Evaluating Progress on the IACC Autism Research Matrix

Report Presented to
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Executive Summary

In directing the Interagency Autism Coordinating Committee (IACC) to develop a research matrix of goals and action items to guide autism research planning, Congress stipulated that the matrix be revised and expanded as current goals are achieved and new goals are identified. At its May 2006 meeting, the IACC decided that now was an opportune time to evaluate the autism matrix in preparation for revision. The Evaluating Progress on the IACC Autism Research Matrix meeting was convened on September 25, 2006 at the Neuroscience Center in Bethesda, Maryland. The meeting was chaired by Dr. Thomas Insel, Director of the National Institute of Mental Health, and included twenty-two scientific experts and public members. Over the course of the day, the Panel reviewed the state of autism research, moving section by section, element by element, through the matrix. The discussion was led by assigned scientific experts for each of the matrix's eight sections; these included: epidemiology, the characterization of autism, the role of the environment, neuroscience, screening, early intervention, specific treatments, and school and community interventions. A brief summary of evaluative comments is provided below for each matrix section:

- With regard to epidemiology, the Panel agreed that several ongoing projects are addressing the epidemiology of autism, including projects focusing on surveillance and analytic epidemiology. However, there was concern expressed about the limited use of clinical evaluations for identifying autism spectrum disorders (ASD) in these projects, as well as the need to expand the focus on analytic epidemiology to supplement surveillance efforts.

- The Panel noted that research on characterizing autism has progressed well in the three years since the inception of the matrix. There have been advances in the definition of core and associated features, the characterization of symptom onset, and the identification of susceptibility genes. The Panel found that research efforts in this area can continue with a few notable course corrections.

- The Panel agreed that a broader representation of expertise than was assembled at the meeting was needed to fully assess progress on the role of the environment in autism. As a result, a subsequent conference call was held that brought together experts in neurotoxicology and epidemiology to further consider environmental aspects. All experts agreed that the role of the environment in autism, broadly defined to include an array of non-genetic risk factors, was given insufficient attention in the first iteration of the matrix. While some progress has been made, particularly with regard to developing infrastructure, this remains an understudied area and major challenges remain.

- In the area of neuroscience, the Panel noted that substantial progress has been made, particularly in the areas of neuroimaging and infrastructure building. They indicated that the field needs to pursue more longitudinal studies of brain development initiated at earlier ages, and develop more advanced methods and infrastructure to obtain higher quality postmortem brain tissue.

- The Panel agreed that notable progress has been made through research focused on screening ASD over the past three years, including the development of screening tools covering a wide range of ages. Continued research in this area needs to be conducted to improve the sensitivity and specificity of screening measures that have been developed.

- Early intervention research was found by the Panel to have progressed well along two main goals: developing interventions for infants and toddlers so that treatments can begin at the time of first symptoms, and identifying which ingredients of early interventions are maximally effective in reducing or ameliorating symptoms. The Panel agreed that more randomized clinical trials are needed of individual comprehensive intervention approaches, and that further research is needed to identify the "active ingredients" of effective interventions.

- With regard to specific treatments, the Panel found that while progress is being made, much remains to be done. Expansion of current efforts was suggested with a particular need for both behavioral and pharmacological interventions that specifically target core features of autism.

- The Panel found that since the inception of the matrix significant progress has been made in developing a variety of new school and community interventions, but that only moderate progress had been made in disseminating already existing interventions. It indicated that some course corrections are needed, including broadening the age-range of research participants in this area.

The Panel's discussion emphasized that the autism research matrix represents at least a ten-year effort to best understand the disorder and identify the best treatments. At only three years, this large and important undertaking is still in its earliest phases. As with any research enterprise of this magnitude, the first step is to create an infrastructure with regard to research tools, methods, and qualified researchers to support increased research and catalyze the kinds of multidisciplinary efforts needed to study such a complex neurodevelopmental disorder. The Panel agreed that significant progress in capacity building has been made during these first three years with respect to opportunities and resources available to autism researchers that did not previously exist, and that the field is poised to make important advances in autism research.

Introduction

In its report on the Fiscal Year 2003 budget for the Department of Health and Human Services (HHS), the Committee on Appropriations requested that the 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." The House and Senate conferees stipulated that, "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," and requested that the matrix be used to help guide further autism research planning.

In response to the congressional report, the IACC convened a panel of eleven premier scientists with expertise encompassing the spectrum of autism research in July 2003. During a two-day meeting, the Panel was asked to identify roadblocks to understanding the causes and best treatment options for autism and to propose a number of research activities and goals designed to overcome these roadblocks. The result of the Panel's deliberations was the first iteration of the IACC Autism Research Matrix.

In August 2003, the draft matrix was distributed to the IACC for discussion and approval. In November 2003, public input was obtained at the Autism Summit Conference. The IACC reviewed all suggestions at its November 21, 2003 meeting and approved the final version, tasking the National Institutes of Health Autism Coordinating Committee with the majority of responsibility for implementation, in collaboration with the Centers for Disease Control and Prevention, the Department of Education, and public members of the autism community.

Evaluating the Autism Research Matrix

Throughout the past three years, the matrix has provided a resource for directing the expansion and intensification of autism research. At its May 9, 2006 meeting, the IACC agreed that it was an opportune time to evaluate progress on the research matrix. The IACC decided that the original Panel members, along with new participants selected to broaden the expertise represented on the Panel, should be invited to review the state of autism research and to evaluate research progress using the matrix as a guide.

The Evaluating Progress on the IACC Autism Research Matrix meeting was convened on September 25, 2006 at the Neuroscience Center in Bethesda, Maryland. The meeting was chaired by Dr. Thomas Insel, Director of the National Institute of Mental Health, and included twenty-two scientific experts and public members. Over the course of the day, the Panel reviewed the state of autism research, moving section by section, element by element, through the matrix. The discussion for each of the eight sections was led by assigned scientific experts in each area. The question before the Panel was whether the research goals and activities outlined in the matrix had been achieved, were in progress, or had yet to begin. For those elements identified as being in progress, the question before the Panel was whether their continuation as designed was acceptable or whether a course correction was needed. After all sections had been evaluated, the Panel was then asked to identify gap areas not originally covered by the matrix.

During the review of the section pertaining to the role of the environment in autism, the Panel agreed that a broader representation of expertise was needed to fully assess progress. As a result a subsequent meeting was called on October 19, 2006 that brought together experts in neurotoxicology and epidemiology to further consider environmental aspects of autism research.

The results of both meetings are reflected in this document, which summarizes the findings of the Panel for each of the elements of the matrix, along with broader findings for each research area considered. Finally, suggestions for additional research needs and opportunities are summarized.

Overview of Findings

The Panel's discussion emphasized that the autism research matrix represents at least a ten-year effort to best understand the disorder and identify the best treatments. At only three years, this large and important undertaking is still in its earliest phases. As with any research enterprise of this magnitude, the first step lies in creating the capacity to address the issue from a multitude of scientific perspectives. Many of the elements of the matrix within the short-term categories were designed to do just this. The Panel found that much of this work has been done successfully. There are opportunities and resources available to autism researchers that did not exist three years ago. There is convergence around seminal findings recognizing that autism is a group of brain disorders, the exact nature of which has yet to be determined, but there are numerous clues to pursue. There is now a body of work to draw on to develop new ways of diagnosing and measuring prevalence of this family of disorders. In addition, there are a growing number of evidence-based strategies to pursue in developing new and innovative ways to intervene. The resulting growth of the field is evident as more scientists turn their attention to questions related to autism.

Despite these successes, much remains to be done over the next several years. This document examines the areas of the autism research matrix element by element, noting the successes, but more importantly suggesting course corrections and new areas of emphasis. Each of these areas build upon the other, and findings from one inform the others. Congress stipulated that the autism research matrix "should be a living document that can be revised and expanded as current goals are achieved and new goals are identified." This report represents the first step in that process. Through the careful evaluation of each item, the effort to revise the autism research matrix will be fully informed as course corrections and new areas are incorporated such that the autism research matrix continues to serve as a useful guide to the autism research effort.

IACC Autism Research Matrix: 12/03

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.	16. Individual characteristics that predict response to behavioral, pharmacological and other treatments are identified. 17. Susceptibility genes and animal models of autism are identified for further study of phenotypic characteristics of autism. 18. Environmental factors (e.g. viruses, medications, lifestyle factors, environmental chemicals) that contribute to the development of autism and their associated developmental windows identified.	29. Provide evidence that 25% of cases of autism can be secondarily prevented from symptomatic expression through early identification and early treatment. 30. Methods developed to allow 90% individuals with autism to develop speech. 31. Genetic and non-genetic causes of autism and their interactions identified. 32. Efficacious drug treatments that target core symptoms of autism developed.
Medium Risk Research	3. Resources established for genotype/phenotype studies (i.e. bioinformatics, genetic repository). 4. Existing data studied to begin to characterize the autism phenome, as part of the larger Phenome Project. 5. Infrastructure, such as enhanced brain acquisition, established for neuropathological investigations, to characterize the morphological aspects of the pathophysiology of autism. 6. Technology and infrastructure developed for multi-site in vivo imaging studies, to identify the neuropathology of autism. 7. Randomized clinical trial developed for the evaluation of the effectiveness of early behavioral intervention and factors predicting response to intervention. 8. 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. 9. Develop research on implementing early identification of children with autism in community settings, and employ a population-based longitudinal cohort.	19.Biological and/or behavioral markers identified to develop indices of risk for the development of autism in infants. 20. 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. 21. Intervention methods for infants and toddlers developed, to lower the age for which there are efficacious interventions. 22. Neuropathology of autism characterized, to identify brain structures and functions associated with autism. 23. Developmental time course characterized for alterations in brain structures and connections in autism. 24. 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.	33. Feasible, sensitive autism screening method for young infants developed. 34. Basic, common neuropathological and neurochemical features of autism defined. 35. Treatment algorithm for autism developed, to provide guidance for practitioners and educators. 36. 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.
Low Risk Research	10. Autism Phenome Project defined and planned 11. Outcome measures improved, to enhance their effectiveness in evaluating treatment studies. 12. Twin resource developed, to study heritability and environment factors influencing autism. 13. 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. 14. Research Communication Network (both local and national) developed to disseminate findings among researchers and the public to increase ongoing communication. 15. Evaluate sensitivity and specificity of existing screening tools, and continue developing efficacious screening measures.	25. 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. 26. Neural circuitry and neurochemistry defined for several functions impaired in autism. 27. 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. 28. First-generation, intensive, community-based prevalence studies with clinical evaluations implemented, to have initial data for detecting changes in prevalence of autism.	37. Longitudinal follow-up of early intervention randomized clinical trial implemented. 38. Second-generation, intensive, community-based prevalence studies with clinical evaluations planned and implemented.
	Short term (1-3 years)	**Medium term (4-6 years)**	**Long term (7-10 years)**

KEY: Red = Characterization of autism (i.e. phenotype/genotype); 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

Epidemiology

The Panel agreed that progress was on-going for the epidemiological items included in the matrix, however these items were limited to questions of prevalence and did not address analytical epidemiological studies. In regards to prevalence studies, the Panel found that several projects are underway, including the Center for Disease Control and Prevention's (CDC's) Autism and Developmental Disabilities Monitoring Network (ADDM). The majority of these studies rely on review of abstracted records by clinical experts and not on direct clinical observations. With regard to analytic epidemiology, important studies have begun, though in early phases, and needs to be reflected in the matrix.

Overall Suggestions for the Epidemiology Area

- Panel members recommended that this area be expanded to include both surveillance and analytic aspects of epidemiology. For example, the Panel recognized the importance of the Centers of Excellence for Autism and Developmental Disabilities, the Childhood Autism Risks from Genetics and the Environment (CHARGE) study, and the Norwegian Mother and Child Cohort Study, among others, and noted that these studies will over the next 3-5 years begin to provide data to address many of the pressing questions potentially answered through analytic epidemiology.
- Future research needs to address the nature of the increase in prevalence of autism spectrum disorders (ASD); does the increase represent an actual rise in the incidence of the disorder or does it merely reflect change in ascertainment and diagnostic criteria?
- More emphasis need to be placed on conducting clinical assessments that can determine the extent of misclassification among those designated as having autism (false positives).
- More prevalence studies using varied methodologies are needed to ensure that the estimates derived from the ADDM methodology are accurate.

Evaluation Results and Suggestions for Individual Matrix Elements

28. *First-generation intensive community-based prevalence studies with clinical evaluations implemented to have initial data for detecting changes in prevalence of autism.*

Evaluation:

- There are multiple efforts currently underway to develop first generation community-based prevalence studies. These include:
    - The ADDM Network, which is implementing community-based prevalence studies in 10 states
    - The Metropolitan Atlanta Developmental Disabilities Surveillance Project (MADDSP), a CDC intramural surveillance system that serves as a model for the ADDM Network.
    - International prevalence studies are also underway, including a door-to-door prevalence study in India run through the International Clinical Epidemiology Network and funded by Autism Speaks. There has been discussion of conducting a similar study in Uganda.

- These studies primarily rely upon review of abstracted records by clinical experts. CDC is currently conducting a clinical validation study to examine the validity of using expert clinical review of records based information.
- The CDC is publishing a report in early 2007 that includes autism prevalence data from two time points in six study sites. One of the six sites is an area in New Jersey, which includes Brick Township.

Suggestions:

- Greater emphasis needs to be placed on direct clinical evaluations in prevalence studies.
- Clarification is needed as to how prevalence studies that have relied on educational data for first-round identification of ASD will move forward given the Department of Education's recent decision on interpreting the Family Educational Rights and Privacy Act (FERPA).
- Changes in prevalence estimates over time need to be examined by following up earlier prevalence studies, such as Brick Township, using the same population, approach, and measures.

38. *Second-generation intensive community-based prevalence studies with clinical evaluations planned and implemented.*

Evaluation:

- With the exception of the MADDSP, little work is being done on intensive community-based prevalence studies that include clinical evaluations.

Characterization of Autism Spectrum Disorders and Associated Genetics

The Panel found that attempts at characterizing autism spectrum disorder have progressed well in the three years since the inception of the matrix. There have been advances in the definition of core and associated features, and characterization of symptom onset. In addition, attempts at identifying susceptibility genes are progressing at a fast pace due to the large number of resources available to investigators. The Panel found that research efforts in this area could continue with a few notable course corrections.

Overall Suggestions for the Characterization Area

- Much of the focus of the matrix in this area was on the phenome project, but additional efforts are needed to advance understanding of the phenotype, including studies that link genotype to phenotype, investigations of natural and treated history, and comorbid conditions. Elements in this area need to better reflect all of the research being done on the ASD phenotype.
- More attention is needed on research efforts directed towards identifying etiologically significant subgroups.
- An increased focus is needed on data sharing and data storage issues, including how rapidly they are made available to the research community. Efforts are also needed to better publicize their availability.

Evaluation Results and Suggestions for Individual Matrix Elements

10. *Autism phenome project defined and planned.*

Evaluation:

- The phenome project has been defined. During this process, it became clear that the phenome project is actually several projects, utilizing previously collected data, as well as prospective data collections. A pilot investigation of the latter type has begun at the MIND institute (privately funded) and in the intramural NIMH, and planning for other investigations is underway.
- The CHARGE study has already enrolled 700 subjects, and characterization has begun using a number of measures. Medical data, biological specimens, immunological features and genomic profiles are all being analyzed as part of the study.
- In addition to these efforts, there are several other projects underway that will increase knowledge of the ASD phenotype. For example, the CDC has funded 16 programs in 17 sites to conduct ASD surveillance under the ADDM Network, which involves detailed abstraction of behavioral, diagnostic, and associated features of the ASDs on a large cohort of children born in 1992 and 1994. Further, the Collaborative Programs of Excellence in Autism (CPEA) and Studies to Advance Autism Research and Treatment (STAART) Network datasets already include over 2,500 well-characterized samples.
- Despite the scope of the phenome project, several investigators working in autism are not aware of the details of this project.

Suggestions:

- Public/private partnerships have been very important to the launching of the phenome project and need to be expanded to continue its support.
- Policies on data sharing need to be established. These policies will facilitate utilization of the National Database for Autism Research (NDAR), currently under development at NIH, which is designated as a major resource for the phenome project.
- The goal itself could be expanded to recognize the numerous other studies related to characterizing autism in addition to the phenome project.

12. *Twin resource developed, to study heritability and environment factors influencing autism.*

Evaluation:

- A few twin studies have been supported, but the concept of a twin registry has not been realized.
- The size of the registry would have to be very large to take into account heterogeneity factors.

Suggestion:

- The registry could set as an initial target the inclusion of data derived from 100 twin pairs, with one or both individuals meeting diagnostic criteria for autism.

3. *Resources established for genotype/phenotype studies (i.e., bioinformatics, genetic repository).*

Evaluation:

- Numerous resources exist for genotype/phenotype studies, supported by public and private sources.
    - The NIMH Center for Collaborative Genetic Studies has established the NIMH Human Genetics Initiative as a national resource with more than 8,000 DNA samples of autistic children and their families.
    - The NICHD/NIDCD Collaborative Programs of Excellence in Autism (CPEA) include 12 multidisciplinary, collaborative sites that share common diagnostic and core measures. CPEA findings have included the identification of several chromosomal areas where defective genes related to autism may be found.
    - The CHARGE study supported by NIEHS has collected biological samples from more than 400 case families and a comparable group of control families.
    - Autism Speaks/National Alliance for Autism Research 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.

- CDC's Centers for Autism and Developmental Disabilities Research and Epidemiology (CADDRE) have developed a collaborative case-cohort protocol, which involves collection and storage of genetic material of a large cohort of 3-5 year old children with ASDs, other neurodevelopmental disorders, and population controls.
- The Norwegian cohort study of 100,000 pregnancies, supported by NINDS, will provide biosamples and phenotypic information on a large sample of children with autism and a general population sample.
- The Simons' Collection has selected 11 centers to collect genetic samples from up to 2,000 simplex families in two years.

- These collections, however, are not making the best use of the latest techniques in genetic research, and the phenotypic characterization is not being advanced.
- There is little investment in the type of multidisciplinary training needed to carry out this work.

Suggestions:

- As samples are merged into repositories, it is important to create resources that will allow for the identification of recruitment strategies and the types of populations from which they were derived (e.g., school samples, neurologist office recruits, etc.).
- Data sharing policies need to be clearly defined.
- More advanced cytogenetic studies are needed to investigate potential de novo mutations and genetic lesions that are included in the repositories.

4. *Existing data studied to begin to characterize the autism phenome, as part of the larger phenome project.*

Evaluation:

- Progress has been made in characterizing the phenome through the analysis of existing data on very large samples (e.g., CPEA studies).

Suggestion:

- There needs to be an increased effort to publicize the availability of data and to work out the details of data sharing agreements.

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.*

Evaluation:

- Although no biomarkers have yet been identified, there are some promising leads, and projects are underway that have the potential to provide biomarker candidates. For

example, grants have been awarded to conduct proteomic studies and recent papers have described gene expression analyses.

Suggestion:

- A more concerted effort is needed to expand this area. Given that these types of studies are very hard to fund through the typical grant process, a public/private partnership would propel the field.

25. *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.*

Evaluation:

- The Panel found that work in this area was progressing well.
- NICHD and Autism Speaks/NAAR have formed a consortium of researchers focusing on the study of infant siblings of children with autism to help identify early features and distinguishing characteristics of autism. A goal of this partnership is to create larger, combined samples of this population at high-risk for autism, and several collaborative multi-site projects are currently underway.
- Additional studies have begun to examine subsequent pregnancies.

17. *Susceptibility genes and animal models of autism are identified for further study of phenotypic characteristics of autism.*

Evaluation:

- Progress in the area of identifying susceptibility genes has been significant due to a number of resources, both public and private, that have been provided to the field.
- The current strategy for identifying susceptibility genes is not likely to identify de novo mutations and does not in general address epigenetic questions.
- The conceptualization of the phenotype remains underdeveloped.

Suggestions:

- Animal models can be very useful in this area among many others, and need to be made into a separate goal.
- Broader approaches towards the study of susceptibility genes need to be adopted that account for de novo mutations.

31. *Genetic and non-genetic causes of autism and their interactions identified.*

Evaluation:

The achievement of this goal is dependent on the identification of genes that increase vulnerability to autism and the determination of environmental factors that increase risk. These are both long-term goals and evaluation of progress on this element is premature.

Role of the Environment in Autism

There was agreement that the role of the environment in autism, broadly defined to include an array of non-genetic risk factors, was given insufficient attention in the first iteration of the matrix. A greater involvement of experts in an array of exposure-related concerns (e.g., viruses, maternal health conditions, diet and lifestyle, environmental contaminants) is needed to clearly define what is meant by 'environment' and develop better-informed strategies to address this topic. While some progress has been made, particularly with regard to developing infrastructure, this is still an understudied area and major challenges remain. Many Panel members cited the limitations of existing methodologies for exposure assessment and expressed the need for improved biomarkers of personal exposure to specific compounds. The incomplete characterization of the autism phenotype, lack of biomarkers of disease and disease progression and inadequate animal models were among the factors cited hindering progress in identifying and understanding environmental contributions. Interdisciplinary research approaches capable of incorporating neurobiologic and genetic information emerging from other areas of the matrix are needed to develop and test focused hypotheses regarding environmental inputs to disease etiology or expression.

18. *Environmental factors (e.g., viruses, medications, lifestyle factors, environmental chemicals) that contribute to the development of autism and their associated developmental windows identified.*

Evaluation:

- The Panel agreed that some infrastructure is in place to begin to address some environmental issues, and that some progress has been made in addressing medically related and limited lifestyle factors.
- The National Institute of Environmental Health Sciences (NIEHS) and Environmental Protection Agency (EPA) funded Children's Centers for Environmental Health and Disease Prevention have brought together multidisciplinary teams to support a range of studies, from epidemiological and clinical investigations of ambient environmental risk factors to the development of toxicant-induced animal models of specific autistic features.
- The Genes and Environment Initiative, a large trans-NIH initiative led by NIEHS in partnership with the National Human Genome Research Institute (NHGRI), includes an Exposure Biology component with targeted initiatives for the development of new technologies for monitoring environmental exposures and biologic response to exposures. The goal of this program is to apply these technologies to understand gene-environment interactions in disease.
- Investigators of the CDC-funded CADDRE Program have developed a multi-site research protocol to investigate select environmental exposures, phenotypic outcome, and genetic components in young children.
- NIEHS is supporting the CHARGE study, which has collected data from over 400 case families and a comparable group of control families on a broad array of environmental exposures and physiologic factors.

Suggestions:

- There is only one element in the matrix that focuses on the role of environmental factors, yet this is one of the most visible areas in autism research. A more comprehensive approach needs be adopted, with inclusion of a number of related elements that reflect the breadth of the field.
- A more standardized definition of what is meant by 'environment' needs to be developed to allow clearer direction in this area of research.
- The development of animal models for which targeted environmental agents can be tested is important to evaluate mechanisms and susceptibility genes that may interact with environmental factors.
- Multi-site studies of subsequent pregnancies in women with autistic children are needed to obtain biologic measurements and provide some exposure monitoring during the pregnancy and in the early childhood. Identifying the phenotypic and genotypic characteristics of the subjects will greatly advance this area of work.
- There is mixed support for the feasibility and utility of efforts to determine autism prevalence before 1985. The ability to obtain these types of data is diminishing and some Panel members were skeptical that a methodology for conducting such a study could be developed that would allow valid comparison with contemporary prevalence estimates. An alternative method may be to follow-up with individuals identified in early prevalence studies.
- Experimental paradigms that lend themselves to the investigation of multifactorial etiologies need to be employed in which consideration is given to the interaction of environmental and genetic factors in the context of developmental trajectories.
- Consideration of autism as a multi-organ disease is needed.
- There is a need to develop technology for identifying biomarkers that can detect exposure to a wide variety of environmental factors which can then be applied in autism research.
- The feasibility of measuring environmental chemicals that may possibly persist in tissue samples need to be examined in post mortem tissue.
- The literature suggests a number of chemicals that are neurotoxic and/or may affect neurodevelopment, including for example endocrine disrupting chemicals or pesticides, pyrethroid pesticides, and persistent halogenated compounds. These chemicals need to be further explored in relation to autism.
- There were mixed views regarding the best approach for prioritizing studies of environmental exposures. Some Panel members identified a significant number of exposures, or classes of exposures, that were known to affect brain development, and that merited exploration in the context of autism. Others supported more tightly focused studies of one or a limited number of exposures, and stressed that candidate exposures be selected as those with the greatest biologic plausibility for interacting with known or suspected biologic substrates in autism. Mood-altering medications that are often taken by pregnant women need to be examined through epidemiologic and mechanistic studies.
- Metals are known neurotoxins and need to be evaluated in comprehensive studies of multiple sources of exposures over key developmental time periods. Most work in this area on metals has been focused on thimerosal-containing vaccines, rather than the wide range of sources of exposures to mercury and other metals that include food, dental amalgams, personal care products, etc.

- Children with autism differ in immunocompetence compared with matched controls. A new generation of studies focused on immune system dysregulation and interactions between immune development and neurodevelopment is needed. Further studies are needed to investigate the role that vaccines and immunotoxic chemicals may play in autism.
- Reported associations with maternal and paternal age also suggest potential contributions of environmental factors. Further studies to evaluate an association with increasing paternal and maternal age in diverse populations, and related environmental/behavioral exposures (such as use of assisted reproductive technology) may be informative and are recommended.

Neuroscience

In the area of neuroscience, the Panel found that substantial progress had been made, but that much remains to be done. In the past three years since the inception of the matrix, the field has converged on a number of important findings, such as evidence that brains of many individuals with autism are enlarged at least early in life. These findings are of potential importance and suggest a number of research avenues to be pursued. Overall, the Panel agreed that significant progress is being made, but that the field needs to continue finding innovative ways of overcoming the very significant challenges of conducting full-scale, multidisciplinary studies in the neurosciences related to autism.

Overall Suggestions for the Neuroscience Area

- More effort is needed in developing evidence-based rodent and primate models of autism or of features of autism.
- Efforts need to be increased in devising innovative noninvasive imaging techniques (both structural and functional) with an emphasis on techniques that can be used in very young children. Continued efforts are needed to overcome the challenges of conducting multi-site imaging studies.
- A concerted effort is needed to increase the availability and quality of post mortem tissue.

Evaluation Results and Suggestions for Individual Matrix Elements

5. *Infrastructure, such as enhanced brain acquisition, established for neuropathological investigations, to characterize the morphological aspects of the pathophysiology of autism.*

Evaluation:

- Significant progress has been made in providing the necessary infrastructure through the efforts of the National Autism Brain Bank, the NICHD Brain and Tissue Bank, the Autism Tissue Program and the Autism Brain Project. There has also been work on improving collaboration between these resources, as in the case of the National Autism Brain Bank and the NICHD Brain and Tissue Bank.
- However, these resources are still inadequate because of an insufficient number of brains and an extended postmortem period. The specimens also include a number of varying co-morbidities and are of limited developmental range.
- In addition, there are no matched controls available.

Suggestion:

- Strategies are needed to establish a nationally coordinated tissue repository with regional collection centers established to allow samples from autistic individuals and controls to be collected and preserved quickly using standardized procedures. A much larger number of brains must be acquired. Once acquired, tissue specimens need to be logged into a national database that would facilitate research by an international network of scientists. Efforts are

already underway, including those to be undertaken by Autism Speaks and CAN to promote donations.

6. *Technology and infrastructure developed for multi-site in vivo imaging studies, to identify the neuropathology of autism.*

Evaluation:

- Progress has been substantial due to activities such as the Pediatric Neuroimaging Initiative, the collaborative work of STAART and CPEA investigators, and the establishment of the Biological Informatics Research Network.
- This progress is evidenced by significant advancement of the field such as the convergence around the idea that precocious growth of certain brain regions such as the cerebral cortex is one of the consistent features of autism.
- However, there are still issues with multi-site imaging studies that have yet to be solved. There is a critical need to develop a common standardization technique for normalization of data across sites. The pediatric brain gives rise to different grey/white signal characteristics that complicate segmentation. A better understanding of how brain maturation interacts with signal quality is needed, as well as improved procedures to carry out grey/white segmentation analyses.

Suggestion:

- Multi-site longitudinal studies that are coupled to efforts in early diagnosis are needed. This will require consensus across sites on all aspects of methodology, from the standardization of image acquisition and analysis to a common test battery for early diagnosis. These studies ought to begin at as early an age as possible, ideally age 12-months or younger, and will require improvements in the analysis of images from infant and toddler brains.

26. *Neural circuitry and neurochemistry defined for several functions impaired in autism.*

Evaluation:

- There is substantial progress in this area as it constitutes a major effort of several NIH institutes. The use of functional magnetic resonance imaging (fMRI) in human subjects and increasingly sophisticated techniques in animal models has provided new evidence concerning the normal organization of systems involved in social behavior, emotion, memory, communication and motor behavior.
- The process is ongoing and in no need of a course correction.
- However, the basic neurodevelopmental studies that focus on implicated neurocircuitry could be stronger and more relevant to autism.

Suggestion:

- An enhanced effort to look specifically at the neurodevelopmental aspects of mechanisms underlying the development of social behavior, as well as repetitive behaviors, is needed. These studies need to include rodent and primate models in addition to human functional imaging studies.

22. *Neuropathology of autism characterized, to identify brain structures and functions associated with autism.*

Evaluation:

- Progress has been made in this area in that there has been convergence on the view that a number of brain regions are preferentially involved in the "visible" pathology of autism, including regions of the cerebral cortex and the amygdala among others. In addition, a number of studies have reported on the involvement of connections between cortical regions in conjunction with dysregulated brain growth.
- Other regions of the brain have not received as much analysis.
- Moreover, the specificity of neuropathological features to autism has not yet been established for any structure. The cerebellum, for example, while clearly pathological in autism, also appears to exhibit pathology in a variety of other neurodevelopmental disorders.

Suggestions:

- The establishment of the neuropathology of autism relies on the availability of adequate numbers of postmortem brain specimens. As noted in #5 above, there is need for increased quantity and markedly improved quality of brain specimens.
- There is an ongoing need for implementation of sophisticated quantitative histological procedures across many brain regions in the same brain. The Autism Brain Project provides a good start in this area.
- In addition, more comparative studies are needed across neurodevelopmental disorders. For example, we know that there is pathology in the cerebellum in autism, but is this pathology specific to autism or found in other neurodevelopmental disorders as well? We need much better control material and clinical contrast material to do these types of comparisons.
- Neuropathology need to be more closely linked to phenotypic variables and comorbid features to address issues of heterogeneity. In some preliminary efforts related to this, the Autism Genetic Resource Exchange, Cure Autism Now and the Autism Tissue Program are entering into an agreement in which clinical data will be collected from those families in which sample brain materials have been collected. Efforts such as this need to be increased.

23. *Developmental time course characterized for alterations in brain structures and connections in autism.*

Evaluation:

- This element is dependent on the results of #22 above, and therefore evaluation of progress is premature. However, longitudinal studies of brain structure and connections in autism are underway, although in early stages.

Suggestion:

- In general, more longitudinal studies of brain development are needed, and they must be initiated at much earlier ages, ideally at birth and at least by six months of age. The discovery of genetic markers may be of particular importance to inform these studies, as well as in vivo studies of structural and functional connectivity in infant siblings at high risk for ASD.

34. *Basic, common neuropathological and neurochemical features of autism defined.*

Evaluation:

- Success in this element is dependent on results from areas represented in several of the elements above, and therefore evaluation of progress is premature.
- Very little is known about the neurochemistry of autism; most information comes from work on related disorders such as Fragile X. For example, there is focus on glutamate receptors through research on Fragile X, but there is little research addressing glutamate's involvement in autism.
- With increased quality of brain tissue acquired for post mortem studies (see element #5 above), more reliable immunohistochemical and molecular neurobiological studies can be undertaken. Such studies may highlight particular deficits in select neurochemical systems.

Suggestion:

- Certain neuroactive substances have been implicated in normal social behavior. As one example, there is substantial interest in the role of oxytocin both in normal social behavior and in the pathology of autism. There is also interest in therapeutic interventions using techniques that alter such neurotransmitter activity. Yet, research on specific neurotransmitter systems has been minimal, and deserves increased attention.

Screening

The Panel agreed that notable progress has been made in this area of research over the past three years. Several screening tools are currently being developed, covering a wide range of ages, and research aimed at identifying early behavioral, psychophysiological, and genetic risk indices is continuing. While this research is progressing, continued research needs to be conducted to improve the sensitivity and specificity information for screening measures that have been developed. It was also noted that, because much of the research on early screening has been conducted on high-risk populations, such as infant siblings and clinic-referred populations, it will be important to determine whether findings with such high-risk populations generalize to the broader population.

Overall Suggestions for the Screening Area

- There is a lack of information on the sensitivity and specificity of screening measures. While continued research with high-risk populations is warranted, emphasis needs to be placed on conducting diagnostic evaluations on a large population-based sample to evaluate false negatives.
- Additional research is required to determine how well findings from studies employing high-risk samples (e.g., infant siblings of children with autism or children referred to infant development programs) generalize to the wider population of infants exhibiting autism symptoms.
- Studies that can help identify barriers to the use of screening tools by health care professionals are needed, as are methodologies for increasing awareness and use of screening tools.
- Studies involving general population screening will need to identify effective strategies for optimizing parental follow-through for recommended follow-up exams and treatment.

Evaluation Results and Suggestions for Individual Matrix Elements

15. *Evaluate sensitivity and specificity of existing screening tools, and continue developing efficacious screening measures.*

Evaluation:

- A number of screening tools have been developed for detecting autism. These include, among others:
    - The Modified Checklist for Autism in Toddlers (M-CHAT)
    - The Screening Test for Autism in Toddlers (STAT)
    - The Social Communication Questionnaire (SCQ)
    - The First Year Inventory (FYI)
    - Early Screening for Autism Questionnaire (ESAT)
- These screening tools pertain to different ages, with M-CHAT and STAT appropriate for toddlers, SCQ for preschool and elementary school age children, and the FYI and ESAT appropriate for 12-month-old infants.

- Some of these tools are already fairly well developed. The M-CHAT, for example, has population-based data available to evaluate sensitivity and specificity. Most other tools are in earlier stages of development.

Suggestions:

- Additional studies are needed that compare the efficacy of autism screening tools with other early developmental screening tools (e.g., language assessment) in order to determine whether the autism-specific focus improves sensitivity and specificity.
- More focus is required on studying barriers to use of existing screening measures.
- Longitudinal studies that follow children who have been screened during the infant-toddler period to assess the longer range predictive power of early screening are needed.

9. *Develop research on implementing early identification of children with autism in community settings, and employ a population-based longitudinal cohort.*

Evaluation:

- Utilization of existing large-scale, population-based studies will allow for cost-efficient investigations of the impact of early identification procedures. Some recently funded projects in this area are now in their early stages.
- The CDC has funded specific research evaluating the effectiveness of various strategies for implementing screening into community practice settings.

Suggestions:

- While there are some population-based studies underway, more are needed using varied research methodologies.
- Lack of parental follow-though may be an important barrier to early diagnosis and treatment in population based early diagnosis studies and needs to be targeted for research regarding screening and referral practices that optimize parental adherence.

19. *Biological and/or behavioral markers identified to develop indices of risk for the development of autism in infants.*

Evaluation:

- There are several ongoing and proposed studies focusing on early behavioral, psychophysiological, and genetic risk indices and many of these are being conducted with multiplex autism families. Research findings have included:
    - Indications that prominent 12-month risk markers include impairment in: eye contact, visual tracking, disengagement of visual attention, orienting to name, imitation, social smiling, social interest and affect, and sensory-oriented behaviors.
    - Infants later diagnosed with ASD show gestural and language delays by 12 months, and atypical temperament and activity levels at 6 months of age.

- Current studies are utilizing psychophysiological measures (e.g., visual and auditory event related potential [ERP]), eye-tracking, and attentional measures in an attempt to increase detection at younger ages.
- While many studies have been conducted with infant sibling populations, it is unclear how well risk indices identified in these populations will generalize to a non-risk population.
- The relationship between early markers and diagnostic outcomes based on comprehensive gold-standard assessments remains to be determined.

Suggestions:

- Sensitivity and specificity of risk indices need to be tested more thoroughly. Current studies tend to focus on group differences rather than predictive utility for individual children.
- Susceptibility genes (or sets of genes) and/or other biological factors will likely be useful to index infants for whom increased vigilance is recommended, but these will be unlikely to have adequate diagnostic sensitivity/specificity. "Risk profiles" that incorporate both biological and behavioral measures need to be developed.
- Current studies suggest that behavioral indices below 6 months are subtle, if they exist at all. Biological measures (e.g., head circumference, peripheral biomarkers, and/or psychophysiological indices) may yield higher levels of sensitivity within this age range, indicating a need for further research.
- Research aimed at identifying prenatal biological markers is needed.

33. *Feasible, sensitive screening method for young infants developed*.

Evaluation:

- 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 to assess the risk of autism in all infants.
- While the groundwork is being laid for this later year goal, screening methods are not yet this advanced.

Early Intervention

The main goal of research in this area is to rigorously study the effectiveness of early intervention for reducing or ameliorating autism symptoms such that children can reach their optimal level of function. This goal includes, for a subset of children, no longer meeting the diagnostic criteria for autism spectrum disorder. The Panel identified two sub-goals necessary for achieving this outcome: (1) developing interventions for infants and toddlers so that treatments can begin at the time of first symptoms; and (2) identifying which ingredients of early interventions are maximally effective in reducing or ameliorating symptoms. The Panel found that progress has occurred along both of these lines.

Overall Suggestions for the Early Intervention Area

- While a few randomized clinical trials (RCTs) of individual comprehensive intervention approaches for preschool age children have been conducted, other approaches have not been studied in RCTs. Comparisons between different intervention approaches need to be examined.
- Comprehensive interventions are composed of varying parts, not all of which may be effective or unique. Further research is needed to identify the "active ingredients" of effective interventions.
- Thus far, no randomized comprehensive early intervention studies initiated during childhood have been published, although such studies are underway. This needs to be identified as a high priority research area.
- More work needs to be done in identifying ASD in infants under 12 months of age, so that earlier interventions can be developed. Studies aimed at developing intervention methods appropriate for infants could be conducted in parallel.
- The long-term matrix goal of developing interventions that result in 90% of children with autism developing speech by the age of 5 requires a standard approach to measurement and reporting.

Evaluation Results and Suggestions for Individual Matrix Elements

7. *Randomized clinical trials developed for the evaluation of the effectiveness of early behavioral intervention and moderator variables predicting response to intervention.*

Evaluation:

- There are several ongoing randomized studies looking at comprehensive early intervention approaches, for instance, at the University of Washington and at the Kennedy Krieger Institute.
- Several new studies to examine comprehensive early interventions using randomized designs are in varying stages of development.
- One randomized study of a comprehensive approach has been published in the past three years. While both study groups received intervention and made significant gains in language and IQ, no group differences were found; however, the methodological confounds were

substantial, in that the control group ended up receiving most aspects of the experimental treatment.

- Careful examination of mediators and moderators of treatment response is of high importance since this will allow researchers to begin to individualize treatments based on the children's symptom profiles. However, this will require carefully designed studies with large samples, necessitating multi-site studies.
- Non-RCT intervention studies with small samples have examined mediating and moderating variables, but these have mainly been limited to the severity of autism, IQ, and initial behavioral or language skills.
- Examination of mediators and moderators needs to move beyond IQ, language, and symptom severity to examine more basic aspects of child learning patterns as well as family and community variables.

Suggestions:

- Studies comparing different treatments and examining nonspecific factors such as therapeutic alliance and attention control need to be conducted.
- While dosage has been examined in two randomized, controlled comprehensive interventions, more research is needed to examine specific thresholds.
- Multi-site studies are needed to examine mediators and moderators of treatment effects. Such studies will need large enough samples to allow for wide variation in child and family characteristics and sophisticated statistical designs are needed.

20. *Multi-site randomized clinical trial implemented to identify moderator variables and effective ingredients (e.g., dose, intensity, mode of delivery, age of onset) of early intervention treatments.*

Evaluation:

- The Panel agreed that the identification of effective intervention ingredients is in progress. Recent examples include published results from RCTs examining:
    - The core symptoms of joint attention and symbolic play.
    - A mode of delivery for teaching pre-linguistic and linguistic communication to nonverbal preschoolers.
- Determining effective ingredients within comprehensive interventions appears to be the most difficult aspect of this objective and the area with least progress.
- With regard to moderator variables, demographics are routinely examined in current papers. These typically include: child's IQ, age at the start of the intervention, parental IQ, socioeconomic status, and symptom severity.
- Specific child characteristics, including object interest, social initiative, and avoidance, are beginning to be examined as moderators.

Suggestions:

- Most projects addressing this goal focus on the identification of moderator variables or specific intervention ingredients, but projects are needed that address all aspects of this goal. This will require large, multi-site RCTs.

- Biological characteristics as moderators of response to treatment have not yet been reported in any prospective studies; this is of particular concern given recent findings suggesting that dysmorphology may predict severity of course in autism. At least one RTC is currently examining biological characteristics (e.g., magnetic resonance imaging, magnetic resonance spectroscopy) as a moderator variable of response to early intervention. Studies incorporating biological variables as potential moderators of response to intervention are recommended.
- Family and community variables need to be considered, as well as child variables, in examining mediators and moderators of treatment efficacy.

21. *Intervention methods for infants and toddlers developed, to lower the age for which there are efficacious interventions.*

Evaluation:

- Progress is occurring in developing interventions tailored for the specific characteristics of children under age 3. A few RCTs are underway or in development to examine efficacy of methods for treating 12-24 month olds with autism.
- Developing effective interventions for infants younger than 12 months is dependent upon progress in identification of autism risk before 12 months of age. Efforts are underway, as seen in the Infant Sibling Study Network and the First Words Project.
- Efforts to work toward this goal are hampered by the lack of diagnostic tools for defining autism at ages younger than 18-24 months.

Suggestions:

- The goal is ultimately to be able to target a specific type of intervention for a child based on his or her profile. Treatments fitted to individual child profiles need to be emphasized in this element.
- Research to develop approaches to early intervention with infants and toddlers is recommended.

37. *Longitudinal follow-up of early intervention randomized clinical trial implemented.*

Evaluation:

- No papers have yet been published from RCTs on longitudinal follow-ups.
- Some conference presentations have addressed this subject and there are studies in development.

Suggestion:

- Follow-up studies of children who have participated in early intervention RCTs are strongly encouraged.

29. *Provide evidence that 25% of cases of autism can be secondarily prevented from symptomatic expression through early identification and early treatment.*

Evaluation:

- There was agreement that this long-term goal was possible, particularly given earlier identification and more intensive treatments.
- Most reports of "best outcomes" come from nonrandomized studies of rigorous Applied Behavior Analysis (ABA) approaches using mixed teaching methods. Recent published studies report approximately 50% recovery.
- There was concern among some Panel members that 25% represents an arbitrary target for this goal.

Suggestions:

- RCTs are needed to validate the recovery numbers from nonrandomized studies of ABA.
- Many children classified with ASD are later declassified, only to be reclassified again later. Standard definitions of "recovery" need to be developed.
- Studies are needed that identify children who retain gains made from early intervention without substantial ongoing intervention from those who require continuing support to function optimally throughout childhood and adulthood.
- Factors that allow for a successful transition from early intervention during the preschool age period to that of elementary school (during which time intervention tends to be less intensive) are not well understood and need to be examined.
- Research is needed to identify the ongoing maintenance levels of intervention required to sustain the benefits of early intervention.
- Studies that examine characteristics of effective preschool group interventions are needed. Children with autism are eligible for preschool beginning at age 3, but there are not any comparative studies of preschool group models.

30. *Methods developed to allow 90% of individuals with autism to develop speech.*

Evaluation:

- Progress is being made in this area and several research groups are comparing approaches for developing speech in nonverbal children.
- This outcome is seldom reported in early intervention studies, and there is not a common metric or accepted method for examining it. Lack of such metrics, practices, and expectations for reporting detrimentally affects progress on this objective.

Suggestions:

- Since most published studies do not report the percentage of children with useful speech as an outcome variable, this type of reporting needs to be encouraged.
- Standard outcome metrics are required across studies for this area. Definitions of "useful speech" and "nonverbal" are needed.

Specific Treatments

In the area of specific treatments, the Panel found that progress has been made, but that much remains to be done. Little was suggested by way of course correction other than the expansion of research efforts. The needs in this area are great. Children with autism are likely to receive much more extensive health care and special education services than children with other developmental disabilities, and many (perhaps most) continue to require a high level of support throughout their adult years. The challenge of meeting the clinical needs of this population is now recognized as a significant public health issue, and research to identify efficacious interventions is a high priority. Panel members highlighted a particular need for interventions that specifically target core features of autism.

Overall Suggestions for the Specific Treatments Area

- Treatment studies need to be conducted with larger numbers of subjects and more diverse representation of participants and families, requiring a greater emphasis on multi-site collaborations.
- Emphasis needs to be placed on continued follow-up of children enrolled in studies so that long-term outcomes related to early treatment can be examined.
- There is a need to develop valid and reliable measures that are sensitive to treatment effects, particularly for brief interventions, and that represent meaningful change, particularly for core deficits. In addition, measures need to be developed that are useful across the developmental spectrum.
- Multiple treatment approaches need to be tested in the same trial (e.g., behavioral and pharmacologic approaches).
- Moderator and mediator analyses need to be emphasized, since they are critical for developing individualized treatments; however, such analyses will require much larger sample sizes.
- More treatments need to be developed for school-age children, adolescents transitioning to adulthood, and adults with autism.
- Current studies need to be replicated, with increased attention to short- and long-term follow-up.
- The focus of psychopharmacological studies needs to be broadened beyond those looking at treatment with psychostimulants for hyperactivity/inattention and antipsychotics for aggression/self-injury.
- Eventually, transportability into the community and other aspects of effectiveness need to be examined for treatments found to be efficacious.

Evaluation Results and Suggestions for Individual Matrix Elements

11. *Outcome measures improved, to enhance their usefulness in evaluating treatment studies.*

Evaluation:

- Progress in this area is noted as more projects testing either psychosocial or pharmacological interventions use standardized common measures. Additionally, new measures continue to be developed, tested, and disseminated.

- Significant progress has been made in standardizing diagnostic instruments for use in clinical drug trials that target certain symptom clusters (e.g., aggression, self-injury, property destruction is one such cluster; interfering repetitive behavior another). However, there is still a need for outcome measures to monitor change in social behavior and communication.
- The expected change on certain measures has not been defined. What is the expectation for change and how much change is meaningful? This is an especially critical area of concern when looking at core deficits.
- In addition, there is a need for outcome measures that are sensitive to change for use with a range of developmental ages.

Suggestions:

- An outcome measure to monitor change in social behavior and communication is needed for psychopharmacological studies.
- There is a need to focus on more sensitive measures of core symptoms and at varying developmental ages.

2. *Efficacy established for pharmacological, behavioral and other treatments that target symptoms associated with autism.*

Evaluation:

- The Panel found that progress on this element is ongoing and in no need of a course correction.
- Significant progress has been made in identifying efficacious pharmacological interventions directed at target symptoms.
    - Double-blind placebo controlled trials have found risperidone to be an efficacious treatment for irritability and aggression.
    - Methylphenidate has been found to reduce hyperactivity in some children with autism and other pervasive developmental disorders.
    - Trials are underway examining aripiprizole for its effects on irritability and aggression; olanzapine for its effects on irritability; and escitalopram for its effects on interfering repetitive behavior.
- Progress has also been made on identifying efficacious behavioral treatments for core deficits, primarily with younger children.
    - Most of the research has focused on Applied Behavior Analytic treatment, with some noteworthy successes. One study, for example, showed that a comprehensive treatment program resulted in some positive effects on IQ and academic measures, but with less success on social and communication outcomes. More research on comprehensive treatments is needed across a range of outcomes.
    - Several small-scale controlled trials have been conducted on core deficits, including trials directed towards social communication deficits, social impairment, and associated problems of parent mental health and child anxiety, with varying effect sizes. More studies with larger samples are recommended.

- Psychopharmacologists and behavior therapists have begun to interact in meaningful ways. For example, one large-scale study is comparing the effect of risperidone treatment alone versus risperidone plus parent management training on irritability and associated noncompliance.

16. *Individual characteristics that predict response to behavioral, pharmacological and other treatments are identified.*

Evaluation:

- Few treatment studies have been able to explore moderators or mediators of treatment response, due in part to the lack of measurement of variables that might be moderators and mediators, and due in part to the relatively small sample size.
- Progress has been made in identifying drugs that have effects on particular target symptom domains, but there has been little progress in identifying more objective biological measures that would be predictive of response, such as genetic markers, electrophysiological measures, or neurochemical measures.
- An important subgroup of people with autism includes those with co-morbid epilepsy, yet these individuals have received little focus in psychopharmacological studies, despite the fact that they will require different pharmacological approaches.

Suggestions:

- Because the variation in response to treatment is so great, much larger treatment studies are needed. This would allow for better analysis of mediators and moderators such that sub-group differences could be found. Not only would this result in more targeted treatments, but it would lead to a better characterization of autism as well.
- More replication of treatment studies across sites would also provide much needed data for examining moderators and mediators.
- Electrophysiological markers may prove to be an important measure of individual characteristics that could inform targeted treatments, especially in the subgroup of individuals with co-morbid epilepsy, and need to be investigated more fully.

35. *Treatment algorithm for autism developed, to provide guidance for practitioners and educators.*

Evaluation:

- Although there have been some preliminary attempts at developing treatment algorithms, with some including both behavioral and psychopharmacological approaches, the development of algorithms depends upon having a much fuller range of effective treatments; therefore, evaluation of progress on this element is premature.

32. *Efficacious drug treatments that target core symptoms of autism are developed.*

Evaluation:

- Until more is known about the pathophysiology of autism, it is unlikely that efficacious drug treatments will be found that target core features.
- However, work has progressed in identifying efficacious behavioral interventions that will target core symptoms.

Suggestion:

- The element needs to be broadened to include behavioral, cognitive and psychosocial interventions, all of which may target core features of autism.

School and Community Interventions

The Panel found that since the inception of the matrix significant progress has been made in developing a variety of new school and community interventions, but that only modest progress had been made in disseminating already existing interventions. The interventions currently in the field will provide an adequate beginning of a framework for addressing the longer range goals in this area. However, some course corrections are needed. For example, there is a need to increase the age-range of research in this area, given that nearly all interventions focus on preschool age children.

Overall Suggestions for the School and Community Interventions Area

- Additional emphasis on a lifespan approach to school and community research is required:
  - The scientific knowledge and funded research in this area is strongest at the preschool level. It is weaker at the elementary school level, and there is very little activity at the middle school and high school levels.
  - With improvements in screening and early diagnosis and early intervention, there will be a very different school-age population; a much larger proportion of whom will be verbal and in regular classrooms.
  - Increased focus on adolescents' transition to work, as well as middle-aged and senior adults who are working is needed. It is important to develop interventions that will support more fulfilling vocational experiences and recreational and social lives.
- The majority of targeted children and adults in schools and communities are also going to be on psychopharmacological treatments. Educational and community interventions need to be better integrated with psychopharmacological interventions.
- Generic interventions that have been developed for children broadly identified as having developmental disabilities may be applied to individuals with autism. Positive Behavior Support is one such example.
- Most research in this area tends to include primarily White, middle-to-upper class participants. Greater emphasis is needed in recruiting diverse participants to this area of research.
- More randomized, controlled intervention trials are needed in community and school settings with longer term outcomes.

Evaluation Results and Suggestions for Individual Matrix Elements

13. *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.*

Evaluation:

- There is agreement that there are a number of interventions that are being employed, implemented and disseminated.

Suggestions:

- Most interventions are targeted toward younger children and there is limited activity at the elementary, secondary, and adult levels. Research in this area needs to have more of a lifespan approach.
- Proof of concept studies need to be put into randomized, controlled trials in school and community settings.

8. *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.*

Evaluation:

- There are a variety of innovative projects funded in this area, and they include a broader range of ages than those in element 13.

Suggestions:

- More research is needed on educational outcomes into adolescence and the transition into adulthood.
- There is a need for more randomized, controlled trials in schools.

27. *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.*

Evaluation:

- This element was a year 4-6 goal, and assumed that efficacious intervention approaches would be identified earlier. There is some evidence of dissemination through personnel preparation and in-service training.

Suggestion:

- There is little evidence of support for interventions at the middle and secondary school levels, and this needs to be addressed.

24. *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.

Evaluation:

- There are only a few projects that appear to be addressing efficacious intervention issues. Some current studies are laying the groundwork for research on this later element.

Suggestion:

- Additional projects in this area will need to be started in the next year or two.

36. *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.*

Evaluation:

- This element is well in advance of where activity is currently. It is estimated that researchers are four years out from addressing this goal.

Suggestion:

- Continue and increase current research efforts to provide the foundation for addressing this element.

Additional Research Needs and Opportunities

The Panel discussed a number of additional research opportunities and gap areas. These included:

- Pharmacological interventions, particularly for core symptoms of social and language dysfunction, and greater involvement of the Food and Drug Administration (FDA) and the pharmaceutical industry in drug discovery and development.

- Research to service: getting useful information for and to providers, patients and their families; understanding factors that influence the adoption of evidence-based practices in community settings.

- Services research is not emphasized in the matrix; it was suggested that this area of research be included in future revisions.

- Investigations of adolescents and adults, homogeneous subgroups, cognition and behavior, co-morbid medical conditions, and racially and ethnically diverse populations.

- Standardization of data collection procedures.

- Development of model systems, particularly animal models, and possibly also cellular and circuitry models.

- Exploration of the role of the environment.

Finally, the Panel agreed that the structure of the matrix need to be updated and improved to more adequately display areas in which research progress has been made. Additionally, the current format does not adequately depict or enhance the rich cross-disciplinary interaction that is occurring and further needed in the field. The matrix could be re-structured in ways to better capture and showcase the full spectrum and complexity of progress being made in autism research.

APPENDIX A

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** Participants in post-meeting conference call on the Role of the Environment section who did not attend the 9/25 meeting.*

APPENDIX B

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APPENDIX C

PUBLIC COMMENTS

After the draft report was presented to the IACC on November 17, 2006, the Committee agreed that it should be posted on NIMH's website with an invitation to the public for comment. Public comments were accepted until January 16, 2007. A summary of the received comments, categorized by matrix section, is included below.

Epidemiology

A responder agreed with some panel members who expressed skepticism about the utility of efforts to determine autism prevalence before 1985, but suggested that it should still be possible to determine whether the prevalence of adults who currently meet criteria for ASD is similar to the prevalence of children currently meeting the criteria.

A responder suggested that prevalence research be connected to initiatives to improve general developmental screenings, rather than focused solely on obtaining prevalence estimates.

A responder emphasized the need for more genetic epidemiology research, as well as careful selection of controls and randomization within these types of studies.

Characterization of Autism

In response to the report's mention of potential use of animal models, a responder urged caution in extrapolating from animal behavior or brain anatomy to that of humans.

A responder questioned the usefulness of animal models given that the clinical diagnosis of autism includes criteria based on human relationships.

A responder suggested that the inclusion of the full range of autism spectrum disorders in twin studies will enhance the ability to tease apart factors influencing symptom expression.

A responder emphasized the need for more nuanced standardized measures aimed at characterizing ASD.

A responder expressed concern that genetic markers could lead to a prenatal test for autism, which would raise ethical concerns.

A responder suggested that the report not refer to autism as a "multi-organ disease" and that research on the gastrointestinal system consider the effects of general cortisol responsiveness and other factors more specific to the digestive system.

Role of the Environment

A responder urged the study of electromagnetic frequencies in the development of autism.

A responder asked that more research be done on the use of Thimerosol in antibiotics.

A responder noted that toxicology studies are of utmost importance to determine the body burden of any number of toxins in autistic individuals.

A responder urged more immunological research in ASD, including improvements in technology to carry out these studies.

A responder supported more studies on environmental exposure and ASD, including prenatal exposures.

Neuroscience

A writer cautioned against the unethical treatment of animals in intervention studies using animal models.

A responder supported the recommendation that neuropathology on brain tissue included in stereological, morphological and biochemical studies should continue to be a priority. Such protocols should be standardized and utilized across sites.

A responder noted that while the need for non-affected, or "control", tissue available in brain banks is acknowledged, defining "control" will take careful consideration and thoughtful clinical analysis of both pre- and post-mortem records. In addition, tissue from donors with disorders that have known genetic causes should be included in the repository in order to facilitate comparative studies.

A responder recommended that clinical data from brain bank donors be expanded to include a broader range of measures in order to assist in characterization of donors.

A responder noted that the concept of localized collection facilities for brain tissue should be coupled with a strong information technology infrastructure to organize and best distribute tissue from each center.

Screening

A responder noted that research aimed at improving screening should not be undertaken until effective interventions are discovered and services provided to all those that would be identified through improved screening.

A responder supported studies on the discriminant and predictive validity of broad-band screening tools, which may lead to simpler solutions in early detection for primary care physicians.

A responder recommended more research examining the issue of misdiagnosis of ASD.

A responder noted the need for more research into ethical practice with regard to communication of the diagnosis, and decisions about treatment.

A responder supported consideration of cultural issues in the development of new screening tools.

Early Intervention

A responder noted that there is a need for randomized, controlled trials (RCTs) of comprehensive early interventions.

A responder recommended that not all interventions studies need to be RCTs, and was concerned about the trend toward this type of design as being too restrictive in analyzing effectiveness.

Specific Treatments

Several responders emphasized the need for expansion of research on interventions for adolescents and adults.

Research leading to the development and dissemination of assistive technology to enhance communication was suggested as being needed by a responder.

A responder cautioned against spending scientific resources on intervention studies that do not have sufficient scientific justification to warrant exposure of human subjects to potentially harmful treatments.

A responder noted the desire on the part of individuals with autism and parents of children with autism for an alternative to Applied Behavioral Analysis, and suggested a need for research on the efficacy of other types of interventions.

A responder suggested that greater emphasis needs to be placed on psychosocial rehabilitation, instead of on “recovery.” Teams consisting of a psychologist, behavioral analyst, and speech pathologist should use age-appropriate standardized instruments to assess autistic children’s developmental functioning.

A responder noted the need for more studies of specific strengths or superior abilities in individuals with ASD, and how these specialized skills may be used to improve functional life skills.

A responder noted that there is a need for studies on the concomitant medical problems of individuals with ASD.

A responder supported studies examining the role of common psychopharmacological treatments for ASD in the well-being of these individuals.

A responder noted that efficacy studies should not be focused on to the exclusion of effectiveness studies.

A responder was surprised that no mention was made in the document of the impact of EPSDT "wrap-around" services.

A responder noted the importance of communication skills and suggested that they are the most important treatment variables to consider.

School and Community Interventions

A responder strongly agreed that there should be a greater emphasis on services research.

A responder suggested that the opinion of individuals with ASD with regard to the services they have received should be considered when evaluating such programs.

A responder supported more research that compared the different existing educational methodologies and tools that are used with children with autism.

A responder encouraged more studies on inclusion, including impediments to success.

A responder indicated that the need for interventions to improve adaptive functioning and quality of life is not emphasized enough in the current Autism Research Matrix.

A responder noted that research on educational strategies and services to enhance the well-being of the parents of autistic individuals is missing from the Autism Research Matrix.

Other

Several individuals with ASD and their family members requested that scientists refrain from calling autism a "disease". The point was made that other developmental disabilities and cognitive differences (such as cerebral palsy and mental retardation) are not referred to as diseases. Similarly, a document signed by many individuals asked for a shift from thinking about autism from a "deficit" model to a model that recognizes neurological differences and attempts to empirically understand strengths and competencies of individuals with autism.

There were requests to shift the emphasis from prevention and cure of autism, which is perceived as devaluing of individuals with ASD, to research designed to identify cognitive strengths and optimize adaptation/functioning.

A letter from the American Occupational Therapy Association, Inc., pointed out that occupational therapy is often a component of interventions at all ages, and would provide an important perspective in collaborative, multidisciplinary studies. Occupational therapists could contribute to several areas on the Autism Research Matrix, particularly studies on the role of environment, early intervention, the development of screening and assessment tools, school

based interventions and services, interventions to improve functioning in late adolescence and adulthood, and development of assessment tools sensitive to treatment effects.

A responder recommended research to examine the overall well-being of individuals with ASD who reside in residential facilities vs. those in home-based environments, including the impact of family on functional outcome.

A responder suggested that autistic individuals be included on the IACC.

A responder indicated that the draft report is fundamentally incoherent.