speaks do?

- Prioritize funding in the following areas:
 - Early intervention research, including the Toddler Treatment Network, encouraging the integration of outcome data across the several Autism Speaks funded clinical trials for toddler intervention
 - Exportable methods of early intervention, such as parent-delivered interventions and web-based training methods
 - Treatment studies that incorporate biological measures of response to treatment
 - Studies that identify moderators or mediators of response to treatment
 - Intervention studies aimed at improving the outcomes of lower-functioning and/or nonverbal children with ASD
 - Treatments that reduce core autism symptoms (social and language functioning, repetitive behaviors)
 - Treatments that incorporate a whole body approach by addressing medical conditions associated with ASD (e.g., GI, sleep, seizures, allergy, food intolerances, metabolic conditions)
 - Treatments that address the psychosocial and/or medical needs of school age children, adolescents and adults with ASD, including issues such as teasing and bullying, social isolation, comorbid anxiety and depression, regression in adolescence, transition to the work force and college, quality of life, and aging adults with ASD, among others
 - Development of ways to improve patient compliance with medical procedures (dental, blood draws, MRIs, electrodes, swallowing pills, sticking to a diet, and so on)
 - Validation of biomedical interventions that are widely used by parents but have not been evaluated for efficacy or safety
 - Training methods for providers in the community, including physicians, psychologists, educators, and other providers
 - Consensus standards for treatment study methods, including clinical endpoints
 - Development of practice guidelines for treatment across the lifespan
 - Development of training models for physicians and other health care providers
 - Clinical trials networks, such as ATN and CTN, for testing the efficacy of treatments

- Sponsor workshops on following topics:
 - Workshop of expert clinicians and basic scientists to establish standardized outcome measures and identify common clinical endpoints that can be used in both treatment research and in mouse models
 - Convene a group of expert clinicians and researchers to establish common measures for clinical trials that will generate a white paper for the field
 - Through the ATN, sponsor satellite symposia at national subspecialty conferences to establish a research agenda to better evaluate and treat the associated medical conditions in autism
 - Subsidize clinical internship and medical fellowship programs that would provide training for health care providers to work with an ASD population

- Support novel approaches/opportunities that potentially will accelerate discovery:



- Methods and technologies that support translational research, including animal models, assays, and so on
 - Continued investment in animal models demonstrating recovery (Fragile X, Rett syndrome)
 - Include clinicians in the development of an animal model consortia so that they can work collaboratively with basic scientists to bring the clinic to the bench
 - Create a mentorship program for young investigators interested in conducting clinical research that would provide stipends to the mentors who would then serve as advisors to young investigators on study design and methodology
 - Sponsor clinical and research trainees from countries outside the U.S., funded by the outside country, seeking to build scientific and clinical expertise in their country
 - Encourage the development of toolkits for parents and create training videos for parents that can be accessed via the AS website
- Form partnerships that can facilitate discovery and dissemination of clinically relevant findings:
 - Partner with the LEND and American Academy of Pediatrics training programs to educate physicians, psychologists, nurses, and other health care providers about autism
 - Work collaboratively with the ATN, the American Academy of Pediatrics, and other professional societies to establish evidence-based guidelines and practice parameters
 - Identify pharmaceutical and biotechnology partners interested in participating in drug discovery and genetic workshops/research
 - Work with the FDA and the NIH to provide funding for drug development in autism
 - Collaborate with law enforcement and other first responders to tackle (1) excess mortality in autism due to accidents through parent and first responder training, and (2) inappropriate treatment of individuals with ASD in legal situations
 - Think tank sponsored by the Autism Consortium, the SIMONS foundation, and AS to address the clinical implications of genetic findings

Metrics: What does success look like?

Shorter term (within 5 years)

- At least two medical treatments exist that address core symptoms of autism
- Increased numbers of treatments that address the medical conditions associated with autism are empirically-tested and used in clinical settings
- More physicians readily recognize the medical conditions that individuals with ASD suffer from and are able to prescribe appropriate treatments and/or referrals
- Increased numbers of children at risk for autism are receiving early intervention services, which are paid for by their health insurance
- Early intervention approaches that are feasible for low income communities, such as parent-delivered interventions, are available and methods for training parents in such methods via the web are accessible by a wide range of parents
- Consensus on a set of guidelines and standards for treatment outcome research improves quality of research



- Two standards of medical care a year are established
- Increased numbers of psychosocial/behavioral and medical treatments effective for adolescents and adults are available

Longer term (within 5-10 years)

- One-third of individuals with ASD are prevented from developing the syndrome through early detection and treatment
- A treatment algorithm, based on an individual's personal profile, exists that helps physicians and other health care providers deliver individualized treatments based on the specific condition(s) an individual is suffering from
- Treatment centers for autism are well-defined and received certification; Centers exist within 100 miles for every family that has a family member with ASD
- Schools and other educational and health care providers understand the challenges associated with transitioning from preschool to elementary school so that gains during the preschool period are sustained
- The treatments needs of individuals with ASD are well understood in adolescents and adults, and more treatments addressing these needs are available
- FDA begins fast-tracking clinical trials for drugs targeting core symptoms of autism
- A federal mandate for insurance coverage for autism services is passed
- Access to clinical care is increased through training of physicians, psychologists, teachers, and other care providers
- Most communities in the U.S. offer effective early intervention programs, and countries throughout the world are engaged in training programs for early intervention

Longer term (within 5-10 years)

- Training programs and fellowships for clinicians and researchers interested in autism are established
- Standards of care and practice guidelines are adopted by health care providers nationwide, and insurance companies will reimburse for services
- Novel drugs are in the drug discovery pipeline
- List of the most effective treatments for particular subtypes of autism has been
- Federally funded Autism Treatment Centers of Excellence are established in most major cities
- Animal models are successfully used to screen potential drugs for the development of effective therapeutics
- A number of children thought to be at-risk during early screening do not develop a diagnosis of autism as the result of early intervention programs
- White paper is published that describes the clinical implications of certain genetic findings
- Treatment standards are adopted internationally



- Economic burden is decreased as early intervention prevents children from developing autism and reduces symptoms, thus minimizing costly services later on in life
- Treatments are extended to adults so conditions are ameliorated and cost to society is reduced

DISSEMINATION AND POLICY

Over the past decade, awareness and understanding of ASD has increased dramatically. In part due to Autism Speaks' highly successful awareness campaign, public and professional awareness of ASD has registered double digit percentage gains, and we now know more about autism's possible causes, biological mechanisms, diagnosis and treatment, all of which raises community expectations for access to better care, more effective treatments, and less suffering. Clearly, an efficient and effective process for rapidly disseminating knowledge and translating research insights into patient care solutions is essential for meeting those expectations and for delivering the broad, life-changing impact to the global autism community that is Autism Speaks' core mission.

Dissemination is a key component of the translation process. It involves diffusion, where new information or technology is introduced and spread passively through a population, and active social marketing, which encourages changes in practice or behavior. Dissemination content includes a wide range of materials and modalities, from the latest research findings to clinical tools like the American Academy of Pediatrics' (AAP) Autism Toolkit and Autism Speaks' 100 day kit.

There are many unmet dissemination needs in the autism community. The sheer variety, volume, and complexity of autism research, for instance, limit the public's ability to understand and absorb new findings. As a result, demand for accessible information that accurately describes the science and its implications for families has never been greater. Healthcare providers and educators, who share an appetite for new tools and resources to enhance the quality of their work, are similarly struggling to understand and care for their patients. Because needs evolve over time in response to new developments, the importance of a dynamic process that can accommodate shifting priorities and emerging opportunities should be stressed. For example, if current momentum in genetic and early diagnosis research holds, the autism community will soon be contending with the introduction of new technologies, such as DNA-based autism risk assessment, that if properly disseminated and deployed, could have broad, life-altering consequences for a significant portion of affected individuals and their families.

Goals and theories of change

A successful dissemination effort is dependent on many factors, including the nature of the content and the desired outcome. For instance, while getting the aforementioned AAP toolkit to all practicing physicians, psychologists, nurses, and other health care providers in the US is largely a distribution exercise with a high likelihood of success, making sure all the recipients *adopt* the new practice guidelines in the toolkit is a significantly more difficult challenge. As findings from cancer and obesity research suggest, even when best practices are available, their presence alone does not guarantee widespread behavior change and impact on the community. Therefore, effective dissemination requires evaluation of audience response and adaptation and the process and maintenance of behavior change, so that effective strategies for achieving this key goal can be developed.



While more dissemination is clearly in order, with so many competing needs, an equally important challenge is to find ways to prioritize dissemination that best serves the interest of the community. This problem takes on added dimensions when considering international stakeholders, priorities, and related cultural and resource issues. For instance, AAP's recently revised autism clinical guidelines, even with their clear and compelling benefits to children and families, will have little traction in countries without the screening tools, expertise or resources to support their implementation. Moreover, in many societies, even those in North America and Europe, stigma remains a powerful barrier to progress. Feeding off ignorance and lack of proper support, fear of stigmatization and social isolation could prevent parents from seeking appropriate intervention even when it is readily available. Clearly, without addressing such issues, dissemination of best clinical practices will have little impact on those in need under these circumstances.

Ultimately, effective dissemination of knowledge and technologies helps make parents more sophisticated consumers of health and education care for their children, increases access to care, and enhances the quality of care delivered the world over.

Goal #1 Within the next three years, community-based processes for identifying dissemination priorities, content, implementation strategies, and evaluation methods are developed. Given the influences of content, intent, target audience, and desired outcome on the design, development, implementation, and effectiveness of a dissemination effort, a process to identify stakeholders' priorities and values to help develop and refine the most effective dissemination strategy is essential for delivering solutions to autism communities around the world. These priorities and values should be weighed along with knowledge regarding what practices are empirically validated and ready for dissemination.

While dissemination models from other diseases can be used to guide similar activities in autism, the current state of autism science and the influences of culture, infrastructure, and resources on healthcare and services suggest the need for a more customized community-based development process. A general model that can be customized for a specific type of content in a specific setting is needed. The goals of the effort and the implementation plan should take into account possible local limitations, such as infrastructure and available expertise, to make sure both are practical and feasible in the communities in which individuals with autism and their care providers live. The development of a dissemination effort is likely to be an iterative process that involves testing assumptions, piloting mechanisms, and opportunities for community feedback.

A successful dissemination effort begins with a detailed understanding of the priorities and values of the target audience. There is no evidence to support the assumption that needs, capacity, and expertise are similar in all communities, and to assume so would invite ineffective solutions and failure to progress. For instance, if stigma is likely to inhibit parental acceptance of an autism diagnosis, or even re-evaluation for developmental delay, anti-stigma efforts must take precedence over all other activities. Research needs to identify the community-specific factors that can promote or impede adoption of clinical practices.

A cost-effective strategy is to capitalize on existing platforms for knowledge dissemination, such as the AAP Continuing Medical Education efforts, medical and graduate school curriculum and training programs, and the Autism Treatment Network. Such platforms also add credibility that will influence adoption.

Goal #2 Within the next three years, practice and behavior change in autism healthcare and services are facilitated. The goal of establishing and sustaining community-based best practices for autism care and services requires changes in the way relevant healthcare and education services are



conceived and delivered. In other words, in addition to diffusion of the latest knowledge, there is also a need for research aimed at understanding the factors that can promote or impede the adoption and implementation of evidence-based practices by health care providers, insurers, and policy makers, as well as informed and active social marketing to change practices and behavior. Moreover, it is important to evaluate different models to determine which are most effective for improving adoption and maintenance over time.

There are potentially many goals for a dissemination effort, from simply providing information, to targeting specific changes in practice, to assessing which models of community implementation are most effective. As it was noted earlier, behavior change, especially as related to healthcare and services, is the most challenging because it also involves the organization and financing of care, which could vary from one location to another and is subject to influences of shifting political and social agendas, as well as the state of the economy. In addition to identifying appropriate incentives to enable such change, an ongoing effort is also needed to monitor and sustain change. It is important to note that as conditions at the point of delivery evolve, practices and behavior may need further adjustment in order to maximize benefit to the community.

Education of families of children with autism is a high priority. Typically, sophisticated consumers of health and education care are the best advocates for research and high quality care. Unfortunately, the sheer volume of potential options for care and treatment is often confusing, if not intimidating, and represents a major barrier to informed and appropriate care decisions by the families. Since these families constitute an invested audience, the emphasis should be on creating materials that are usable and specific to their needs in their community. By educating the families, they are empowered to make decisions that are in their best interest and are more able to identify and advocate for unmet needs.

Ultimately, however, we want to improve the way that communities provide care. This will require provider-level change, but more importantly, system-level change that creates incentives for implementing high quality screening, diagnosis and intervention. One of the major obstacles to delivering services is identifying those in need. The lack of a timely, scalable, and systematic screening and referral process delays access to appropriate care and services and lessens the likelihood of a better prognosis. Furthermore, as mentioned earlier, what qualifies as appropriate care is entwined with local values, available resources, and other factors.

Lack of access to appropriate care. Moreover, a major barrier is *lack of access* to well-trained providers due to three factors: (1) too few providers, (2) costs of services are prohibitive, and (3) feasibility (e.g., intensive treatments that require that one parent leave the workforce to oversee the program). To remove this barrier, several things should be done. First, research must identify the most effective models for community-based delivery of services. This will require identifying factors that impede or promote the adoption of practices. Second, training and capacity-building is needed so that the number of well-trained professionals increases. Professional training should be enhanced for physicians, nurses, psychologists, educators, and intervention therapists. Third, the promotion of partnerships between researchers and stakeholders in the development of treatment-related solutions will maximize feasibility and ease dissemination and adoption. Fourth, advocacy efforts aimed at legislative changes in insurance coverage for autism services are critical. Fifth, the continued development, through research, of effective treatments that are feasible and cost-effective is needed.



Who will benefit?

Every individual with autism who was diagnosed late or whose education or health services are less than optimal would benefit from diffusion of more evidence-based models of care. Dissemination of knowledge and best practices will benefit families, scientists, and healthcare and education professionals. It also benefits society by reducing social and economic burden and making its members more compassionate toward those in need. Ultimately, however, more effective dissemination benefits the families of the global autism community. As we have seen in North America and Western Europe, increased public and professional awareness and knowledge about autism has resulted in a less stigmatized community that is a more effective advocate for its needs, more public and private research dollars raised and committed, and enhanced expertise and responsiveness in healthcare and education communities. With further dissemination efforts, it is reasonable to expect a continued upward trajectory in countries like the US, Canada and the UK and improved conditions for affected families in other parts of the world.

Implementation: What should Autism Speaks do?

- Prioritize funding in the following areas:
 - Dissemination research aimed at identifying factors that promote or impede adoption of evidence-based clinical practices
 - Implementation of research aimed at identifying the best models for development of community- based large scale services
 - Research focused on community-specific dissemination priorities, content, implementation strategies, and evaluation approaches
 - Supplements to existing community-based treatment programs that enhance scientific return (e.g., longer term follow up within the target community, addition of an evaluation component)
 - Supplements to existing community-based treatment programs to conduct cost-benefit analyses
 - Research that increases understanding of the financial burdens of ASD and the impact of those burdens on changing access to care
 - Research that focuses on understanding the factors that hinder or promote insurance reimbursement for services
- Sponsor workshops on the following topics:
 - State of the science workshop on dissemination science for autism
 - Workshops that bring together families and clinicians in the community with researchers to facilitate better understanding of the barriers to care and needs of the community
 - The economics of autism, including cost-benefit analyses related to financial and other burdens of ASD and factors that will lessen this burden
 - Identification or development of best practices in how to communicate scientific findings to the public
- Support approaches/opportunities that potentially will accelerate discovery, development, and/or dissemination:
 - Encourage scientists who are studying dissemination science in other fields to become interested in autism



- Encourage institutions focused on dissemination science, such as the Department of Health Metrics at the University of Washington, to focus on autism
- Partnerships that can facilitate discovery and dissemination of clinically relevant findings:
 - Within Autism Speaks, help staff in the Awareness Department create accessible content that accurately describes clinically-relevant autism research findings and their implications for the families
 - Within Autism Speaks, work closely with the Government Relations Department to continue to spearhead state- and federal-level changes in insurance benefits for autism services
 - Work closely with organizations such as the American Academy of Pediatrics, the American Psychological Association, other NGOs (e.g., Gates Foundation), as well as other professional organizations, to leverage existing medical education programs
 - Partner with outside disease-specific organizations to promote understanding and awareness of co-morbid medical or genetic conditions (IRSF, Epilepsy Foundations, etc.), as well as those that specialize in evaluating public knowledge and filling gaps in education such as Research!America

Metrics: What does success look like?

Shorter term (within 5 years)

- More accessible content that accurately describes clinically-relevant research findings and their implications for the families
- Established and implemented models for identifying community-based dissemination priorities, content, implementation strategies, and evaluation methods, with use in both the US and international territories
- Well-understood cost-benefits related to autism services
- Identified factors that promote or impede adoption of practices
- Piloted community-based, large scale models of services
- Insurance benefits for autism services are provided by more individual states in the US

Longer term (within 5-10 years)

- Implemented models for identifying community-based dissemination priorities, content, implementation strategies, and evaluation methods in the US and several international territories
- Dissemination efforts in the US and several international territories have resulted in change to healthcare practice and behavior relative to screening and referral to services or intervention
- Community-based, effective models for services are in place, and individuals with autism have appropriate access to empirically-based services
- Cost-benefit analyses lead to federal-level, large-scale legislative changes in insurance benefits

BIOINFORMATICS

Over the last two decades, advances in autism research have led to enormous growth in the amount of data generated by the scientific community. The ultimate goal of Autism Speaks is to improve the lives of those affected by autism spectrum disorders. The science of biomedical informatics – the broad discipline concerned with the study and application of computer science, information science, informatics,



cognitive science, and human-computer interaction to research, science, and healthcare – is an important means towards that end. Informatics tools are especially pivotal in translational science, the process of moving from discovery to practical application. Whether utilized to improve services and support, medical interventions, or educational programs, they have the potential to make a significant impact on the lives of individuals and families coping with autism spectrum disorders.

Autism Speaks and its predecessors were pioneers in the development and support of autism research databases and tools that serve to store and organize data and allow investigators to query large-scale datasets. Autism Speaks is currently investing in at least eleven data bases: AGRE, AGP, ATP, ATN, AS Website, BSRC, Donor Data Base, Grants Management data base, Grants Analysis Data Base, IAN, and ISAAC. A review of the software, hardware, and human resources that are currently maintaining and developing most of these data bases was undertaken in the spring of 2008. It will be critical for Autism Speaks to have on board the appropriate level of information technology support to keep the organization at the forefront in this domain. One recommendation is to critically evaluate the current IT human resources to ensure that adequate expertise and capability exists and to examine points of redundancy and synergy among the organization.

There have been ongoing national efforts to create a collaborative bioinformatics initiative for the field, and collaboration between AS and the National Institutes of Health (NIH) could leverage resources and maximize the strengths of both groups. The National Database for Autism Research (NDAR) is a bioinformatics system being created by the NIH to support research in autism and help accelerate scientific discovery. NDAR's goal is to serve as a policy leader for these collaborative efforts by establishing guidelines for data sharing, developing data standards for the community, maintaining a registry of all funded study protocols in autism, providing tools for genomics and meta-analyses, and promoting data sharing.

In order to facilitate translational research, it is also critical to develop the tools that will help researchers model and analyze complex biological data. The availability of these tools will encourage researchers to contribute their data and provide an incentive to share and adhere to standards. Another NIH initiative, the Biomedical Informatics Research Network (BIRN), has been very important in addressing these issues. The BIRN represents a virtual collaborative designed to provide critical tools for researchers to evaluate data across the biomedical community.

BIRN offers a diverse array of software tools and infrastructure resources to the biomedical community and is committed to developing and sharing new software tools and data sets to support the advancement of data acquisition protocols, data analysis, data management, and universal practices in collaborative and multi-site research. They are committed to an open source policy, and all software downloaded from BIRN is made readily available. It is important that Autism Speaks provide researchers within the field of autism with the same opportunities for data mining and data analysis. Taken together, both research informatics and computational informatics will help researchers understand the complex biological problems in autism that are critical to support the translation of knowledge from discovery to delivery.

Time for an Autforum? The advent of scientific web communities has proven extremely promising and effective in the field of Alzheimer research (Alzforum) and now schizophrenia (Schizforum) and is important for the field of autism. Alzheimer Research Forum Web site (<http://www.alzforum.org>) is an independent research project that aims to develop an online community resource to manage scientific knowledge, information, and data about Alzheimer disease. Its goals are to promote rapid communication,



research efficiency, and collaborative, multidisciplinary interactions. It has become a global online research community, with approximately 30-50% of all active Alzheimer researchers visiting it regularly. The Alzforum creates and maintains public databases for basic science research, reports on the latest scientific findings across all disciplines in Alzheimer research, and produces discussion forums to promote debate, speed the dissemination of new ideas, and break down barriers across the numerous disciplines that can contribute to the global effort to cure Alzheimer disease. The data suggest that the Alzforum has stimulated the pace of scientific discovery in Alzheimer disease by leaps and bounds. Alzforum's guiding principle is that the site would be "the daily tabloid for Alzheimer disease research¹²." Registration is free and the home page is dynamic, useful, and entertaining. Among its features are the latest news, a live discussion, "image of the week," opinion polls, conference reports, and commentaries by prominent scientists. It is spearheaded by highly informed science journalists.

A more recent development is SWAN, a Sematic Web Application in Neuromedicine. The SWAN project is another collaborative in which Alzforum curators are collaborating with informatics researchers to develop novel approaches that will enable communities to share richly contextualized information about scientific data, findings and hypotheses. SWAN developed through a collaboration among Alzforum, informaticians at Harvard University, and IBM. SWAN focuses its analysis on the social and practical aspects of the scientific ecosystem's actual functioning, with the goal of improving it (see Figures 16 and 17 from Clark and Kinishita, 2007).

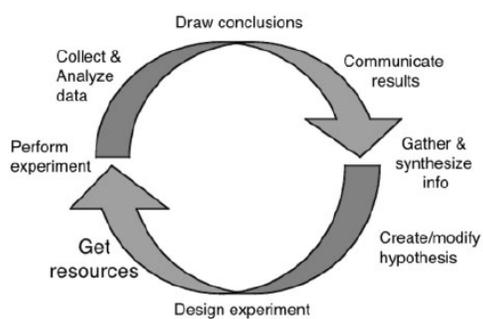


Figure 16 Scientific knowledge acquisition schema.

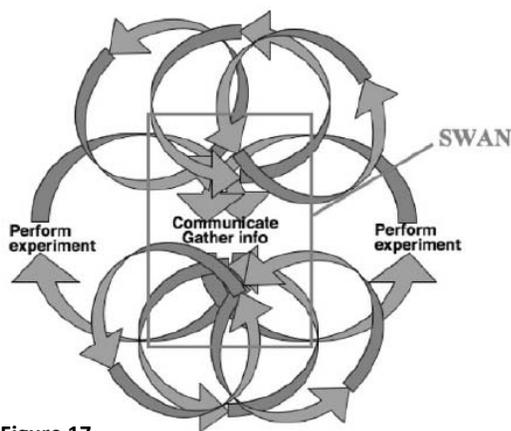


Figure 17 SWAN and the scientific knowledge ecosystem.

One way to significantly impact the autism research community would be to create a scientific web community for autism, termed Autforum, which could leverage the knowledge gained from the investments of Alzforum. This would be a significant way to promote data sharing and collaboration across a diversity of disciplines. Such an endeavor would potentially have wide ranging consequences for the autism research community and families.

In order to support the research pipeline outlined in this strategic plan, an ongoing commitment by Autism Speaks to the development and maintenance of key informatic tools is critical and timely. As we consider the 2009-11 priorities for bioinformatics, several strategies and tactics should be kept in mind:

¹² See Clark, T. and Kinoshita, J. (2007) Alzforum and SWAN: the present and future of scientific web communities. *Briefings in Bioinformatics*, 8: 163-171.



- Tactics that foster collaboration and data sharing are critical (e.g., AGRE, ATP). Implementation of standardization in phenotyping will help remove one barrier to data sharing. Similarly, policies for data-sharing across projects need to be standardized and implemented.
- Investment in data platforms that are integrative, flexible, and sustainable will be most cost effective. Currently, the AGRE program houses one of the largest collections of phenotype and genotype data for families with two or more children with autism spectrum disorders. However, the databases that house the clinical and genetic data are not integrated and mechanisms for generating large-scale datasets are not user friendly. Similarly, the Internet System for Assessing Autistic Children (ISAAC) is the primary data management system for AGRE and other large-scale research efforts and was developed to offer researchers access to a web-based management system with a library of key standardized forms. ISAAC has had an extraordinary impact on the autism community and has served as the prototype for other large scale initiatives such as the NIH National Data Base for Autism Research (NDAR). ISAAC, currently in use by over 400 researchers worldwide, serves as a repository of phenotypic information but needs to be better integrated with other types of data, such as genotype data, to offer researchers the functionality to flexibly analyze the relationships among a wide range of data.
- The provision of data systems that will support translational research are increasingly important in moving from the bench to the bedside, and the reverse.
- Because of the large amount of information that is being generated daily and because some sources of readily-accessible information are not credible (e.g., some internet sites), mechanisms that serve as clearinghouses of information for key stakeholders (families, clinicians, researchers) are becoming increasingly important.
- Due to the high costs of creating and sustaining large scale data bases, leveraging internal and external resources through public-private partnerships will be essential. In developing such collaborations, oversight by financial stakeholders is important. Among the potential partners are the Simons Foundation (e.g., Simons Simplex Collection) and NIH (e.g., National Data Base for Autism Research, Biomedical Informatics Research Network).
- Advances in gene-chip technology, proteomics, neuroimaging, and metabolomics require more sophisticated integrated databases that can support the vast scientific needs of the research community. In order to accommodate and support both the organizational growth of Autism Speaks' science program and the emerging needs of science, there is a need for information systems and computational tools that will help researchers integrate, model and analyze complex biological data more efficiently and facilitate the dissemination of information to families.

Goals and theories of change

The management, availability and use of data are of critical concern. In fact, the management of the information is just as critical to success as the data itself. Gaps are evident across four key areas: data collection, data sharing, dissemination, and computational informatics. Data systems that are flexible and sustainable are critical tools that researchers need to manage the complexity of the data. If Autism Speaks wants to have a global view of all the latest findings in autism research across all disciplines, the informatics plan has to be able to grow in size and scope to ultimately serve as a knowledge sphere that would pull in information from other external databases to help identify research gaps in the autism field and point to areas and connections from which the field has benefited. The following are deemed to be critical goals for the successful development of an inclusive, sustainable, and forward-thinking informatics platform for autism.



Goal #1 Within three years, common measures and standards for data collection are identified that will serve as guidelines for autism researchers domestically and internationally.

Many large scale research efforts have independently developed a set of core measures across a variety of cognitive and behavioral domains. The inclusion or exclusion of particular measures is determined by the scientific rationale and study design. Unfortunately, a lack of uniformity across studies makes it difficult to merge datasets and interpret findings across studies and research groups.

Goal #2 Within three years, larger data sets and improved analytic tools are made available that will better allow scientists to parse subgroups and make critical discoveries despite etiological and clinical heterogeneity.

The volume, size, and diversity of genetic datasets are astounding. Access to many of the large-scale resources (e.g., AGRE/AGP) is limited to a select number of researchers, and the lack of a standardized data sharing plan across research efforts limits the access to AS-funded data. Maintaining resources to support and manage the storage and dissemination of large-scale genetic datasets (microarray/linkage/genotyping) is paramount. Also, more clearly defined policies for data sharing, such as requiring that AS-funded researchers provide public access to publications through PubMed, will help ensure that all AS-funded researchers make their findings available and also have access to other data that they can use as replication samples or for meta-analyses.

Currently, AGRE stores genotyping data for over 900 multiplex families using two different analysis platforms, Affimetrix and Illumina, and the availability of those datasets to researchers has been instrumental in moving the field forward. However, sending hard drives to researchers in the mail is not effective. Autism speaks needs to invest in upgrading the existing resources and in the infrastructure required to create an integrated system that will accommodate biological, genomic, proteomic, imaging, clinical, environmental and cross-cultural data without having to share a common platform. A query tool that will be able to seamlessly integrate data across various databases is critical to these efforts and the resources to support these tools (manpower, computing power) are a necessity. Developing a data dictionary for the field is going to be critical as the field moves towards an ontology for autism research. Evaluating other disease models, such as those for HIV and Alzheimer, to see the successful approaches they used will be an important step.

It is important to look towards other disease groups to understand the resources and tools needed to mine the volumes of data that have been generated by geneticists and neurobiologists studying autism. As previously described, one such scientific web community, the BIRN network, provides a framework for the development of tools and resources that can be made available to the broader scientific community of autism researchers. BIRN is a geographically distributed virtual community of shared resources that hopes to advance the diagnosis and treatment of disease. BIRN was a pioneer in changing how biomedical scientists and clinical researchers made discoveries by fostering communication and collaboration across many of the disciplines. This NIH-supported initiative provides researchers with a collaborative environment rich with tools that permit uniform access to hundreds of researchers, enabling cooperation on multi-institutional investigations. Most relevant to autism, the BIRN network tests and releases new integrative software tools that enable researchers to pose questions and share knowledge across multiple animal models (mouse, human, and non-human primate). The BIRN network may present opportunities for collaboration on the development of tools that can be made available to autism researchers.



Goal #3 *Within five years, -web-based resources and tools are developed that support the integration, analysis and modeling of data and wide-scale dissemination of information to and communication among scientists, professionals, individuals with ASD and their families.* The scale of analysis required to explore the underlying biology of autism is proportional to the heterogeneity of the disorder. There is a need for computational biology approaches and data integration tools that are going to allow researchers to look deeper into data and make sense of the clinical and genomic landscape. Similar to the approach used in Alzforum, we should consider developing a resource for rapid dissemination of information, communication, and exchange between scientists and families.

Goal #4. *Within three years, web-based training on administration of assessments, treatment protocols and other autism toolkits is made available.* Such web-based training tools can increase capacity and empower service providers to administer the highest quality care to individuals with autism. Furthermore, providing a telemedicine-like forum to be able to perform international trainings would be very important as Autism Speaks moves towards collaborations internationally.

Who will benefit?

The translation of knowledge into practice is a guiding principle for a successful bioinformatics plan. It is clear that the successful implementation of a thoughtful and strategic bioinformatics plan would yield a significant return on investment. The direct beneficiaries of these investments would be the researchers, clinicians, funders, and the individuals affected with autism. The availability of large data sets and flexible tools for analyzing and querying such data sets will accelerate scientific discovery of the causes and treatments of autism.

Providing a website where clinicians can gain knowledge about the latest treatment guidelines and practice parameters in their particular fields could have a significant impact on capacity building world-wide, providing better access to empirically-supported best practices for individuals with ASD and their families. An Alzforum-type website would potentially promote communication among researchers, enhance integration and creative use of available information, and accelerate scientific discovery for the benefit of individuals with ASD and their families.

Implementation: What can Autism Speaks do?

- Prioritize funding in the following areas:
 - Identification of common consensus standards for phenotypic characterization
 - Continued development of flexible, accessible, large scale biorepositories, including AGRE, ATP, and others
 - Web-based resources and tools that support integration, analysis, and modeling of data
 - Web-based resources that facilitate information exchange and communication among scientists
 - Web-based resources for training clinicians, educators, and parents
 - Web-based data collection methods
 - Development and testing of web-based training tools for clinicians and parents
 - Computational biology (e.g., systems biology, molecular modeling, computational genomics, pathway analyses) and other bioinformatics strategies to mine existing data



- Sponsor workshops on following topics:
 - Convene a workgroup comprised of clinicians and researchers who can develop a white paper on standards for phenotypic characterization of individuals with autism across the lifespan
 - Workshop to explore a public-private partnership among the NIH and key funders for the development of an Autforum in order to support scientists and the broader autism community

- Support novel approaches/opportunities that potentially will accelerate discovery:
 - Work collaboratively with NDAR to develop an ontology and data dictionary for the field
 - Require data sharing plans of all Autism Speaks' grantees and ensure that they are appropriately reviewed and evaluated
 - Develop a public access policy whereby all Autism Speaks grantees must publish in journals that provide public access to publications via Pub Med
 - Develop resources to support data management that would provide a library of standardized forms (ISAAC) that would be made available to all autism researchers
 - Continue to support informatics infrastructure to maintain and develop ISAAC , AGRE, OSCAR, and ATP as important resources for the scientific community

- Form partnerships that can facilitate discovery and dissemination of clinically relevant findings:
 - Review methods used by researchers studying other diseases to evaluate their models for data integration, data sharing, and dissemination
 - Make use of existing resources such as IAN to obtain information from parents about pressing needs, co-morbidities, treatments, and so on
 - Partner with Simons Foundation to create common software platform for the AGRE, AGP, and Simons Simplex Collection genetic data bases to facilitate future data base integration

Metrics: What does success look like?

Shorter term (within 5 years)

- White paper that reflects consensus on a set of guidelines and standards for data collection
- All AS grantees are using lists of common measures outlined in the consensus white paper
- Data sharing policy is adopted by major funders of autism research, including AS, NIH, and NDAR
- Public access policy is adopted requiring all Autism Speaks' grantees to publish in journals that provide access to publications on PubMed
- Increase in the number of researchers contributing shared datasets and accessing data
- AS website accommodates training videos for parents from experts in the field across a diversity of disciplines



- A public-private partnership is established for the development of Autforum, a scientific web community for autism
- An ontology for autism and a data dictionary to support it are developed and available

Longer term (within 5-10 years)

- Autforum is established and utilized by a wide range of scientists, practitioners, and the public
- All datasets generated by research funded by AS are maintained at a central repository that allows for data integration and collaboration
- Parents, educators, clinicians, and researchers can access the AS website for practice and treatment guidelines, intervention protocols, and common measures for research
- Parents of individuals with autism can access a website that will serve as a clearinghouse of information on latest research updates and science updates

GENERAL RECOMMENDATIONS FROM THE SCIENTIFIC ADVISORY COMMITTEE (FALL 2008 MEETING)

As the body of experts that advises Autism Speaks on their strategic plan, the Scientific Advisory Committee (SAC) offered several additional recommendations, which are summarized below. *First*, each member of the SAC independently identified his or her top ranking strategic goals and the results of this exercise were tallied, as shown below:

Second, the SAC noted that Autism Speaks should place high priority on innovation rather than

Goal Prioritization Exercise Results (most frequently endorsed goals shown in bold)

1. Etiology
 - a. **Biomarkers that identify risk and inform treatment**
 - b. Genetic investigation with stem cells to accelerate drug discovery
 - c. Environmental factors contributing to autism spectrum disorders
2. Biology
 - a. **Animal Models of autism to discover causes and treatment**
 - b. Understanding of common biochemical pathways leading to drug discovery
3. Diagnosis and Phenotyping
 - a. Genetic diagnostic methodology
 - b. **Identification of relevant etiological and clinical subtypes that inform treatment**
 - c. Understanding of adult development and aging
 - d. Developing tools for screening that are culturally relevant and can be adapted to ongoing projects
4. Treatment and Prevention
 - a. **Exportable, scalable early intervention programs**
 - b. Standardized clinical evaluation guidelines
 - c. Standards of early and adolescent intervention established
 - d. Clinical trials of medications for core symptoms and associated medical conditions
 - e. FDA approved drugs for autism treatment
5. Dissemination and Policy
 - a. **Wide accessibility to early behavioral interventions for young children**
 - b. Standard guidelines for treatment
 - c. Increased clinical access through clinical provider network
6. Bioinformatics
 - a. Aut-forum / science website
 - b. **Web-based diagnosis and treatment training modules**



incremental research. They strongly endorsed developing a funding mechanism designed to respond quickly to opportunities and novel ideas. AS has already implemented changes in its review criteria to reflect greater emphasis on innovation and relevance to AS' mission. Furthermore, in 2009, following the SAC recommendation, Autism Speaks will establish the Trailblazer Awards which will be modeled after the Rapid Response Innovation Awards offered by the Michael J. Fox Foundation for Parkinson's Research. The Trailblazer Award mechanism will be a rolling application to support highly novel autism-related research that addresses significant roadblocks and can open new avenues for understanding the causes and treatments for autism spectrum disorders. No preliminary data are required, but the project needs to have the potential to substantially impact our understanding of the causes or effective treatments for autism. Awards will be made for one year at a level of \$100,000 or less. The Trailblazer Award mechanism shares the same goal as the HR-HI initiative (i.e., stimulate innovation), but the methods for achieving this goal differ in several ways from those used in the HR-HI initiative: (1) the Trailblazer Awards will fund research topics that are investigator-initiated (rather than advisory committee initiated); (2) it will provide smaller amounts of seed money to a greater number of scientists; (3) the projects will be smaller in scope, allowing for rapid feedback on the feasibility and promise of the novel idea. This will allow AS to fund even riskier ideas without expending large amounts of resources; (4) external review will be rapid and final, whereas the review of HR-HI proposals is designed to be an iterative, collaborative process designed to promote eventual funding of larger scale projects; and (5) because the number of awards will be greater, exploration into a wider range of novel ideas will be possible through this mechanism.

Third, the SAC recommended that Autism Speaks continue to explore opportunities to form strategic partnerships, including partnerships with other disease foundations that share similar goals (e.g., Epilepsy Foundation, United Mitochondrial Disorders Foundation), government and private funding agencies in other countries (e.g., UK, Middle East), NIH, Gates Foundation, World Health Organization, pharmaceutical companies, and biotechnology companies.

Fourth, noting the high level of retention of scientists (particularly predoctoral fellows) funded through the fellowship program, the SAC strongly recommended that fellowships continue to be a core part of the funding portfolio at Autism Speaks. The possibility of providing career development awards should also be considered.

Fifth, the SAC strongly recommended that the science component of Autism Speaks' website be better designed, "meticulously curated," and better utilized to promote research and science information dissemination. Among the ideas discussed were more detailed and personal science stories that are more reader friendly for the general public, conference and other event postings, interviews with funded scientists, job postings, and others. Collaboration with the Interactive Autism Network and International Society for Autism Research on this effort was recommended.

Sixth, the SAC remarked on the great usefulness of interdisciplinary workshops that focus on topics in which Autism Speaks wishes to stimulate investment. Such workshops serve to develop communication among diverse types of scientists and clinicians that is needed to move in novel directions and provide translation from the bench to the bedside and vice versa.



PART FIVE: SUMMARY

Strategic directions and priorities

Five strategic directions were identified by multiple workgroups and the Scientific Advisory Committee. Their near universal endorsement is noteworthy as they may provide insight into particularly effective common strategies that can potentially influence success in several domains. *First*, the need for *an individualized approach to diagnosis and treatment* was identified as an important common goal by four of the five strategic plan workgroups and the SAC. Specifically, the need to identify *biomarkers or clinical features that index meaningful subtypes of ASD*, point to specific etiologies, and predict response to treatment was endorsed by all of these groups. It is recognized that autism is comprised of many different diseases with different etiologies, symptom profiles, courses and prognoses, and treatment responses. Given the multiple etiologies related to autism, incorporation of more comprehensive genetic and environmental exposure testing, assessment of underlying and associated medical conditions, and eventually the identification of new biomarkers will enable clinicians to provide more individualized and more targeted and effective treatments. Progress in this area will require a multi-pronged approach, including but not limited to studies focused on identification of useful biomarkers, (e.g., electrophysiological, immunological, metabolic), examination of genetic and other biomarkers as predictors of vulnerability to environmental triggers and moderators of response to treatment, and closer collaboration between researchers and clinicians, among others.

Second, the need for *better tools and more attention focused on understanding environmental risk factors and gene-environment interactions* was highlighted throughout. Prevention and treatment of autism through alteration of potential environmental factors is now considered a fundamental goal of research. Closer collaboration between geneticists and environmental scientists will be necessary, as well as new methods for measuring exposures and analyzing their interaction with genetic factors. A wide range of environmental factors needs to be vigorously explored including but not limited to exposure to toxins, vaccines, chemicals, immune challenges, and the role of early behavioral intervention in altering the course of brain and behavioral development. Methods for identifying children who are medically vulnerable to adverse effects of environmental events need to be developed. Closely tied to this theme is the need to develop methods of early assessment of risk. The identification of infants at risk for autism will allow implementation of prevention strategies during the early postnatal and toddler period when significant changes in brain development are occurring.

A *third* strategic goal endorsed across the workgroups and SAC was the urgent *need to translate genetic and other biological findings into clinically useful tools* that can facilitate risk assessment and drug discovery. Again, multiple strategies will be required, including the development of appropriate animal models, development of preclinical assays to fast-track screening of novel treatments, practice guidelines for the communication, and use of new and sometimes poorly-understood genetic findings or exposure data within a clinical setting. It was agreed that the development of model systems that uniformly characterize the most relevant biological and behavioral abnormalities found in autism is paramount in moving the field forward. More generally, there is a need for the development of clinical standards and practice parameters for clinicians serving individuals with autism and their families. A better understanding of the factors that promote or impede acceptance of empirically-supported practices will be an important step in the dissemination of findings to the clinical community.



Fourth, in an effort to balance short and long term goals and improve the lives of persons with ASD now, the need to develop treatments that can address the core symptoms and associated medical conditions from which people with ASD suffered was recognized. There is a new to identify new treatment approaches, both behavioral and medical, that are appropriate for individuals across the life span. In particular, there is a new to promote the development of a comprehensive care model that can addresses common medical conditions, such as GI and sleep problems, as well as depression and anxiety. Addressing such issues will require new approaches to clinical diagnosis and assessment, training of physicians and other health care providers in recognizing and treatment persons with ASD, and testing the efficacy and safety of medical and other treatments.

Fifth, the need to direct resources into *dissemination of empirically-validated treatment approaches*, such as early behavioral intervention, that could significantly alter the life trajectory and improve outcomes and quality of life for many individuals with ASD and their families today was strongly endorsed. In fact, this goal was identified as the number one priority by the Scientific Advisory Committee. This will require investing in (1) studies that demonstrate the effectiveness of feasible, exportable, and scalable early intervention programs, (2) the identification of factors that promote or impede the implementation of such programs in the community, (3) novel methods for provider training that can be accessed by the wider community (e.g. web-based technologies), (4) implementation of training programs that can build capacity of the community to provide interventions, and (5) changes in insurance benefits for early intervention and other empirically-validated treatments.

Given the rapidly expanding knowledge base pertaining to autism and related fields of inquiry and the complexity of the ASD, the *development of central information repositories* that are highly useful and flexible for scientific exploration will be vital for moving the field forward toward discovery of prevention and treatment methods. These information systems need accommodate international efforts and provide a platform for web-based training modules and wide-scale information dissemination.

Furthermore, *closer collaboration and improved communication* among scientists of different disciplines and between families and scientists, clinicians and researchers, public and private funders, and stakeholders and scientists world-wide will allow for the discovery of more effective treatments and prevention strategies and their dissemination and implementation in the broader community, so that all individuals with ASD and their families can benefit from the work we are striving to accomplish.

Summary of goals and priorities for 2009-11

Table 9 provides a summary of the goals, strategies, objectives, and initiatives identified in the 2009-2011 strategic plan for science. Table 10 provides a summary of the priorities for funding of investigator-initiated proposals.

Although many challenges exist, including the current downturn in the world economy which is certain to affect funding for autism research and services, there is reason to be optimistic about our ability to make significant discoveries, translate those discoveries into treatments and prevention strategies, and disseminate these into the wider community for the benefit of individuals with ASD and their families. The number of scientists devoted to studying autism and the amount of resources (albeit still far below what is needed) have never been higher. In large part due to Autism Speaks' efforts, the stakeholder community has developed a strong and unified voice, increasing our ability to influence policy and resources. President Obama recognizes the urgent need to investigate the causes and treatment of individuals with ASD, making



federal support for autism research and policy changes that could influence access to treatment more possible now than ever before. New and exciting technological advances and bioinformatic resources are becoming available at an extremely rapid pace, making new discoveries and fast dissemination of information possible. All of these factors give us real hope that the lives of individuals with ASD and their families will be improved through our efforts. To this goal, we remain steadfastly committed.

Autism Speaks Science Leadership

Geraldine Dawson, Ph.D., Chief Science Officer

Sophia Colamarino, Ph.D., Vice President, Research

Alycia Halladay, Ph.D., Director, Environmental Sciences

Clara Lajonchere, Ph.D., Vice President, Clinical Programs

Anita Miller Sostek, Ph.D., Vice President, Scientific Review and Operations

Andy Shih, Ph.D., Vice President, Scientific Affairs



Table 9. Goals, Strategies, Objectives, and Initiatives

Goal	Strategies	Objectives	Initiatives
1 - Identify autism genetic and environmental risk factors and their interaction	<ul style="list-style-type: none"> • Create and integrate large scale genetic and environmental exposure data bases • Develop analytic tools for examining gene-environment interactions • Leverage existing projects and international partnerships to enhance genetic and environmental data collection • Promote data-sharing and large scale data base integration • Enhance collaboration between geneticists, environment scientists, and clinicians 	<ol style="list-style-type: none"> 4. To create resources for discovery of autism susceptibility genes 5. To identify, collect, and evaluate environmental exposure data 6. To facilitate novel directions in the exploration of environmental factors and gene-environment interactions 	<ul style="list-style-type: none"> • Autism Genetic Resource Exchange • Autism Genome Project (AGP) • Collaborative Risk and Outcome Scientific Study (CROSS) • Gene and Environment Contributions to Risk for Autism (GECRA) • National Children's Study (NCS) Collaboration • Environmental Factors Initiative • International Autism Epidemiology Initiative • High-risk/High impact Initiative • Weatherstone Fellowships • Trailblazer Awards
2 - Identify the underlying biological mechanisms of autism	<ul style="list-style-type: none"> • Develop appropriate of animal models • Use of animal models to study biological pathways, drug responses, and recovery • Develop pre-clinical assays to study effects of risk genes and environmental factors on biological pathways and fast track screening of novel treatments • Create state-of-the art tissue program, including brain, stem cell, and other tissues • Use of Allen Institute for Brain Sciences to study gene expression and brain development • Use of novel brain imaging technologies to study early brain development 	<ol style="list-style-type: none"> 5. To stimulate innovative studies using animal models to understand biological mechanisms and test novel treatments 6. To develop in vitro and in vivo methods for pre-clinical testing of drugs 7. To create state-of-the art tissue bank 8. To facilitate development and application of novel brain imaging techniques 	<ul style="list-style-type: none"> • AS-MRC collaboration on Rett syndrome recovery • AS-Allen Brain Institute Collaboration on brain development • Autism Tissue Program Initiative • AS-Simon Foundation-NIH initiative to create state-of-the-art Autism Tissue Bank • High-Risk High-Impact projects on Mitochondrial Disorder and Novel approaches to brain imaging
3 - Develop improved and more efficient diagnosis and risk assessment methods	<ul style="list-style-type: none"> • Explore the validity and reliability of briefer, scalable methods of diagnosis that would allow acquisition of larger data bases • Develop consensus standards for diagnosis and phenotyping in research studies to facilitate data base integration across studies • Develop methods for screening and diagnosis for infants and toddlers, including biomarkers • Examine the utility and feasibility of genetic, medical, and metabolic assessments as part of a diagnostic work-up and as predictors of response to specific treatments • Encourage and prioritize research on adults and aging 	<ol style="list-style-type: none"> 6. To develop briefer, scalable methods of diagnosis that are useful in multiple research and clinical environments 7. To reach a consensus in the field on a standard set of diagnostic and phenotype measures 8. To identify reliable and valid risk/bio markers for autism 9. To assess the utility and feasibility of genetic/medical testing as part of a diagnostic workup 10. Increase knowledge on adult outcomes and aging in ASD 	<ul style="list-style-type: none"> • AGRE/NIH study exploring the use of parent questionnaires for screening and diagnosis • HR-HI IAN Studies exploring the validity of parent questionnaires for screening and diagnosis and assessment of nonverbal persons • Workgroup on Phenotyping Standards • AGRE and AGP studies on gene discovery • Baby Siblings Research Consortium • Conference on Translating Genetic Discoveries into Clinical tools • Autism Treatment Network • Prioritize research on adults and aging through pilot and basic/clinical grants

<p>4 - Identify effective treatment and prevention strategies for individuals with ASD¹³</p>	<ul style="list-style-type: none"> • Develop and test the efficacy of interventions for infants • Develop best practice guidelines for medical and behavioral interventions • Develop and test the efficacy of medical and behavioral/psychosocial treatments for school age, adult, and nonverbal individuals • Improved outcome measures for treatment studies are needed 	<ol style="list-style-type: none"> 6. To have effective, scalable interventions for infants and toddlers 7. To provide treatments that address the medical conditions associated with ASD 8. To publish practice guidelines for medical care 9. To have effective treatments for school age, adult, and nonverbal individuals 10. To develop sensitive and reliable outcomes measures for use in treatment studies 	<ul style="list-style-type: none"> • Toddler Treatment Network • Autism Treatment Network • Treatment Initiative/Grants Program • Clinical Trials Network • Innovative Technology for Autism Initiative • High-Risk High Impact Initiative • Interactive Autism Network • RFA on Treatment of GI Problems
<p>5 - Promote widespread dissemination of empirically-validated methods for screening, diagnosis, and treatment to the broader community worldwide</p>	<ul style="list-style-type: none"> • Convene “thought leaders” on effective dissemination and service delivery systems to discuss and develop a strategic plan for addressing the lack of dissemination of best practices in the community • Establish functional linkages to promote communication and partnership among the government and professional groups invested in dissemination of health care to prevent duplication of effort, reduce cost and effort, and increase collaboration • Work closely with Awareness, Government Relations, and Family Services components of Autism Speaks to coordinate with their efforts at policy change and dissemination • Survey existing models for dissemination of autism best practices or similar models for other diseases • Pilot dissemination model through Global Autism Public Health Initiative nationally and internationally 	<ol style="list-style-type: none"> 4. To improve communication among the government, private, and professional groups invested in dissemination of clinical practices 5. To develop a coordinated vision for dissemination of empirically-based best practices into the community both nationally and internationally 6. To pilot GAPH model of dissemination of empirically-based practices 	<ul style="list-style-type: none"> • Global Autism Public Health Initiative • Autism Treatment Network • Interactive Autism Network

¹³ Strategies, objectives and initiatives for meeting Goal 1 and 2 will accelerate discovery of the causes of autism and biomarkers that will identify subtypes of autism that respond to specific treatments and animal model studies of treatment/recovery (See Goals 1 and 2)



Table 10. Funding Priorities for Investigator-Initiated Proposals

Etiology

1. Large scale studies using state of the art technologies for autism susceptibility gene discovery
2. Epidemiological and laboratory-based studies of a wide range of environmental risk factors
3. Population-based epidemiological studies on the frequency and distribution of genetic risk alleles
4. Reverse phenotyping approaches
5. High-risk and medically vulnerable samples to study the role of vaccines as a risk factor for autism
6. Studies of families with specific genetic characteristics
7. Studies using genetically more homogeneous populations to enhance gene discovery
8. Twin studies focused on genetic and environmental factors
9. Longitudinal studies of high-risk cohorts (e.g. infant siblings) that examine genetic and environmental risk factors
10. Longitudinal population-based studies that examine genetic and environmental risk factors
11. Known genetic diseases that overlap with autism (e.g. Fragile X)
12. Animal models exploring genetic and environmental risk factors and their interaction
13. Research that follows up on recent work demonstrating recovery in animal models
14. Interdisciplinary approaches (e.g. genetics, environmental science, neuroscience)
15. Role of specific risk factors for specific behavioral outcome or subtype
16. Translation of risk factor findings into clinical benefits such as risk assessment tools (e.g., genetic screening, screening for high risk exposures, metabolic indices of oxidative stress)
17. New technologies for exposure assessment
18. Bioinformatic or computational biology approaches to explore genetic and/or environmental influences

Biology

1. Projects that include efforts to subtype through biomarkers
2. Projects focused on the development of biomarkers of treatment progression
3. Impact of treatments on behavior, brain, and other biological endpoints
4. Clinical studies for defining pathophysiology in autism, including novel approaches to characterizing the biology of immune, GI, and metabolic systems
5. Methodology to identify metabolic indices of oxidative stress/damage, mechanisms by which they occur, and how they relate to environmental exposures, autism symptoms, and etiology
6. Mechanisms and indices of inflammation as it relates to ASD
7. Collaborative investments in a state-of-the art autism tissue program
8. Use of brain tissue to further explore nature of biological brain abnormalities
9. Use of induced-pluripotent stem cell technologies to advance understanding of neural abnormalities in autism
10. Projects characterizing the biology of very early development (prenatal, infancy)
11. Development and application of model systems and bioassays
12. Standardization of methods for evaluating animal models of ASD
13. High-throughput testing of treatments for their ability to biologically normalize pathophysiology in model systems
14. Animal models to study genetic and environmental risk factors and their interaction

Diagnosis and Phenotyping

1. Autism screening instruments for infants
2. Studies on more efficient, empirically valid diagnostic methods, such as a shortened version of the ADI
3. Studies focused on screening, diagnostic, and assessment of ASD in higher functioning and older individuals, including aging adults
4. Studies that link biological and phenotypic data, either through informatics efforts or data repositories
5. Studies that identify subtypes of ASD linked to etiology, course, and/or response to treatment
6. Studies that improve screening, diagnosis, and treatment of underrepresented and underserved populations
7. Studies that examine systems-based approaches to care to better understand gaps in the system of care and improve best practices through training and information dissemination, including those that identify factors that will allow better access to diagnosis and treatment of individuals with ASD
8. Studies that focus on development of systems for building expertise through training that can be implemented broadly, such as "train the trainer" models and use of web-based methodologies



Funding Priorities (continued)

Prevention and Treatment

1. Early intervention research, including the Toddler Treatment Network, encouraging the integration of outcome data across the several Autism Speaks funded clinical trials for toddler intervention
2. Exportable methods of early intervention, such as parent-delivered interventions and web-based training methods
3. Treatment studies that incorporate biological measures of response to treatment
4. Studies that identify moderators or mediators of response to treatment
5. Intervention studies aimed at improving the outcomes of lower-functioning and/or nonverbal children with ASD
6. Treatments that reduce core autism symptoms (social and language functioning, repetitive behaviors)
7. Treatments that incorporate a whole body approach by addressing medical conditions associated with ASD (e.g. GI, sleep, seizures, allergy, food intolerances, metabolic conditions)
8. Treatments that address the psychosocial and/or medical needs of school age children, adolescents and adults with ASD, including issues such as teasing and bullying, social isolation, comorbid anxiety and depression, regression in adolescence, transition to the work force and college, quality of life, and aging adults with ASD, among others
9. Development of ways to improve patient compliance with medical procedures (dental, blood draws, MRIs, electrodes, swallowing pills, sticking to a diet, and so on)
10. Validation of biomedical interventions that are widely used by parents but have not been evaluated for efficacy or safety
11. Training methods for providers in the community, including physicians, psychologists, educators, and other providers
12. Consensus standards for treatment study methods, including clinical endpoints
13. Development of practice guidelines for treatment across the lifespan
14. Development of training models for physicians and other health care providers
15. Clinical trials networks, such as ATN and CTN, for testing the efficacy of treatments

Dissemination

1. Dissemination research aimed at identifying factors that promote or impede adoption of evidence-based clinical practices
2. Implementation research aimed at identifying the best models for development of community based large scale services
3. Research focused on community-specific dissemination priorities, content, implementation strategies, and evaluation approaches
4. Supplements to existing community-based treatment programs to enhance scientific return
5. Supplements to existing community-based treatment programs to conduct cost-benefit analyses
6. Research that increases understanding of the financial burdens of ASD and the impact on that burden of changing access to care
7. Research that focuses on understanding factors that hinder or promote insurance reimbursement

Bioinformatics

1. Identification of common consensus standards for phenotypic characterization
2. Continued development of flexible, accessible, large scale biorepositories, including AGRE, ATP, and others
3. Web-based resources and tools that support integration, analysis, and modeling of data
4. Web-based resources that facilitate exchange and communication among scientists and information exchange
5. Web-based resources for training clinicians, educators, and parents
6. Web-based data collection methods (e.g. OSCAR)
7. Development and testing of web-based training tools for clinicians and parents
8. Computational biology (e.g. pathway analyses) and other bioinformatics strategies to mine existing datasets and develop tools for analysis of data across disease groups



