DEPARTMENT OF HEALTH AND HUMAN SERVICE

National Institutes of Health
National Institute of Mental Health

Congressional Appropriations Committee Report on the State of Autism Research

signed
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Executive Summary

The Conference Report on the Consolidated Appropriations Bill for FY 2003, which included the appropriations for the Departments of Labor, Health and Human Services and Education and related agencies, (Conference Report No. 108-10), requested that the Interagency Autism Coordinating Committee (IACC) convene a panel of expert scientists to evaluate the field of autism research and develop a matrix of action items that could be used in planning for research in the years ahead. This report summarizes the activities that followed this request, which included a 2-day meeting of an expert panel, the development of a draft version of an autism research matrix, the public rollout and discussion of that draft matrix at the recent Autism Summit, and the adoption of an initial version of the matrix by the IACC. The specific action items of the matrix are presented in this document, along with explanatory notes and initial plans for implementation. A background summary of the state of autism research in the major areas of epidemiology, genetics, neurobiology and treatment is also included.

The autism research matrix was developed by a process of reviewing the status of important scientific content areas for autism, identifying roadblocks within these areas, and then formulating activities to overcome the roadblocks. These proposed activities were then placed in a matrix according to the level of risk for their success and the timeframe for undertaking them. The matrix includes content areas of communication and collaboration, characterization of autism, school and community interventions, early intervention, epidemiological studies, specific treatments, neuroscience, screening, and the role of the environment in autism.

Introduction

In its report on Fiscal Year 2003 budget for the Department of Health and Human Services (HHS), the Committee on Appropriations stated:

> The conferees request that the NIH Interagency Autism Coordinating Committee (IACC) convene a panel of outstanding scientists to assess the field of autism research, and identify the roadblocks that may be hindering progress in understanding its causes and best treatment options. As a next step, the IACC should take the recommendations of these findings and develop a matrix of short-to-long range and low-to-high risk action items to address some of the roadblocks identified by the panel. This matrix would then be used to help guide further autism research planning at NIH, and as a tool for the entire autism community. It should include opportunities for voluntary and private funding organizations, and hopefully will lead to opportunities for collaboration with other government agencies and the autism community as well. The matrix should be a living document that can be revised and expanded as current goals are achieved and new goals are identified. Once the matrix has been developed, the IACC should provide a report to Congress on the state of autism research. (Conference report No. 108-10, pages 1099-1100)

The IACC was created in response to a mandate in the Children's Health Act of 2000 (P.L. 106-310), in order to coordinate research and other efforts with respect to autism activities within HHS and the Department of Education (DoE). In addition, HHS has expanded its efforts relevant to autism in several major areas in accordance with other stipulations in the Children's Health Act. The Children's Health Act also requires an annual Report to Congress on overall activities related to autism. This annual report provides an overview of activities at agencies of HHS, including the National Institutes of Health (NIH), the Centers for Disease Control and Prevention (CDC), and the Health Resources and Services Administration (HRSA), and the DoE that constitute the implementation of each section of the Act. Annual reports are available at http://www.nimh.nih.gov/autismiacc/index.cfm.

The state of autism research has advanced substantially in the past year with the increased infrastructure that has permitted expansion of research into the causes and best treatment options for autism. For instance, NIH has now funded a total

of eight centers under the Studies to Advance Autism Research and Treatment (STAART) Centers Program http://www.nimh.nih.gov/autismiacc/staartcenters.cfm. These centers complement the 10 Collaborative Programs of Excellence in Autism (CPEA) Centers Network, and two Children's Environmental Health Research Centers that focus on autism. These network activities have expanded while there are also increased numbers of individual grants being funded to support autism research. Over the past few years, NIH has considerably expanded its autism research portfolio and enhanced its coordination of autism research. NIH support of autism research grew from $22 million in FY 1997 to $93 million in FY 2003 with estimated increases to $97 million in FY 2004 and $99 million in the FY 2005 President's Budget request. NIH supports autism research in the areas of genetics, neurobiology, early diagnosis, services and treatment, while the CDC has expanded its efforts in supporting research on the epidemiology of autism. These activities provide a framework for allowing investigators to study important questions about autism.

To summarize, in order to broadly assess the field of autism research in multiple domains, the conferees requested that a panel of scientists be convened to identify roadblocks to understanding the causes and best treatment options for autism. In response to this request, the IACC selected and convened a panel of science experts in autism. This 2-day meeting was held in July 2003 in Bethesda, Maryland. The panel was composed of premier scientists from across the spectrum of autism research.

IACC Scientist Panel Members:

David Amaral, Ph.D
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Tony Charman, Ph.D.
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Professor
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Fred Volkmar, M.D.
Professor
Yale Child Study Center
Yale University

This science panel developed and prioritized goals and activities to overcome roadblocks hindering progress in autism research. These action items were then placed into a matrix reflecting the proposed timing and level of risk of each entry. In August 2003, a draft of the proposed autism research matrix was distributed to all members of the IACC for discussion and approval. In order to obtain public input at the Autism Summit Conference held on November 19 and 20, 2003, the draft matrix was rolled out and there was a presentation of its contents and extensive discussion about it. The IACC provided input and final approval of the draft matrix at the November 21, 2003 IACC meeting. Plans for implementation were also discussed at the IACC meeting, and the IACC will evaluate progress on a yearly basis. The NIH Autism Coordinating Committee will assume the major responsibility for implementation, including documenting in-progress activities and developing initiatives. Implementation is discussed in more detail later in this document. The major roadblocks identified are listed below, followed by the matrix as approved.

Roadblocks to Understanding Causes and Best Treatment Options for Autism:

<u>Characterization of Autism Spectrum Disorders and Associated Genetics</u>

- Lack of consensus regarding the phenomenological distinctions between autism and related developmental problems (e.g. attention problems, specific language impairment, anxiety)

- Lack of a national autism twin registry that allows researchers access to large sample of well-defined twins with at least one twin affected with autism

- Lack of multi-site, high-risk population studies (i.e. subsequent pregnancies and infant siblings of individuals with autism) that will allow for increased knowledge regarding risk factors, early development of autism, and enhanced characterization of the disorder

- Lack of adequate statistical methods and informatics for genotyping studies

<u>Screening</u>

- Need for models of successful implementation of screening practices into community settings

Early Intervention

- Lack of a tested model for early intervention in children under the age of 2

Specific Treatments

- Unsatisfactory standardization of outcome measures used in treatment studies

- Difficulties with the review process for grant applications involving autism treatment studies

Role of the Environment in Autism

- Scarcity of organized medical data and common comprehensive assessments across research sites that allow for identification of early markers and risk factors

Neuroscience

- Dearth of technology for non-invasive imaging techniques for neuroscience studies (e.g. connectivity research)

- Insufficient knowledge regarding genetic underpinnings of autism (i.e. susceptibility genes) that help facilitate neurobiological research

- Shortage of brains for national registry used for post-mortem studies

- Lack of a formal network for researchers in developmental neurobiology that will allow for enhancement of investigations in this area

School and Community Interventions

- Need for enhanced collaboration with the Department of Education and other relevant service agencies to develop and test efficacious treatments

- Discrepant policies on early intervention/school transition by geographical region

Epidemiology

- Unanswered questions about changes in prevalence and characterization, which require repeated cross-sectional, intensive community-based surveys that include clinical evaluations

- Lack of unbiased population-based sample for epidemiological studies

- Restrictions to implementation of epidemiological research due to regulations that limit access to school records

Communication and Collaboration

- Need for enhanced mechanisms to involve voluntary organizations, industries and potential donors in all stages of research design and implementation

- Insufficient of coordination between relevant stakeholders and scientists for communicating accurate science findings to the public

IACC Autism Research Matrix: 12/03

Goals	Short term (1-3 years)	Medium term (4-6 years)	Long term (7-10 years)
High Risk Research	1. Peripheral (non-brain) biomarkers (e.g. gene expression assays from blood cells, or blood levels of specific molecules) developed to provide the biological characterization (i.e. phenotype) of autism 2. Efficacy established for pharmacological, behavioral and other treatments that target symptoms associated with autism	1. Individual characteristics that predict response to behavioral, pharmacological and other treatments are identified 2. Susceptibility genes and animal models of autism are identified for further study of phenotypic characteristics of autism 3. Environmental factors (e.g. viruses, medications, lifestyle factors, environmental chemicals) that contribute to the development of autism and their associated developmental windows identified	1. Provide evidence that 25% of cases of autism can be secondarily prevented from symptomatic expression through early identification and early treatment 2. Methods developed to allow 90% individuals with autism to develop speech 3. Genetic and non-genetic causes of autism and their interactions identified 4. Efficacious drug treatments that target core symptoms of autism developed

Goals	Short term (1-3 years)	Medium term (4-6 years)	Long term (7-10 years)
Medium Risk Research	1. Resources established for genotype/phenotype studies (i.e. bioinformatics, genetic repository) 2. Existing data studied to begin to characterize the autism phenome, as part of the larger Phenome Project 3. Infrastructure, such as enhanced brain acquisition, established for neuropathological investigations, to characterize morphological aspects of the pathophysiology of autism 4. Technology and infrastructure developed for multi-site *in vivo* imaging studies, to identify the neuropathology of autism 5. Randomized clinical trial developed for the evaluation of the effectiveness of early behavioral intervention and factors predicting response to intervention 6. Innovative intervention strategies developed to improve outcomes in the school and community settings throughout the lifespan, including transitions (e.g. academic functioning, social and adaptive behavior, family functioning, employment) in collaboration with the Department of Education and other federal agencies 7. Develop research on implementing early identification of children with autism in community settings, and employ a population-based longitudinal cohort	1.Biological and/or behavioral markers identified to develop indices of risk for the development of autism in infants. 2. Multi-site randomized clinical trial implemented to identify moderators and effective ingredients (e.g. dose, intensity, mode of delivery, age of onset) of early intervention treatments 3. Intervention methods for infants and toddlers developed, to lower the age for which there are efficacious interventions 4. Neuropathology of autism characterized, to identify brain structures and functions associated with autism 5. Developmental time course characterized for alterations in brain structures and connections in autism 6. Continue formulating, evaluating and implementing appropriate efficacious intervention strategies incorporating research-based findings to improve outcomes in the school and community settings throughout the lifespan, including transitions (e.g. academic functioning, social and adaptive behavior, family functioning, employment) in collaboration with the Department of Education and other federal agencies	1. Feasible, sensitive autism screening method for young infants developed 2. Basic, common neuropathological and neurochemical features of autism defined 3. Treatment algorithm for autism developed, to provide guidance for practitioners and educators 4. Appropriate and efficacious interventions are widely recognized and broadly implemented for school and community settings throughout the lifespan, including transitions (e.g. academic functioning, social and adaptive behavior, family functioning, employment) in collaboration with the Department of Education and other federal agencies

Goals	Short term (1-3 years)	Medium term (4-6 years)	Long term (7-10 years)
Low Risk Research	1. Autism Phenome Project defined and planned 2. Outcome measures improved, to enhance their effectiveness in evaluating treatment studies 3. Twin resource developed, to study heritability and environment factors influencing autism 4. Effective interventions expanded, disseminated and implemented to improve outcomes in the school and community settings throughout the lifespan, including transitions (e.g. academic functioning, social and adaptive behavior, family functioning, employment) in collaboration with the Department of Education, and other federal agencies, such as the Department of Labor and Social Security Administration 5. Research Communication Network (both local and national) developed to disseminate findings among researchers and the public to increase ongoing communication 6. Evaluate sensitivity and specificity of existing screening tools, and continue developing efficacious screening measures.	1. Multi-site longitudinal study of subsequent pregnancies and infant siblings of children with autism implemented, to identify risk factors, broader phenotype and early characterization of autism 2. Neural circuitry and neurochemistry defined for several functions impaired in autism 3. Innovative and newly developed intervention strategies evaluated, implemented and disseminated to improve outcomes in the school and community settings throughout the lifespan, including transitions, (e.g. academic functioning, social and adaptive behavior, family functioning, employment) in collaboration with the Department of Education and other federal agencies 4. First-generation, intensive, community-based prevalence studies with clinical evaluations implemented, to have initial data for detecting changes in prevalence of autism	1. Longitudinal follow-up of early intervention randomized clinical trial implemented 2. Second-generation, intensive, community-based prevalence studies with clinical evaluations planned and implemented.

KEY: Red = Characterization of autism (i.e. phenotype); Green = school and community interventions; Grey = epidemiological studies; Orange = early intervention; Purple = Specific treatments; Blue = neuroscience; Pink = screening; Black = Role of the Environment in Autism and remaining items

The text below is a series of explanatory notes for the entries in the matrix. **As requested by the conferees, the matrix will be a living document, subject to ongoing revision. It will be periodically revisited and revised based on achievement of some of the goals as well as on new knowledge and insights.**

Specifics of the Autism Research Matrix

The autism research matrix was designed to include goals and activities for the next 10 years and is divided into short-term (i.e., 1-3 years), medium-term (i.e., 4-6 years) and long-term (7-10 years) goals. The matrix is also divided into three levels according to risk category, where risk is defined both by anticipated difficulty in achieving the goal as well as innovation and potential impact. For example, a goal is considered high-risk research if attempts to reach it will require a high degree of innovation and have a high chance of failure but is of such high importance that it warrants repeated attempts to achieve the goal.

Goals and activities that comprise the autism research matrix generally fall within the following categories: characterization of autism (i.e. phenotype), screening, early intervention, school and community interventions, specific treatments, neuroscience, environmental factors and epidemiology; however, not all items fall into these categories and several items are applicable to more than one of these domains. In fact, for example, the longest term and highest risk goals include preventing cases of autism and determining the causes of autism. In order to achieve these goals, smaller goals will need to be achieved that will allow researchers to combine knowledge of topics such as neuroscience, early detection, and treatment.

The following text summarizes goals and activities in the various separated domains, followed by summaries and explanations of the specific items of the matrix.

Characterization of Autism Spectrum Disorders and Associated Genetics: The general goal in this area is the development and implementation of the Autism Phenome Project, which will provide comprehensive biomedical and behavioral characterization of autism by defining core and associated features, onset, longitudinal course, and subtypes, using various research strategies (e.g., pooling existing data sets, twin studies, samples at high risk for autism, large population-based, case control studies with follow-up). Goals and activities in this area are aimed to lead towards the long-term goals of finding genetic and non-genetic causes of autism and enhancing optimal treatments. Once genetic factors that increase risk for various aspects of the autism phenotype are

identified, systematic research into the potential interaction of these specific variables with environmental variables becomes feasible. In order to complete the Autism Phenome Project, biomarkers for autism will need to be determined and longitudinal studies will be needed to identify risk factors for the development of autism in early infancy, but these are only a few phenotypic parameters of the many that comprise the phenome project.

Low-risk research, short term (1-3 years):

Autism phenome project defined and planned. This will entail collaboration among a multidisciplinary network of researchers, and will include identifying resources and planning research strategies. It will include the pooling of existing data, the creation of multi-site longitudinal studies, and the development of working definitions for phenotypic characterization.

Medium-risk research, short term (1-3 years):

Resources established for genotype/phenotype studies (i.e. bioinformatics, genetic repository). This initiative will create infrastructure to allow geneticists, neurobiologists and clinical researchers to study more expeditiously the genetics and characterization of autism. A centralized genetics repository with detailed diagnostic, behavioral and biological assessments on all participants and family members is one example of such resources.

Existing data studied to begin to characterize the autism phenome, as part of the larger Phenome Project. This item will allow researchers to use data collected as part of previous studies to be used in future studies that explore early development of autism and characterization of autism in diverse samples. Re-examination of longitudinal data collected to follow children with autism in their natural environment over a specified time period would be one example of existing data that could be studied for phenotypic descriptions.

High-risk research, short term (1-3 years):

Peripheral (non-brain) biomarkers (e.g. gene expression assays from blood cells, or blood levels of specific molecules) developed to identify the biological characterization (i.e. phenotype) of autism. This item refers to efforts to identify biological markers for autism to help decipher autism-specific biology from other disorders.

Low-risk research, medium term (4-6 years):

Multi-site longitudinal study of subsequent pregnancies and infant siblings of children with autism implemented, to identify risk factors, broader phenotype, and early characterization of autism. A large, longitudinal study such as this will permit extensive samples of at-risk children to be followed during early and subsequent stages of the development of autism, allowing for in-depth study of developmental patterns as well as emerging behaviors and/or biomarkers specific to autism.

High-risk research, medium term (4-6 years):

Susceptibility genes and animal models of autism are identified for further study of phenotypic characteristics of autism. When specific genes are determined to increase susceptibility to autism, researchers can subsequently study the expression of these genes in depth to determine exactly how these genes work at various levels to "turn on" symptoms of autism.

Screening:

As our knowledge increases about the early development of autism, we now know that there may be signs of autism at quite early ages, perhaps at birth. In order to intervene as early as possible to prevent development of the full symptomatic expression of autism, effective techniques for detecting autism as early as possible need to be developed, and methods for implementing such screening programs into the community need to be developed and evaluated.

Low-risk research, short term (1-3 years):

Evaluate sensitivity and specificity of existing screening tools, and continue developing efficacious screening measures. In order to implement effective community-based screening programs for toddlers (and eventually for infants), screening methods need to be evaluated for their reliability and validity over time.

Medium-risk research, short term (1-3 years):

Develop research on implementing early identification of children with autism in community settings, and employ a population-based longitudinal cohort. Such a resource could be used for studies of intervention, genetics, and phenomenology. A key component of developing research on implementing screening procedures and early identification in the community will be to develop and evaluate different methods for educating practitioners and the public on autism.

Medium-risk research, medium term (4-6 years):

Biological and/or behavioral markers identified to develop indices of risk for the development of autism in infants. Genetic, neurobiological, and molecular biology research are required to identify prenatal or early postnatal markers that would allow infants to be detected as "at risk" for the development of autism. Possible markers could be specific genes or sets of genes, neurotrophic factors, or other molecules.

Medium-risk research, long term (7-10 years):

Feasible, sensitive screening method for young infants developed. Through advances in both behavioral assessment and biological marker identification, it is hoped that one or a combination of these assessment methods could be used to develop a comprehensive screening procedure that could be used to assess risk for autism in all infants.

Early Intervention:

The broad goal in this area is to conduct rigorous studies of early interventions in order to optimize the effectiveness of such treatments. The ultimate goal is to develop and test early intervention programs that secondarily prevent symptomatic expression of autism from developing, such that by school age, children who without such intervention may have been diagnosed with autism no longer fit into this diagnostic category. To achieve this, early intervention methods, particularly for the youngest children (i.e., under age 3) still need to be developed, and sophisticated studies are needed to determine which ingredients of early intervention programs are associated with maximum effectiveness.

Medium-risk research, short term (1-3 years):

Randomized clinical trial developed for the evaluation of the effectiveness of early behavioral intervention and factors predicting response to intervention. Although there have been several studies that have examined the effectiveness of early behavioral intervention, only one randomized clinical trial of early behavioral intervention has been conducted. Substantial variability in response to intervention has been found, and very little is known about the factors (moderator variables) that account for this variability. A well-designed randomized study that examines moderator variables is needed. Such a study could also serve as a feasibility study for designing a multi-site clinical trial.

Medium-risk research, medium term (4-6 years):

Multi-site randomized clinical trial implemented to identify moderators and effective ingredients (e.g. dose, intensity, mode of delivery, age of onset) of early intervention treatments. This would be a large-scale study that takes place in several locations, to rigorously test specific ingredients of early intervention and determine the key factors related to response to intervention.

Intervention methods for infants and toddlers developed, to lower the age for which there are efficacious interventions. At present, most early intervention methods have been developed and used in preschool children. As it has become apparent that signs of autism may be seen as young as 18 months and even 12 months, interventions need to be developed and tested specifically for these age groups.

Low-risk research, long term (7-10 years):

Longitudinal follow-up of early intervention randomized clinical trial implemented. Although several studies have now examined the effectiveness of early intervention, few studies have followed children over time to determine the lasting effects of specific methods of early intervention, particularly for functional outcomes. Such a study is needed to determine the long-term effectiveness of early intervention, compared to other treatments, and factors that promote success.

High-risk research, long term (7-10 years):

Provide evidence that twenty-five percent of cases of autism can be secondarily prevented from symptomatic expression through early identification and early treatment. The goal would be to reduce anticipated symptoms of autism below the threshold for diagnosis in 25% of projected cases. Success with extending efficacious treatment to children of younger ages, along with identification of children for whom such treatment at young ages would be beneficial, should make it possible for some cases of autism to be prevented. Such prevention studies would entail treating children who are showing signs of autism early, to prevent children from meeting diagnostic criteria for autism by age 5.

Methods developed to allow 90% of individuals with autism to develop speech. As part of a successful early intervention program, specific methods would be developed and tested to drastically improve the number of young children with autism that develop meaningful, functional speech by the time of entry into elementary school.

Specific Treatments:
Research is beginning to show that specific medical and behavioral treatments, and combinations of these treatments, are effective in ameliorating various problems that are often associated with autism. Further research is needed to fully evaluate the efficacy and effectiveness of such treatments. Treatments aimed at improving the "core" symptoms of autism are also beginning to undergo rigorous evaluation, but much development and evaluation are needed in order to successfully identify treatments for core symptoms such as communication deficits, social impairments, and restricted and repetitive behaviors.

Low-risk research, short term (1-3 years):

Outcome measures improved, to enhance their usefulness in evaluating treatment studies. Meaningful outcome measures are essential for examining potential benefits and risks of different treatment options. This activity will require a comprehensive appraisal of the current state of outcome measures. It will also require research that develops and compares novel outcome measures for core symptom domains, to create and implement research that uses outcome measures with optimal reliability, validity and usefulness.

High-risk research, short term (1-3 years):

Efficacy established for pharmacological, behavioral and other treatments that target symptoms associated with autism. In order to achieve this goal, there must be repeated randomized, controlled studies indicating efficacy for such interventions in diverse populations of individuals with autism.

High-risk research, medium term (4-6 years):

Individual characteristics that predict response to behavioral, pharmacological and other treatments are identified. Studies investigating the efficacy of specific treatments must comprehensively examine factors that will help explain why certain treatments work for some individuals with autism and not for others.

Medium-risk research, medium term (7-10 years):

Treatment algorithm for autism developed, to provide guidance for practitioners and educators. Such an algorithm would include information about decision-making involved in developing an individualized treatment program, and include information about both

behavioral/psychosocial and medical aspects of intervention. Such an algorithm would allow for common standards regarding the clinical care of individuals with autism across clinicians.

High-risk research, long term (7-10 years):

Efficacious drug treatments that target core symptoms of autism are developed. In order to achieve this goal, research in several domains must advance. Molecular neurobiology and neurochemistry research will help inform scientists about brain molecules that may be appropriate targets for drug therapies. At the same time, advances in our understanding of the core characteristics of autism will assist in improving measurements and potential mechanisms of change for targeting core symptoms of autism.

Role of the Environment in Autism:

In order to achieve the long-term goal of determining both genetic and non-genetic causes of autism and their interactions, shorter term goals include increasing resources for the study of potential environmental factors, and implementing population based epidemiological studies, as well as focused research that examines potential influences of various environmental factors.

Low-risk research, short term (1-3 years):

Twin resource developed, to study heritability and environment factors influencing autism. This item specifically calls for the development of a twin registry that contains comprehensive data on a large number of twins with at least one affected individual in the pair. Such a registry would allow for large-scale studies of both genetic and non-genetic causes of autism.

High-risk research, medium term (4-6 years):

Environmental factors (e.g. viruses, medications, lifestyle factors, environmental chemicals) that contribute to the development of autism and their associated developmental windows identified. In order to identify environmental factors that contribute to autism, as well as when and how they make their contributions, community-based studies are required to determine potential environmental factors, as are studies of the specific mechanisms by which environmental factors work to contribute to specific neurodevelopmental difficulties.

High-risk research, long term (7-10 years):

Genetic and non-genetic causes of autism and their interactions identified. In order for this goal to be achieved, genes that increase vulnerability to

autism will need to be identified, and environmental factors will need to be determined, along with findings that indicate the increased risk and mechanisms of each of these identified determinants.

Neuroscience:
Determining the brain systems and mechanisms that play a role in the development and maintenance of autism will require research advances in several areas of neuroscience, including developmental neurobiology, neuroanatomy, neuropathology, neurochemistry and molecular neuroscience. Increased infrastructure is necessary, such as the development of a centralized repository for biological materials as well as various types of database resources.

Medium-risk research, short term (1-3 years):

Infrastructure, such as enhanced brain acquisition, established for neuropathological investigations, to characterize the morphological aspects of the pathophysiology of autism. The collection of postmortem brain tissue from individuals with autism and their families is necessary for studying brain abnormalities that may be associated with autism. Activities that will enhance the acquisition of such material, such as the centralization of these resources and outreach activities, will allow researchers to obtain maximal high-quality data for their studies.

Technology and infrastructure developed for multi-site in vivo imaging studies, to identify the neuropathology of autism. Although there have been many advances in imaging techniques such as magnetic resonance imaging (MRI) and positron emission tomography (PET), this activity calls for development of novel techniques and enhancement of existing technologies to study specific brain regions hypothesized to be associated with autism.

Low-risk research, medium-term (4-6 years):

Neural circuitry and neurochemistry defined for several functions impaired in autism. With the use of enhanced imaging technologies, researchers will be able to identify specific brain regions and chemicals involved in the development and maintenance of behavioral expressions of autism in areas such as communication, social behavior, executive functions, and repetitive behaviors. Such studies will build on advances made in the behavioral characterization of autism.

Medium-risk research, medium term (4-6 years):

Neuropathology of autism characterized, to identify brain structures and functions associated with autism. The combined use of anatomical and functional imaging methods will permit identification of the brain structures whose function is altered in autism to produce particular functional consequences. Studies of these brain structures in postmortem material will assist in identifying the specific cellular and molecular bases for such altered function. A number of functional systems and cellular/molecular mechanisms will likely be revealed. For example, brain structures known to be involved in various aspects of social behavior may be explored for specific associations with impairments in social functioning that are common in autism.

Developmental time course characterized for alterations in brain structures and connections in autism. Studies in animal models and in humans that examine the development of brain structures throughout the lifespan will identify both pre- and postnatal alterations in brain development associated with autism. One goal will be to identify specific aspects of brain maturation that occur within the same developmental stages as the appearance of critical behavioral skills that are altered in autism.

Medium-risk research, long term (7-10 years):

Basic, common neuropathological and neurochemical features of autism defined. After brain structures and chemicals are found to be associated with specific symptoms of autism, the interplay between brain systems, regions, structures, and chemicals can be explored to determine how they work together to create the behavioral manifestations of autism. It will be especially important to identify the brain regions and mechanisms that are altered to produce the core features of autism. This will require systematic study across symptom clusters and stages of development.

School and Community Interventions:

Most research on interventions thus far has focused on young children and specifically on improving developmental functioning in the areas of language, basic cognitive skills, social functioning and daily living skills. Research is now needed on strategies to improve "real-world" functioning of individuals with autism, throughout their school-age years and beyond. It has also been widely recognized that periods of transition, such as from high school to higher education and/or employment, provide particular challenges for individuals with autism and their families. This effort will involve a range of research methodologies and

strategies to include intervention development; testing of efficacy and effectiveness of existing interventions in diverse community settings; determining roadblocks to implementation of, and access to, effective interventions; and strategies for overcoming roadblocks to widespread dissemination.

Low-risk research, short term (1-3 years):

Effective interventions expanded, disseminated and implemented to improve outcomes in the school and community settings throughout the lifespan, including transitions (e.g. academic functioning, social and adaptive behavior, family functioning, employment) in collaboration with the Department of Education, and other federal agencies, such as the Department of Labor and Social Security Administration. Previous work has found effective interventions for both academic and adaptive success, but these interventions require considerable work for successful implementation in diverse settings.

Medium-risk research, short term (1-3 years):

Innovative intervention strategies developed to improve outcomes in the school and community settings throughout the lifespan, including transitions (e.g. academic functioning, social and adaptive behavior, family functioning, employment) in collaboration with the Department of Education and other federal agencies. Novel intervention strategies are required to ensure that all individuals with autism, throughout the lifespan, are able to be successful in the various dimensions of daily life.

Low-risk research, medium term (4-6 years):

Innovative and newly developed intervention strategies evaluated, implemented and disseminated to improve outcomes in the school and community settings throughout the lifespan, including transitions, (e.g. academic functioning, social and adaptive behavior, family functioning, employment) in collaboration with the Department of Education and other federal agencies. Continued work is necessary to ensure that newly identified effective interventions are implemented into real-world settings in a timely fashion.

Medium-risk research, medium term (4-6 years):

Continue formulating, evaluating and implementing appropriate efficacious intervention strategies incorporating research-based findings to improve outcomes in the school and community settings throughout the lifespan, including transitions (e.g. academic functioning, social and

adaptive behavior, family functioning, employment) in collaboration with the Department of Education and other federal agencies.

Medium-risk research, long term (7-10 years):

Appropriate and efficacious interventions are widely recognized and broadly implemented for school and community settings throughout the lifespan, including transitions (e.g. academic functioning, social and adaptive behavior, family functioning, employment) in collaboration with the Department of Education and other federal agencies.

Epidemiology:

Recently, studies have begun to examine changing rates of autism, both in small community-based studies as well as in larger, population-based studies. However, studies thus far have examined changing rates only by examining cases retrospectively at separate time points. Studies that prospectively examine prevalence by including comprehensive diagnostic evaluations on children will be necessary to understand fully changes in prevalence rates of autism over time.

Low-risk research, medium term (4-6 years):

First generation intensive community-based prevalence studies with clinical evaluations implemented to have initial data for detecting changes in prevalence of autism. These studies will differ from previous research in that they will involve clinical researchers examining all children in a given community who are suspected of having autism, in order to prospectively establish a "base" rate of autism (i.e. prevalence) within the specified community.

Low-risk research, long term (7-10 years):

Second-generation intensive community-based prevalence studies with clinical evaluations planned and implemented. Once a base rate of autism is established through first generation prevalence studies, the intensive community-based prevalence study will need to be repeated over time in order to determine whether the prevalence has changed from the determined base rate.

Communication and Collaboration:

In order to quicken the pace at which research findings are translated into practice within community settings, the goal in this area is to increase the efficiency with which research findings are communicated to other scientists, as well as to practitioners and members of the autism community.

Low-risk research, short term (1-3 years):

Research Communication Network (both local and national) developed to disseminate findings among researchers and the public to increase ongoing communication. Such networks would allow important research findings to be systematically distributed to all members of the autism community in a timely manner, in order to expedite replication studies and subsequent translation into practice.

Adoption and Implementation of the Matrix

The IACC has reviewed, edited, and adopted the matrix presented in this report as the initial version of this guiding document. The NIH Autism Coordinating Committee (NIH-ACC) will now assume primary responsibility for devising an implementation plan that will take into account research activities already underway, including the types of private and partnership activities referred to in the conference language requesting the matrix. The NIH-ACC will also develop new initiatives and priorities intended to implement matrix activities and achieve matrix goals. For example, the NIH-ACC is currently reissuing a program announcement to potential grant applicants entitled "Research on Autism and Autism Spectrum Disorders." The following are other examples of activities that address implementation of various components of the 1- to 3-year time frame matrix items.

Characterization of Autism Spectrum Disorders and Associated Genetics: *Resources established for genotype/phenotype studies (i.e. bioinformatics, genetic repository).* Several efforts are underway to increase acquisition of genetic material into a centralized repository. The NIMH Center for Genetic Studies encourages and supports the collection and timely sharing of research resources for genetic studies on autism through a repository http://www.nimhgenetics.org. NIH also strongly supports the Autism Genome Project (AGP), sponsored by the National Alliance for Autism Research (NAAR). NAAR has assembled a large consortium of autism researchers, including those utilizing biomaterials from the Autism Genetic Resource Exchange (AGRE) sponsored by the Cure Autism Now Foundation (CAN), to conduct a genome-wide scan of over 1,200 pedigrees collected worldwide. NIH recently funded a fast-track administrative supplements program to encourage the collection and timely sharing of research resources for use in AGP and other genetic studies on autism. Data and DNA on 1,000 families selected because of an individual with autism will be added to NIMH's Human Genetics Initiative for sharing with AGP and the broader

scientific community. Additionally, the STAART Centers are currently working on developing protocols to send phenotypic and genetic material to the NIMH Genetics Repository.

Specific Treatments:
Outcome measures improved, to enhance their usefulness in evaluating treatment studies. A workshop in September 2002, entitled "Research on Psychosocial and Behavioral Interventions in Autism: Confronting the Methodological Challenges," provided initial groundwork for this activity (*http://www.nimh.nih.gov/events/autismconference.cfm*). Since this meeting, workgroups have formed and are currently working on assessing the field with respect to outcome measure for young children, school-aged children and adults. A separate workgroup is focused on issues of research design for outcome studies.

Screening:
Evaluate sensitivity and specificity of existing screening tools, and continue developing efficacious screening measures. NIH has funded several grants to investigators to evaluate the validity and reliability of newly developed screening tools. For instance, NIH has funded research on the M-CHAT and the Social Communication Questionnaire. The CDC has also funded specific research evaluating effective strategies for implementing screeners into community practice settings.

Early Intervention:
Randomized clinical trial developed for the evaluation of the effectiveness of early behavioral intervention and moderator variables predicting response to intervention. The University of Washington STAART Center is undertaking such a study that will examine the effects of a specific method of applied behavioral analysis in children from a young age, and compare this treatment with standard community treatment.

Neuroscience:
Infrastructure, such as enhanced brain acquisition, established for neuropathological investigations, to characterize the morphological aspects of the pathophysiology of autism. In October 2003, NIMH awarded funding for the National Autism Brain Bank, which will create a centralized repository for autism brain tissue and support outreach activities to enhance these resources.

Epidemiology:
First generation intensive community-based prevalence studies implemented with clinical evaluations to have initial data for detecting changes in prevalence of autism. CDC is currently funding the Centers of Excellence for Autism and Developmental Disabilities Research and Epidemiology (CADDRE), which are implementing community-based prevalence studies in several states.

These activities address specific matrix items. Planning is currently underway for further collaborative work that will use findings from these activities to lay the groundwork for implementation of some of the higher risk and longer time course matrix items. These and other activities are also currently being expanded to include opportunities for voluntary and private funding organizations to participate through partnerships or to implement independent activities but with coordination to ensure maximum effectiveness. Certain present and planned activities include collaboration with other government agencies. The IACC will ensure that the matrix is a living document, and it will, through future iterative processes, use it to help guide further autism research planning at NIH and as a tool for the entire autism community. In closing, the following are some recent highlights of findings in key areas of autism research that reflect on the state of the science at the time of this initial version of the Autism Research Matrix.

Autism Research Highlights

Epidemiology:
In the past 30 years, over 25 prevalence studies of autism have been conducted internationally. These studies have used varying criteria for autism, and found prevalence estimates ranging from 1.9 to 60 per 10,000 (reviewed in Yeargin-Allsopp, 2002). Given differences in both methods and results among published studies, there is no current consensus regarding autism rates.

The CDC is the Federal agency most directly involved in incidence and prevalence studies of various disorders. One example of a recent (1998) autism prevalence study (though not a full population-based study) conducted by the CDC is the Brick Township, New Jersey study. Findings from this study of children aged 3-10 indicated that the prevalence of strictly defined autism was 4 per 1,000, and the prevalence of autism spectrum disorders was 6.7 per 1,000 (Bertrand et al., 2001). These rates are among the highest that have been reported. In order to provide data from a large population-based study, the CDC conducted the Metropolitan Atlanta Developmental Disabilities Study (MADDS), which found a prevalence rate for the combination of autism, Asperger's disorder

and pervasive developmental disorder--not otherwise specified (PDD-NOS) to be 3.4 per 1,000 (Yeargin-Allsopp et al., 2003).

Genetics:
In the past 10 years, researchers have begun utilizing highly sophisticated approaches for identifying candidate genes involved in susceptibility to autism (Folstein & Rosen-Sheidley, 2001). Recent research in the genetics of autism has indicated that several genes (possibly 5 to 10) are involved in autism susceptibility, and comparison of studies involving twins, siblings and other relatives implicates epistatic (e.g. multiplicative) effects among genes (Dawson et al., 2002). However, no susceptibility genes have been confirmed in replicated research studies.

Although no specific genes have been confirmed, researchers are beginning to identify candidate genes that are linked to endophenotypes, or component parts of the disorder. For instance, a recent study found that a gene on chromosome 15 coding for the gamma-aminobutyric acid (GABA) receptor beta3-subunit (GABRB3) is involved in the autistic symptoms of repetitive behaviors and stereotyped patterns (Shao et al., 2003).

While no gene(s) have been found to directly relate to susceptibility of idiopathic autism, there has been much progress in identification of the genetic basis for Rett's Disorder, a variant autism spectrum disorder (ASD) found almost exclusively in females. A mutation in the methyl-CpG-binding protein 2 (MeCP2) gene on the X chromosome was found and is present in most cases of Rett's Disorder (Amir et al., 1999). More recently, mutations on MeCP2 have been found on a small percent of girls diagnosed with autism (Carney et al, 2003), indicating that this specific mutation may be a cause of autism as well as Rett's Disorder for at least some affected girls. A related recent finding has implicated mutations in two neuroligins (NLGN3 and NLGN4) on the X chromosome to be involved in autism spectrum disorders (Jamain et al., 2003).

Neurobiology:
A recent review highlights the complexities of studying the neurobiology of autism, in that the heterogeneous behavioral expressions of autism may relate to multiple neuropathologic etiologies (Lord, Cook, Leventhal & Amaral, 2000). Nonetheless, neuropathological studies that have employed both post-mortem studies as well as imaging techniques have implicated several areas of the brain to be involved in aspects of autism. Both the medial temporal lobe (MTL), which

includes the amygdala, as well as the cerebellum, has been found to be abnormal in several studies (Akshoomoff, Pierce & Courchesne, 2002; Dawson et al., 2002).

A striking recent finding is increased brain volume when children with autism are young, although not at birth or later in life (Aylward, Minshew, Field, Sparks, & Singh, 2002), leading to a theory of brain growth dysregulation underlying autism (Courchesne et al., 2002).

Treatment:

The past 10 years have been marked by an increase in trials of targeted pharmacological interventions aimed at specific behaviors associated with autism. As an example, a study of risperidone, one of a newer class of anti-psychotic medications, was effective and well tolerated for the treatment of serious behavioral disturbance associated with autistic disorder in children aged 5 to 17 (McCracken et al., 2002). Also near completion is a study evaluating the safety and efficacy of methylphenidate in treating overactivity, impulsivity, and distractibility in children with autism spectrum disorders. Other treatment research has found a lack of efficacy for specific interventions. For instance, a multisite, double-blind, placebo-controlled study found that porcine secretin is not an efficacious treatment for autism (Owley et al., 2001).

A major effort to synthesize the research literature on early intervention was undertaken by the National Research Council at the request of the U.S. Department of Education's Office of Special Education Programs (National Research Council, 2001). The report reviews converging evidence on the components of effective early intervention models and makes recommendations for further research in this area.

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