Consolidated Analysis of Strengths, Weaknesses, Opportunities, and Gaps in ASD Research

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Introduction

The **Consolidated Analysis of Strengths, Weaknesses, Opportunities, and Gaps in ASD Research** is a compilation garnered throughout the ASD strategic planning process including: (1) the evaluation of the autism research matrix in 2006; (2) the Request for Information (RFI) on public input on ASD research priorities in December 2007 - January 2008; (3) the four scientific workshops conducted in January 2008; and, (4) the town hall meeting held in May 2008. The purpose of this document is to serve as a reference document for the IACC Strategic Plan for ASD Research, issued in 2008.

This consolidated analysis is structured according to the six question framework developed for the 2008 Strategic Plan. The 41 research opportunities developed from the January 2008 Scientific Workshops are sorted thematically across the six questions. Within each research opportunity, the strengths, weaknesses and recommendations for addressing gaps pertinent to the opportunity are listed. These strengths, weaknesses, and recommendations were gleaned from input received during one or more of the four steps of the strategic planning process outlined above. For reference, each strength, weakness, and recommendation is annotated to indicate from which source of input it emanated.

Q1: When Should I Be Concerned?
1A1. Predictive validity of existing screens in community settings

Strengths:

- Current screening methods are useful in predicting diagnosis. (Workshop 1A1)
- A number of screening tools have been developed for detecting autism, including: 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). (Matrix #15)
- Current 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. (Matrix #15)
- Some of screening 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. (Matrix #15)

Weaknesses:

- Although screening at early ages has been mandated, the evidence base for implementing this mandate is not available. (Workshop 1A1)
- Lack of parental follow-though may be an important barrier to early diagnosis and treatment in population based early diagnosis studies. (Matrix #9)

Recommendations to Address Opportunities & Gaps:

- Various methods to evaluate the predictive validity of existing screening methods include collaborative grants and state-investigator partnerships. Such efforts would necessarily involve multiple disciplines, and multi-site studies with sufficient populations to show how well the methods generalize across settings. (Workshop 1A1)
- 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. (Matrix #15)
- More focus is required on studying barriers to use of existing screening measures. (Matrix #15)
- 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. (Matrix #15)
- While there are some population-based studies underway, more are needed using varied research methodologies. (Matrix #9)
- Parental follow-through needs to be targeted for research regarding screening and referral practices that optimize parental adherence. (Matrix #9)

- Utilization of existing large-scale, population-based studies will allow for cost-efficient investigations of the impact of early identification procedures. (Matrix #9)

1A2. Collaborative development of streamlines screening/diagnostic approaches

Strengths:

- There is emerging evidence that tools can be developed with sufficiently high sensitivity to support epidemiologic, environmental and genetic studies. (Workshop 1A2)

Weaknesses:

- There is a lack of information on the sensitivity and specificity of screening measures. (Matrix Overall Recommendations for Screening)

Recommendations to Address Opportunities & Gaps:

- There is a need for large numbers of samples collected efficiently to fully understand the interplay of risk factors (genetic or environmental) and prognosis. (Workshop 1A2)
- There is a need for streamlined diagnostic approaches to facilitate enrollment in studies requiring large numbers of participants—e.g., studies of genetic risk—because current diagnostic tools may be impractical and overly burdensome. A streamlined process need not preclude detailed diagnosis and phenotype assessment at later steps in the study. (Workshop 1A2)
- A workshop could be assembled to examine alternatives for implementing streamlined screening and diagnostic procedures, with a focus on short-term solution and mid-term refined approach. (Workshop 1A2)
- 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. (Matrix #15)
- Utilization of existing large-scale, population-based studies will allow for cost-efficient investigations of the impact of early identification procedures. (Matrix #9)

IA3. Screening and diagnostic instruments in underrepresented populations

Strengths:

- Current work on under-represented populations affected by autism is beginning to include specific populations. (Workshop 1A3)

Weaknesses:

- Considerable research suggests a failure to adequately identify or diagnose individuals in underrepresented population.(Workshop 1A3)
- It remains unknown how adequate currently established diagnostic methods are in under-represented populations. (Workshop 1A3)
- Reduced ascertainment reduces the potential impact of early intervention. (Workshop 1A3)

Recommendations to Address Opportunities & Gaps:

- There is a need for studies of the application of current and/or new diagnostic and screening methods in community based samples and/or samples with overrepresentation of minority or disadvantaged families. Such studies could analyze relationships to neurobiological and genetic markers. (Workshop 1A3)
- Possibly, the R01 mechanism could be utilized to focus on underrepresented populations. Alternatively, existing surveillance studies could be augmented to address these issues. (Workshop 1A3)
- Studies designed to validation diagnostic strategies in underrepresented populations could also serve to increase our understanding of barriers to diagnosis and service access. (Workshop 1A3)
- Increased identification and access could reduce disparities in health care and service provision, and potentially improve outcome for disadvantaged/underserved individuals. Identification of specific factors relevant to certain populations might hold some potential for understanding etiology or treatment mechanisms. (Workshop 1A3)
- 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. (Matrix Overall Recommendations for Screening)

1B1. Evaluating diagnostic criteria/approaches

Strengths:

- There is emerging evidence that tools can be developed with sufficiently high sensitivity to support epidemiologic, environmental and genetic studies. (Workshop 1A2)

Weaknesses:

- There has been inadequate clarification of clinical features (cognitive level, regressive features, and co-morbid conditions such as blindness) which could have different meanings in different circumstances. (Workshop 1B1)
- Considerable research suggests a failure to adequately identify or diagnose individuals in underrepresented population. (Workshop 1A3)
- It remains unknown how adequate currently established diagnostic methods are in under-represented populations. (Workshop 1A3)
- Reduced ascertainment reduces the potential impact of early intervention. (Workshop 1A3)

Recommendations to Address Opportunities & Gaps:

- The various subgroups of the ASD population have unique needs, e.g., adults (when no other informant is available), more able children (e.g., Asperger's syndrome vs. autism vs. PDD-NOS), very young children, children with regressive features, children with severe cognitive impairment, and children with complex presentations (blind, deaf). (Workshop 1B1)
- There is a need for studies focused on specific components or special features, examining how these issues are related in autism. (Workshop 1B1)
- In other branches of medicine, it is clear that identification of particular diagnostic subtypes/categories can lead to better understanding of etiology and mechanisms. (Workshop 1B1)
- There is a need for streamlined diagnostic approaches to facilitate enrollment in studies requiring large numbers of participants—e.g., studies of genetic risk—because current diagnostic tools may be impractical and overly burdensome. A streamlined process need not preclude detailed diagnosis and phenotype assessment at later steps in the study. (Workshop 1A2)
- A workshop could be assembled to examine alternatives for implementing streamlined screening and diagnostic procedures, with a focus on short-term solution and mid-term refined approach. (Workshop 1A2)
- 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. (Matrix #15)

- Utilization of existing large-scale, population-based studies will allow for cost-efficient investigations of the impact of early identification procedures. (Matrix #9)
- There is a need for studies of the application of current and/or new diagnostic and screening methods in community based samples and/or samples with overrepresentation of minority or disadvantaged families. Such studies could analyze relationships to neurobiological and genetic markers. (Workshop 1A3)
- Studies designed to validation diagnostic strategies in underrepresented populations could also serve to increase our understanding of barriers to diagnosis and service access. (Workshop 1A3)
- There is a need for the development of biomarkers for oxidative stress, inflammation, immune dysfunction, toxicological impairment, gastrointestinal function, and nutritional status. (Autism Town Hall Meeting)

4C1. Identification of biomarkers to guide treatment selection and evaluation of treatment outcome

Strengths:

- There is increasing evidence of biological markers of autism subtypes. (Workshop 4C1)
- Sophisticated genomic tools are available. (Workshop 4C1)

Weaknesses:

- Little is known regarding the relevance of biological markers of autism subtypes to clinical presentation and optimal treatment selection. (Workshop 4C1)
- There has been little progress in identifying more objective biological measures that would be predictive of treatment response, such as genetic markers, electrophysiological measures, or neurochemical measures. (Matrix #16)

Recommendations to Address Opportunities & Gaps:

- Research is needed to identify brain, physiological, metabolic, genetic and other biological markers and investigate their relationship with response to specific treatments. (Workshop 4C1)
- Biobanking would be required to support this kind of research. (Workshop 4C1)
- 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 should be investigated more fully. (Matrix #16)
- 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. (Matrix Overall Recommendations to Specific Treatments)

1C2. Identify relevant phenotypes that relate to etiology, symptom, presentation, and outcome

Strengths:

- The Phenome Project has been defined. A pilot investigation utilizing prospective data collection has begun at the M.I.N.D. Institute (privately funded) and in the NIMH Intramural Research Program. Planning for other investigations is underway. (Matrix #10)
- The Childhood Autism Risks from Genetics and the Environment (CHARGE) study has enrolled 700 subjects, and characterization and analysis have begun using medical data, biological specimens, immunological features and genomic profiles. (Matrix #10)
- CDC has funded 16 programs in17 sites to conduct ASD surveillance under the Autism and Developmental Disabilities Monitoring (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. (Matrix #10)
- 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. (Matrix #10)
- NICHD and Autism Speaks/National Alliance for Autism Research (NAAR) formed a consortium of researchers focused on studying infant sibs of children with autism to help identify early features and distinguishing characteristics of autism. (Matrix #25)
- Studies are underway to examine subsequent pregnancies of women with autistic children. (Matrix #25)
- The Norwegian cohort study of 100,000 pregnancies, supported by NINDS, will provide bio-samples and phenotypic information on a large sample of children with autism and a general population sample. (Matrix #3)
- The Simons' Collection has selected 11 centers to collect genetic samples from up to 2,000 simplex families in two years. (Matrix #3)

Weaknesses:

- Policies on data sharing need to be established. (Matrix #10)
- There is insufficient recognition of the National Database for Autism Research (NDAR) and the Phenome Project among autism researchers. (Matrix #10, #4)
- Collections such as the CPEA/STAART, CHARGE, NICHD/Autism Speaks/NAAR, Simons' Collection, and the Norwegian studies are not making the best use of the latest techniques in genetic research, and the phenotypic characterization is not being advanced. (Matrix #3)
- There is little investment in the type of multidisciplinary training needed to conduct the needed genotype/phenotype analyses. (Matrix #3)
- The conceptualization of the phenotype remains underdeveloped. (Matrix #25)

Recommendations to Address Opportunities & Gaps:

- Need to advance understanding of the phenotype, including studies that link genotype to phenotype, investigations of natural and treated history, and co-morbid conditions. (Matrix Overall Recommendations on Characterization)
- Need to identify etiologically significant subgroups. (Matrix Overall Recommendations on Characterization)
- There is a need to increase data sharing and address data storage issues, and to publicize for existing resources. (Matrix Overall Recommendations on Characterization)
- Goal of NICHD/Autism Speaks/National Alliance for Autism Research partnership is to create larger, combined samples of the infant sibs/high-risk pop for multi-site studies. (Matrix #25)
- The National Database for Autism Research (NDAR), currently under development at NIH, is designated as a major resource for the phenome project. (Matrix #10)
- Genetic data are more widely available. (Workshop 1C2)
- Need for improved understanding of gender differences in ASD. (Workshop 1C2)
- Need to assess the validity of subgroups longitudinally. (Workshop 1C2)
- Biobehavioral markers that influence aspects of presentation need to be correlated with treatment response. (Workshop 1C2)
- More advanced cytogenetic studies are needed to investigate potential de novo mutations and genetic lesions that are included in the repositories. (Matrix #3)

2B2. Developing biomarkers for autism

Strengths:

- Although no peripheral (non-brain) 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. (Matrix #1)
- 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. (Matrix #1)
- Recent research has found 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. (Matrix #1)
- Infants later diagnosed with ASD show gesture and language delays by 12 months, and atypical temperament and activity levels at 6 months of age. (Matrix #1)
- 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. (Matrix #1)
- There is emerging evidence that tools can be developed with sufficiently high sensitivity to support epidemiologic, environmental and genetic studies. (Workshop 1A2)

Weaknesses:

- 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. (Matrix #1)
- Current studies suggest that behavioral indices below 6 months are subtle, if they exist at all. (Matrix #1)
- 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. (Matrix #1)
- There is a lack of information on the sensitivity and specificity of screening measures. (Matrix Overall Recommendations for Screening)

Recommendations to Address Opportunities & Gaps:

- A more concerted effort is needed to expand research on peripheral (non-brain) biomarkers. Given that these types of studies are very hard to fund through the typical grant process, a public/private partnership would propel the field. (Matrix #1)

- The relationship between early markers and diagnostic outcomes based on comprehensive gold-standard assessments remains to be determined. (Matrix #1)
- 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. (Matrix #1)
- "Risk profiles" that incorporate both biological and behavioral measures should be developed. (Matrix #1)
- 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. (Matrix #1)
- Research aimed at identifying prenatal biological markers is needed. (Matrix #1)
- The development of biomarkers is critical (for both research purposes and for public health reasons) in order to establish reliable early indicators of high risk and impending onset, diagnosis and subtype diagnosis, treatment assignment, and treatment efficacy. (Workshop 2B2)
- Various initiatives to examine, immune, genetic, neural, metabolic, and proteomic markers for prediction of high risk of autism are necessary. (Workshop 2B2)
- 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. (Matrix #33)

2B3. Gene-based phenotyping and cognitive neuroscience

Strengths:

- Clinical testing and genetic research are identifying increasing numbers of genetic mutations that confer high risk of autism. (Workshop 2B3)

Weaknesses:

- There is little investment in the type of multidisciplinary training needed to conduct the needed genotype/phenotype analyses. (Matrix #3)
- Most or all of the genetic mutations that have been linked to increased autism risk are associated with a range of phenotypes that extends beyond the strict definition of autism. (Workshop 2B3)
- There is a lack of sufficient information on the heritability and relevance of potential cognitive, behavioral, neural, or physiological phenotypes to autism and autism-like disorders. (Workshop 3A2)

Recommendations to Address Opportunities & Gaps:

- Need to advance understanding of the phenotype, including studies that link genotype to phenotype, investigations of natural and treated history, and co-morbid conditions. (Matrix Overall Recommendations on Characterization)
- There is a need for multidisciplinary, collaborative (i.e., multi-center) studies that include neuroimaging, electrophysiological measures, and deep phenotyping of patients that share uniform genetic conditions that confer high risk to autism (e.g., MECP2 mutations, 16p11.2 deletions). (Workshop 2B3)
- It is essential to move beyond diagnostic or classification measures to understand underlying variability that can crucially inform our understanding of prognosis, appropriate treatment, pre-emption and prevention. (Workshop 3A2)
- Support family and twin studies to identify novel heritable, or genetically relevant autism phenotypes, and use this to develop and test efficacy of treatments. Multidisciplinary study of a large cohort of cases with assessment of outcomes based on these endophenotypes, or risks that are related to these endophenotypes. (Workshop 3A2)

2B4. New paradigm for clinical genetic evaluation and subsequent diagnosis

Strengths:

- Studies are underway to examine subsequent pregnancies of women with autistic children. (Matrix #25)
- The Simons' Collection has selected 11 centers to collect genetic samples from up to 2,000 simplex families in two years. (Matrix #3)

Weaknesses:

Recommendations to Address Opportunities & Gaps:

- There is a need to improve understanding of genetic risk of autism and related conditions in large populations. (Workshop 2B4)
- There is a need to incorporate easily obtained, inexpensive genetic screening data into diagnostic protocol. (Workshop 2B4)
- Incorporate protocols for initial genetic evaluation of patients into clinical and research diagnostic protocols. Establish clinical advisory boards, policy guidance concerning patient privacy and IRB approvals, and data sharing policies. (Workshop 2B4)
- Address reimbursement issues and budget for non-reimbursable costs for the infrastructure to consent patients and hire genetic counselors. Establish database, diagnostic capabilities. (Workshop 2B4)
- Clinical genetic evaluation efforts could inform treatment and prevention research, as well as assist in pre-emptive or preventative treatment planning. (Workshop 2B4)

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. (Matrix Overall Recommendations for Screening)

1C1. The development of improved categorical and dimensional measures of ASD

Strengths:

- More projects testing either psychosocial or pharmacological interventions use standardized common measures and new measures continue to be developed, tested, and disseminated. (Matrix #11)
- 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). (Matrix #11)

Weaknesses:

- 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. (Matrix #11)

Recommendations to Address Opportunities & Gaps:

- An outcome measure to monitor change in social behavior and communication is needed for psychopharmacological studies. (Matrix #11)
- There is a need for outcome measures that are sensitive to change for use with a range of developmental ages. (Matrix #11)
- We need instruments that are sensitive to core features of autism and associated characteristics relevant to treatment and outcome (e.g., co-occurring symptoms such as ADHD). There is increasing evidence for the existence and relevance of the broader autism phenotype, but only emerging methods for characterizing it. (Workshop 1C1)
- Continuous measures related to treatment response and outcomes are needed, which apply existing quantitative measures for multiple domains of development to treatment research and pharmaceutical and social skills interventions. (Workshop 1C1)
- Develop novel methods for assessing the broader autism phenotype, and conduct taxometrics studies linking broad phenotype to categorical designations of case status. (Workshop 1C1)

Q2. How Can I Understand What Is Happening?
2A1. Multidisciplinary longitudinal study of infants with autism before age three

Strengths:

- The CDC has funded specific research evaluating the effectiveness of various strategies for implementing screening into community practice settings. (Matrix #9)
- Current 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. (Matrix #15)

Weaknesses:

- Lack of parental follow-though may be an important barrier to early diagnosis and treatment in population based early diagnosis studies. (Matrix #9)
- Although screening at early ages has been mandated, the evidence base for implementing this mandate is not available. (Workshop 1A1)
- Limited normative information to evaluate biomedical parameters, such as brain maturity and immune function in typically developing children, is currently available. (Workshop 2A1)

Recommendations to Address Opportunities & Gaps:

- Utilization of existing large-scale, population-based studies will allow for cost-efficient investigations of the impact of early identification procedures. (Matrix #9)
- While there are some population-based studies underway, more are needed using varied research methodologies. (Matrix #9)
- Parental follow-through needs to be targeted for research regarding screening and referral practices that optimize parental adherence. (Matrix #9)
- 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. (Matrix #15)
- 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. (Matrix #33)
- An intensive, multidisciplinary study is needed at early ages to examine the trajectory of neurodevelopmental, behavioral, and biomedical measures, in order to determine earliest discernable onset. A parallel multidisciplinary analysis of typically developing children would be enlightening. (Workshop 2A1)
- Understanding early trajectory may lead to interventions that mitigate behavioral impairments. (Workshop 2A1)

2A5. Identification of large-scale neural systems whose function is altered in pre-adolescent autism

Strengths:

- Progress in developing infrastructure for multi-site *in vivo* imaging studies 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. (Matrix #6)
- Multi-site *in vivo* imaging studies have led to a convergence around the idea that precocious growth of certain brain regions such as the cerebral cortex is one of the consistent features of autism. (Matrix #6)
- There is substantial progress in the areas of neural circuitry and neurochemistry as they constitute 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. (Matrix #26)
- Progress has been made in the area of neuropathology 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 dys-regulated brain growth. (Matrix #22)
- 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. (Matrix #22)

Weaknesses:

- The pediatric brain gives rise to different grey/white signal characteristics that complicate segmentation in *in vivo* imaging studies. (Matrix #6)
- One criticism of the neuroimaging literature in general is that findings have not yet been tied to clinically relevant variables and outcomes. (Workshop 2A5)
- The specificity of neuropathological features to autism has not yet been established for any brain structure. The cerebellum, for example, while clearly pathological in autism, also appears to exhibit pathology in a variety of other neurodevelopmental disorders. (Matrix #22)
- Very little is known about the neurochemistry of autism; most information comes from work on related disorders such as Fragile X Syndrome. For example, there is focus on glutamate receptors through research on Fragile X Syndrome, but there is little research addressing glutamate's involvement in autism. (Matrix #34)

Recommendations to Address Opportunities & Gaps:

- There is a critical need to develop a common standardization technique for normalization of *in vivo* imaging data across sites. (Matrix #6)
- 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. (Matrix #6)
- 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 should 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. (Matrix #6)
- Developmental longitudinal studies are needed to characterize the developmental trajectories of specific large-scale neural networks that have been identified as "end states" in studies of older children and adolescents. These studies should aim to develop earlier biomarkers that predict issues of clinical relevance. Imaging studies are needed at earlier ages, with longitudinal designs, tied to clinically relevant outcomes. (Workshop 2A5)
- There is a need to identify high-order neural systems, e.g., those responsible for social interaction that exhibit altered function in autism. This is especially important for younger brains (pre-adolescence), although such studies face unique technical problems. (Workshop 2A5)
- Basic neurodevelopmental imaging studies that focus on implicated neuro-circuitry could be stronger and more relevant to autism. (Matrix #26)
- Neuroimaging studies are needed that can develop biomarkers for use in treatment studies. (Workshop 2A5)
- 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. (Matrix #22)
- More comparative studies are needed across neurodevelopmental disorders. We need much better control material and clinical contrast material to do these types of comparisons. (Matrix #22)
- Neuropathology should be more closely linked to phenotypic variables and co-morbid features to address issues of heterogeneity. (Matrix #22)
- 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 should receive increased attention. (Matrix #34)

2B1. Gender differences in the biological features of autism

Strengths:

Weaknesses:

- Many studies of autism are preferentially carried out in males. This is due to the 4:1 increased prevalence in males, and thus, the easier recruitment of male subjects. There is very little information, therefore, about whether females have the same biological features of autism as males. (Workshop 2B1)
- Without additional biomedical information on females with autism, it is indeterminate whether similar etiologies are apparent and if similar treatments are appropriate. (Workshop 2B1)

Recommendations to Address Opportunities & Gaps:

- It is critical to determine why there is the 4:1 gender bias, whether the bias imply that something about being female is protective, or whether the assumed 4:1 gender bias is inaccurate. (Workshop 2B1)
- Increased support should be provided for inclusion of females in all biological studies of autism. (Workshop 2B1)
- There is a need for improved understanding of gender differences in ASD. (Workshop 1C2)

2A3. Role of immune and infectious factors in the pathogenesis of autism—human and animal studies

Strengths:

- The Autism Matrix 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. (Matrix #18)
- 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. (Matrix #18)
- 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. (Matrix #18)
- 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. (Matrix #18)
- 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. (Matrix #18)

Weaknesses:

- There was consensus among members of the Autism Matrix Panel 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. (Matrix Overall Recommendations on Environment)
- 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. (Matrix Overall Recommendations on Environment)

Recommendations to Address Opportunities & Gaps:

- Many Autism Matrix Panel members cited the limitations of existing methodologies for exposure assessment and expressed the need for improved biomarkers of personal exposure to specific compounds. (Matrix Overall Recommendations on Environment)
- 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. (Matrix Overall Recommendations on Environment)

- A new generation of studies focused on immune system dysregulation and interactions between immune development and neurodevelopment is needed. Further studies should investigate the role that vaccines and immuno-toxic chemicals may play in autism. (Matrix #18, Autism Town Hall Meeting)
- Mechanistic studies that provide a better understanding of immune-CNS interactions are necessary, including investigation of prenatal and postnatal effects. (Workshop 2A3)
- There is a need for an initiative to support immuno-phenotyping of families (mothers especially) of children with autism in comparison to families of typically developing children. The immuno-phenotyping of children with autism must be conducted both independently and in conjunction with other biomedical indicators, such as brain growth, behavioral and onset measures. (Workshop 2A3, Autism Town Hall Meeting)

2A4. Postmortem brain and tissue acquisition initiative

Strengths:

- 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. (Matrix #5)
- Many quality methods are available to study brain tissue. (Workshop 2A4)
- 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. (Matrix #22)

Weaknesses:

- The existing brain and tissue back 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. (Matrix #5)
- There are no matched controls available for the brains/tissue in the existing banks. (Matrix #5)

Recommendations to Address Opportunities & Gaps:

- 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 should 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. (Matrix #5, Workshop 2A4)
- Efforts are needed to provide resources to enhance brain availability, brain quality, brain cataloging, and tissue distribution. This would involve recruitment, infrastructure, policies, and advisory input. (Workshop 2A4)
- Even studies with small samples yield provocative indications of neuropathology associated with autism. Specific hypotheses including cell loss and mini-column alterations need replication, as these were conducted with small, narrowly defined samples. (Workshop 2A4)
- Development of international partnerships for brain and tissue acquisition should also be pursued and the use of digital resources to distribute samples for analysis, if possible. (Workshop 2A4)

- Establish the number of deaths of individuals with autism, and then set a goal for acquisition of brain specimens based on a percentage of annual deaths. Determine how many control brains are available for autism studies and establish a mechanism for resource sharing. (Workshop 2A4)

Q3. What Caused This to Happen and Can It Be Prevented?
3A1. Large-scale resource of genomic data on ASD

Strengths:

- 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. (Matrix #3)
- Recent Studies have found strong evidence that genetic factors includeing SNPs and copy number variants (CNVs) contribute significantly to risk of ASD. (Workshop 3A1)
- CNV and candidate gene sequencing studies have found strong evidence implicating specific loci or genes in ASD. The genes identified show evidence of common pathways (e.g. synaptic proteins). These findings suggest that the number of genes that potentially contribute to ASD is large and many of the alleles involved have clear deleterious effects on gene function. Expanding genetic screening efforts into much larger patient samples promises to identify new genes. (Workshop 3A1)

Weaknesses:

- These collections, however, are not making the best use of the latest techniques in genetic research. (Matrix #3)
- There is little investment in the type of multidisciplinary training needed to carry out this work. (Matrix #3)
- Candidate risk alleles have been identified; however, further work is needed to more completely define the large set of potential ASD genes, to determine the contribution of individual genes to ASD risk, and to understand the role of environmental factors in disease expression. (Workshop 3A1)
- Genetic analysis of much larger patient samples is needed in order to identify new risk alleles and to understand their contribution to disease. (Workshop 3A1)

Recommendations to Address Opportunities & Gaps:

- 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.). (Matrix #3)
- Data sharing policies need to be clearly defined. (Matrix #3)
- More advanced cytogenetic studies are needed to investigate potential de novo mutations and genetic lesions that are included in the repositories. (Matrix #3)
- Obtain samples, in the range of 10,000 to 30,000 to conduct SNP/CNV detection platforms and new massively-parallel DNA sequencing methods. (Workshop 3A1)
    - All samples will be screened using cost-effective and currently available microarray-based SNP/CNV platforms.
    - The complete coding genome will be sequenced in a subset of 8000 individuals from a collection of simplex families.
    - Whole-genome shotgun sequencing in smaller subset of patients, the numbers of samples and depth of sequencing to be determined based on new projections of the cost per sample.
    - Data repositories and informatics tools for disseminating and displaying data will be developed and integrated with the central databases of the collection.
    - Further development of computational methods for analysis of gene function including systems biology approaches that would complement studies of molecular mechanisms.
    - Leverage anticipated epidemiological studies of environmental risk factors to better understand the potential interplay between environmental exposures and genetic risk factors. (Workshop 3A1)

3A2. Informing the genetics and neurobiology of ASD based on new heritable phenotypes in populations

Strengths:

- Recent evidence that endophenotypes increase power in genetic studies. Better defines phenotypes for translation to animal models and treatment development. (Workshop 3A2)

Weaknesses:

- There is a lack of sufficient information on the heritability and relevance of potential cognitive, behavioral, neural, or physiological phenotypes to autism and autism-like disorders. (Workshop 3A2)

Recommendations for Addressing Opportunities & Gaps:

- It is key to move beyond diagnostic or classification measures to understand underlying variability that can crucially inform our understanding of prognosis, appropriate treatment, pre-emption and prevention. (Workshop 3A2)
- Support family and twin studies to identify novel heritable, or genetically relevant autism phenotypes, and use this to develop and test efficacy of treatments. Multidisciplinary study of a large cohort of cases with assessment of outcomes based on these endophenotypes, or risks that are related to these endophenotypes. (Workshop 3A2)

3B5. Develop resources for appropriate control and comparison groups for biological, genetic and other studies of ASD

Strengths:

- 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 biospecimens 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. (Matrix #3)
- 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. (Matrix # 5)
- 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. (Matrix #6)
- 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. (Matrix #6)

Weaknesses:

- A few twin studies have been supported, but the concept of a twin registry has not been realized. (Matrix #12)
- The size of a twin registry would have to be very large to take into account heterogeneity factors. (Matrix #12)
- The genotype/phenotype collections, however, are not making the best use of the latest techniques in genetic research, and the phenotypic characterization is not being advanced. (Matrix #3)
- There is little investment in the type of multidisciplinary training needed to carry out this work. (Matrix #3)
- In the brain & tissue banks, 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. (Matrix #5)
- In addition, there are no matched controls available in the brain and tissue banks. (Matrix #5)
- There are insufficient control, typically developing children in genetic repositories and tissue banks. There is not enough known about the interface/overlap of ASD with other developmental disabilities and the extent to which genetic or other risk factors act specifically or more generally in predisposing to or causing these conditions. (Workshop 3B5)
- Existing banks are not population bases, or adequate for well designed assessment of many environmental exposures. (Workshop 3B5)
- 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. (Matrix #6)

Recommendations to Address Opportunities & Gaps:

- A twin registry should set as an initial target the inclusion of data derived from 100 twin pairs, with one or both individuals meeting diagnostic criteria for autism. (Matrix #12)
- 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.). (Matrix #3)
- Data sharing policies need to be clearly defined. (Matrix #3)

- More advanced cytogenetic studies are needed to investigate potential de novo mutations and genetic lesions that are included in the repositories. (Matrix #3)
- 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 should 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. (Matrix #5)
- Expand availability of samples collected via non-autism diagnoses and typically developing children, including via MRRCs (intellectual disabilities), genetic studies of other neurodevelopmental disorders such as Tourette's syndrome, ADHD, schizophrenia, that national children's study, and pediatric neuroimaging databases, etc., to permit cross disease boundary comparisons and understand gene frequencies in control populations. (Workshop 3B5)
- 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 should 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. (Matrix #6)

3B1. Risk Factor studies in other populations with unique well-characterized features

Strengths:

- There is precedent for major discoveries based on opportunistic approaches in other disorders (including psychiatric and neurologic conditions) for studying unique populations. This approach can be used to approach issues of etiologic heterogeneity. (Workshop 3B1)

Weaknesses:

Recommendations to Address Opportunities & Gaps:

- Studies in certain special populations (e.g., non-vaccinated, or high levels of environmental exposures and/or with known conditions (ASD subgroups, other genetic disorders, medical conditions) and/or certain other risk factors (e.g., older parents) can provide efficient opportunity for new risk factor discovery. Studies in informative international populations, large well-characterized clinical populations, and registry-based samples are also possible under this initiative. (Workshop 3B1)

3B2. Studies of risk factor exposures from pre-conception to early postnatal life

Strengths:

- The Research Matrix Panel noted that with regard to analytic epidemiology, important studies have begun, though in early phases. (Matrix Intro to Epi section).
- 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 Childe 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. (Matrix Overall Recommendations on Epi).

Weaknesses:

- A more standardized definition of what is meant by 'environment' should be developed to allow clearer direction in this area of research. (Matrix #18)
- Few studies have collected data on exposure occurring in what is likely the most etiologically relevant window. This is also likely the most relevant exposure window for mechanisms underlying de novo mutations and epigenetic changes. (Workshop 3B2)

Recommendations to Address Opportunities & Gaps:

- 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. (Matrix #18)
- 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 should be further explored in relation to autism. (Matrix #18)
- There were mixed views regarding the best approach for prioritizing studies of environmental exposures. Some Research Matrix 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 should be examined through epidemiologic and mechanistic studies. (Matrix #18)
- Metals are known neurotoxins and should 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. (Matrix #18)

- Support epidemiological studies that are designed to collect exposure data during preconception, prenatal, perinatal, and early postnatal prediagnostic windows. (Workshop 3B2)
- Collect critical exposure data in high-risk populations (e.g., prospective studies of mothers of affected children at the start of, and potentially, prior to subsequent pregnancy) where there can be efficiencies in evaluating gene-environment interaction. (Workshop 3B2)
- Study large population-based pregnancy cohorts which will include simplex as well as multiplex families. (Workshop 3B2)
- Studies should include child, maternal, and paternal exposures and could also involve assessment of the social environment. These studies also should be genetically informative in that they collect DNA samples on children and family members. Studies should include evaluation of potentially informative, complex phenotypes (e.g., developmental and behavioral trajectories, medical comorbidities, brain imaging). (Workshop 3B2)

3B3. Analysis of mechanisms underlying the interplay of genetic and environmental factors

Strengths:

- 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. (Matrix #17)
- The Research Matrix 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. (Matrix #18)
- 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. (Matrix #18)
- 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. (Matrix #18)
- 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. (Matrix #18)
- 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. (Matrix #18)

Weaknesses:

- The current strategy for identifying susceptibility genes is not likely to identify de novo mutations and does not in general address epigenetic questions. (Matrix #17)
- The conceptualization of the phenotype remains underdeveloped. (Matrix #17)
- There was only one element in the matrix that focused on the role of environmental factors, yet this is one of the most visible areas in autism research. A more comprehensive approach should be adopted, with inclusion of a number of related elements that reflect the breadth of the field. (Matrix #18)

Recommendations to Address Opportunities & Gaps:

- Overall, the Research Matrix Panel viewed the exploration of the role of the environment as a notable gap and research opportunity. (Matrix Additional Research Needs & Opportunities)

- Broader approaches towards the study of susceptibility genes should be adopted that account for de novo mutations.(Matrix #17)
- To understand the genetic and non-genetic causes of autism and their interactions it is critical to identify the 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. (Matrix #31)
- A more standardized definition of what is meant by 'environment' should be developed to allow clearer direction in this area of research. (Matrix #18)
- 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. (Matrix #18)
- 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. (Matrix #18)
- Experimental paradigms that lend themselves to the investigation of multifactorial etiologies should 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. (Matrix #18)
- 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. (Matrix #18)
- The feasibility of measuring environmental chemicals that may possibly persist in tissue samples should be examined in post mortem tissue. (Matrix #18)
- 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 should be further explored in relation to autism. (Matrix #18)
- There were mixed views regarding the best approach for prioritizing studies of environmental exposures. Some Research Matrix 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 should be examined through epidemiologic and mechanistic studies. (Matrix #18)
- Metals are known neurotoxins and should 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. (Matrix #18)
- 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. (Matrix #18)

3B4. Methods development for biologic exposures/biomarkers

Strengths:

- 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. (Matrix #1 & Workshop 3B4)
- 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:
    - There have been 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. (Matrix #19)
    - Infants later diagnosed with ASD show gesture and language delays by 12 months, and atypical temperament and activity levels at 6 months of age. (Matrix #19)
- 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. (Matrix #19)
- Biomarkers are currently being used in etiologic and diagnostic applications for a variety of complex conditions (e.g., newborn screening). (Workshop 3B4)

Weaknesses:

- 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. (Matrix #19)
- The relationship between early markers and diagnostic outcomes based on comprehensive gold-standard assessments remains to be determined. (Matrix #19)
- The success of research on environmental risk factors hinges on having efficient and accurate biomarkers of exposures. (Workshop 3B4)
- Also needed are valid and easily measured biomarkers of intermediate neruodevelopmental endpoints. (Workshop 3B4)

Recommendations for Addressing Opportunities & Gaps:

- 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. (Matrix #1)
- 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. (Matrix #19)

- 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 should be developed. (Matrix #19)
- 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. (Matrix #19)
- Research aimed at identifying prenatal biological markers is needed. (Matrix #19)
- Support technology or methods for biomarker development including those for biomarkers that are cost-effective for use in large population-based studies. (Workshop 3B4)
- Include research on approaches to handle small sample volumes from a variety of matrices (e.g., bloodspots, placenta, saliva, urine, meconium, tissue, etc.) as well as biomarkers of xenobiotic exposures, immune markers, pathogens, and hormones. (Workshop 3B4, Autism Town Hall Meeting)
- Methods supporting analyses of stored (repository) samples. (Workshop 3B4)
- Validation studies of biomarker performance (including reproducibility across different shipping and storage times, labs, matrices, and platforms). (Workshop 3B4)
- Methods for informatics approaches to, and statistical analyses of, large biomarker datasets linked to, or incorporating, phenotypic/clinical data sets. (Workshop 3B4)
- Participants at the Autism Town Hall meeting suggested that efforts be made to detect co-morbid conditions (e.g., mitochondrial abnormalities). (Autism Town Hall Meeting)
- Determine the role of environmental toxins in affecting co-morbid conditions, i.e., oxidative stress, mitochondrial abnormalities, and immune, gastrointestinal and neurological impairments. (Autism Town Hall Meeting)
- Conduct large-scale studies to examine biomarkers of environmental stressors (Autism Town Hall Meeting).

Q4. Which Treatments and Interventions Will Help?
4A3. Efficacy trials for comprehensive intervention models for individuals with ASD across the ages

Strengths:

- 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. (Matrix Intro to Specific Treatments)
- The Research Matrix Panel found that progress in establishing efficacy for pharmacological, behavioral and other treatments that target symptoms associated with autism was proceeding and did not need course correction. (Matrix # 2)
- 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. (Matrix #2)
- Progress has also been made on identifying efficacious behavioral treatments for core deficits, primarily with younger children. (Matrix #2)
    - 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. (Matrix #2)
- 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. (Matrix #2)
- Progress has been made in identifying drugs that have effects on particular target symptom domains. (Matrix #16)
- Work has progressed in identifying efficacious behavioral interventions that will target core symptoms. (Matrix #32)

- There exits now a variety of comprehensive interventions model programs for individuals with ASD that have been tested in small studies, but have not been examined in efficacy trials. (Workshop 4A3)

Weaknesses:

- 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. (Matrix #16)
- There has been little progress in identifying more objective biological measures that would be predictive of treatment response, such as genetic markers, electrophysiological measures, or neurochemical measures. (Matrix #16)
- Limited efficacy information prevents comprehensive intervention programs from identification of mediators and moderators, active ingredients of intervention, and analysis of costs. (Workshop 4A3)
- Limited efficacy information also results in the absence of information upon which service providers might base their decisions about program adoption. (Workshop 4A3)
- In the area of specific treatments, the Research Matrix 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. Panel members highlighted a particular need for interventions that specifically target core features of autism. (Matrix Intro to Specific Treatments)

Recommendations to Address Opportunities & Gaps:

- 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. (Matrix Overall Recommendations to Specific Treatments)
- Emphasis should be placed on continued follow-up of children enrolled in studies so that long-term outcomes related to early treatment can be examined. (Matrix Overall Recommendations to Specific Treatments)
- 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. (Matrix Overall Recommendations to Specific Treatments)
- Multiple treatment approaches need to be tested in the same trial (e.g., behavioral and pharmacologic approaches). (Matrix Overall Recommendations to Specific Treatments)
- Moderator and mediator analyses should be emphasized, since they are critical for developing individualized treatments; however, such analyses will require much larger sample sizes. (Matrix Overall Recommendations to Specific Treatments)

- More treatments need to be developed for school-age children, adolescents transitioning to adulthood, and adults with autism. (Matrix Overall Recommendations to Specific Treatments)
- Current studies need to be replicated, with increased attention to short- and long-term follow-up. (Matrix Overall Recommendations to Specific Treatments)
- 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. (Matrix Overall Recommendations to Specific Treatments)
- Eventually, transportability into the community and other aspects of effectiveness need to be examined for treatments found to be efficacious. (Matrix Overall Recommendations to Specific Treatments)
- 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. (Matrix #16)
- More replication of treatment studies across sites would also provide much needed data for examining moderators and mediators. (Matrix #16)
- 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 should be investigated more fully. (Matrix #16)
- Research is needed to identify the unique needs of high functioning individuals with ASD and to develop appropriate interventions for them. (Autism Town Hall Meeting)
- Retrospectively investigate documented cases of recovery in individuals who utilized novel treatments for clues with regard to heterogeneity, biomarkers, risk factors, and outcome measures. (Autism Town Hall Meeting)
- Increase the inclusion of individuals with ASD in research priority setting (Autism Town Hall Meeting)

4B2. Investigation of efficacy and safety of commonly used and untested treatments for ASD

Strengths:

Weaknesses:

- Evidence suggests that a wide range of treatments that have not been adequately empirically evaluated are in common usage. (Workshop 4B2, Autism Town Hall Meeting)

Recommendations to Address Opportunities & Gaps:

- It is imperative that these widely used treatments be tested systematically for efficacy and safety, including comparative designs to evaluate relative efficacy and subgroup variation. (Workshop 4B2, Autism Town Hall Meeting)
- Retrospectively investigate documented cases of recovery in individuals who utilized novel treatments for clues with regard to heterogeneity, biomarkers, risk factors, and outcome measures. (Autism Town Hall Meeting)

- **5A3. Evaluation of community-based intervention models informed by multidisciplinary best practices**

Strengths:

- Evidence from the field of mental health has been valuable in identifying and evaluating effective community based programs base on best-practice models. (Workshop 5A3)
- Such studies have shown that collaboration between research and community providers leads to faster and more sustainable development and translation of evidence based practices. (Workshop 5A3)

Weaknesses:

- Although many university-based efficacy studies of evidence-based practices exist, there is a dearth of empirically-validated community-based effectiveness studies of intervention for individuals with autism. (Workshop 5A3)
- Some community based models for individuals with autism throughout the lifespan are currently in use, but have not been evaluated. (Workshop 5A3)
- There is a need to identify best practices models currently being used in the community and measure their effectiveness. (Workshop 5A3)

Recommendations to Address Opportunities & Gaps:

- Assess the quality, effectiveness, and delivery methods of existing community-based intervention programs, such as: positive behavior support interventions, social skills training, parent training, prevocational and vocational training programs, recreational programs, as well as comprehensive programs, among others. (Workshop 5A3)
- Conduct studies that test the efficacy of existing models of community intervention and assess factors that enhance quality, impact, feasibility, and cost-effectiveness. (Workshop 5A3)
- Conduct studies that determine best practices to treatments in school settings. (Autism Town Hall Meeting)

4B1. Role of co-morbidity in ASD treatment

Strengths:

- It is well established that co-morbid medical and psychiatric conditions are highly prevalent in individuals with autism. (Workshop 4B1)
- Clinical evidence suggests that the treatment of co-morbid conditions can improve behavior and reduce autism symptoms. (Workshop 4B1)
- There are common mechanisms in immune, gastrointestinal, and CNS functions, with functional interactions between these systems. (Workshop 4B1)

Weaknesses:

- The Research Matrix Panel discussed a number of additional research opportunities and gap areas. These included investigations of co-morbid medical conditions. (Matrix Additional Research Needs and Opportunities)
- There is a need to understand the effects of co-morbid medical and psychiatric conditions on autism symptom expression and problem behaviors, and role of such conditions in the treatment of ASD. (Workshop 4B1)
- 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. (Matrix #16)

Recommendations to Address Opportunities & Gaps:

- Several important research questions on co-morbidity need to be addressed:
    - Does the presence of co-morbid medical (e.g. gastrointestinal symptoms, sleep problems) and/or psychiatric conditions (e.g. depression, anxiety), influence the efficacy of treatment of core symptoms?
    - Should co-morbid conditions in individuals with autism be treated in the same manner as individuals without autism? Or are autism-specific treatment strategies for co-morbid conditions necessary?
    - Does treatment of co-morbid conditions alleviate core symptoms in some instances? (Workshop 4B1)
- Participants at the Autism Town Hall Meeting emphasized the need to develop and evaluate treatments for underlying co-morbid conditions, such as oxidative stress, mitochondrial abnormalities, and chronic infections. (Autism Town Hall Meeting)

4A1. Interventions for older children and adults with ASD

Strengths:

- There are a variety of innovative projects funded in the area of innovative interventions 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. (Matrix #8)
- Current emphasis on early intervention has shown that appropriate treatment can have significant impact on outcome in ASD (Workshop 4A1)

Weaknesses:

- The strong focus on early intervention has had the unintended consequence of very limited development or evaluation of interventions for older individuals. (Workshop 4A1)
- There is a lack of efficacious, or even carefully evaluated, interventions for older children, adolescents or adults with ASD. (Workshop 4A1)
- Most interventions are targeted toward younger children and there is limited activity at the elementary, secondary, and adult levels. (Matrix #8 and 13)
- 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. (Matrix Intro to Specific Treatments).
- There is a lack of efficacious, or even carefully evaluated, interventions for older children, adolescents or adults with ASD. There is a need a need for such studies, particularly those with functionally relevant outcomes, such as employment, quality of life, relationships, and so on. (Workshop 4A1)
- More treatments need to be developed for school-age children, adolescents transitioning to adulthood, and adults with autism. (Matrix Overall Recommendations to Specific Treatments)

Recommendations to Address Opportunities & Gaps:

- 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.
  - There should be increased focus on adolescents' transition to work, as well as middle-aged and senior adults who are working. It is important to develop interventions that will support more fulfilling vocational experiences and recreational and social lives. (Matrix Overall Recommendations for School & Community Interventions)
- More treatments need to be developed for school-age children, adolescents transitioning to adulthood, and adults with autism. (Matrix Overall Recommendations for Specific Treatments)
- More research is needed to determine and disseminate best practices to treatments in school settings. (Autism Town Hall Meeting)
- 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. (Matrix Overall Recommendations for School & Community 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. (Matrix Overall Recommendations for School & Community Interventions)
- 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. (Matrix Overall Recommendations for School & Community Interventions)
- More randomized, controlled intervention trials are needed in community and school settings with longer term outcomes. (Matrix Overall Recommendations for School & Community Interventions)
- There is need for studies that focus on functionally relevant outcomes, such as employment, quality of life, relationships, and so on. (Workshop 4A1)
- Research is needed to support evaluation and early stage development of behavioral and/or medical/pharmacological interventions for older children, adolescents, and adults with ASD. High priority would be given to studies of interventions that address all the domains of functions relevant to adults with autism, including communication, independence, self-care, health and safety, social relationships, employment. (Workshop 4A1)
- Research is needed to identify the unique needs of high functioning individuals with ASD and to develop appropriate interventions for them. (Autism Town Hall Meeting)

4A2. Intervention and prevention approaches for infants and toddlers at risk for autism

Strengths:

- A few randomized clinical trials (RCTs) of individual comprehensive intervention approaches for preschool age children have been conducted. (Matrix Intro to Early Intervention).
- 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. (Matrix #7)
- Several new studies to examine comprehensive early interventions using randomized designs are in varying stages of development. (Matrix #7)
- 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. (Matrix #7)
- 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. (Matrix #7)
- The Research Matrix 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. (Matrix #20)
- 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. (Matrix #20)
- Specific child characteristics, including object interest, social initiative, and avoidance, are beginning to be examined as moderators. (Matrix #20)
- 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. (Matrix #21)
- 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. (Matrix #20)

Weaknesses:

- 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. (Matrix Overall Recommendations for Early Interventions)

- Thus far, no randomized comprehensive early intervention studies initiated during childhood have been published, although such studies are underway. (Matrix Overall Recommendations for Early Interventions).
- 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 should be conducted in parallel. (Matrix Overall Recommendations for Early Interventions)
- 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. (Matrix #7)
- Most RCTs that seek to identify moderator variables and effective ingredients (e.g, dose, intensity, mode of delivery, age of onset) focus on the identification of moderator variables or specific intervention ingredients, but projects are needed that address all aspects. This will require large, multi-site RCTs. (Matrix #20)
- Determining effective ingredients within comprehensive interventions appears to be most difficult and an area with little progress. (Matrix #20)
- 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. (Matrix #20).
- 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. (Matrix #21)
- Efforts to develop interventions for infants younger than 12 months are hampered by the lack of diagnostic tools for defining autism at ages younger than 18-24 months. (Matrix #21) No papers have yet been published from RCTs on longitudinal follow-ups. (Matrix #37)
- Some conference presentations have addressed this subject and there are studies in development. (Matrix #37)

Recommendations for Addressing Opportunities & Gaps:

- Exploratory and efficacy studies of interventions appropriate for infants and toddlers at risk that incorporate measures of family functioning, biological measures of response to treatment, and outcome measures that include indices of neuroplasticity, family functioning, core and associated symptoms, adaptive behavior, and longer term outcomes. (Workshop 4A2)
- The role of the family as partners in the intervention, as well as the impact of the intervention on the family, needs to be investigated. The degree and nature of the burden experience by families, its impact on family functioning, and whether early intervention serves to alleviate the burden needs to be understood. (Workshop 4A2)
- 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. (Matrix Overall Recommendations for Early Interventions)

- The Research Matrix 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. (Matrix Overall Recommendations for Early Interventions)
- 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 approaches to intervention need to be examined. (Matrix Overall Recommendations for Early Interventions)
- 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. (Matrix Overall Recommendations for Early Interventions)
- Thus far, no randomized comprehensive early intervention studies initiated during childhood have been published, although such studies are underway. This should be identified as a high priority research area. (Matrix Overall Recommendations for Early Interventions)
- 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 should be conducted in parallel. (Matrix Overall Recommendations for Early Interventions)
- Studies comparing different treatments and examining nonspecific factors such as therapeutic alliance and attention control need to be conducted. (Matrix #7)
- While dosage has been examined in two randomized, controlled comprehensive interventions, more research is needed to examine specific thresholds. (Matrix #7)
- 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. (Matrix #7)
- Specific child characteristics, including object interest, social initiative, and avoidance, are beginning to be examined as moderators. (Matrix #20)
- Studies incorporating biological variables as potential moderators of response to intervention are recommended. (Matrix #20)
- Family and community variables need to be considered, as well as child variables, in examining mediators and moderators of treatment efficacy. (Matrix #20)
- 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 should be emphasized in this element. (Matrix #21)
- Research to develop approaches to early intervention with infants and toddlers is recommended. (Matrix #21)
- Follow-up studies of children who have participated in early intervention RCTs are strongly encouraged. (Matrix #37)

- Participants at the Autism Town Hall Meeting emphasized the need to develop and evaluate treatments for underlying co-morbid conditions, such as oxidative stress, mitochondrial abnormalities, and chronic infections. (Autism Town Hall Meeting)

2A2. Understanding mechanisms of neuroplasticity in autism

Strengths:

- Animal research has demonstrated that environmental experiences directly influence synaptic formation and stabilization, as well as gene expression. (Workshop 2A2)
- Animal models of developmental and degenerative disorders have demonstrated the role of early enrichment in mitigating the effects of genetic risk and injury. (Workshop 2A2)
- Multi-site *in vivo* imaging studies have led to a convergence around the idea that precocious growth of certain brain regions such as the cerebral cortex is one of the consistent features of autism. (Matrix #6)

Weaknesses:

Recommendations to Address Opportunities & Gaps:

- Early behavioral intervention in young children with autism has been shown to increase cognitive ability and reduce autism-related symptoms, with a significant proportion of children having dramatic improvement in symptoms. (Workshop 2A2)
- Basic neurodevelopmental imaging studies that focus on implicated neuro-circuitry could be stronger and more relevant to autism. (Matrix #26)
- Conduct research regarding reversibility of neurological abnormalities and potential regenerative treatments—i.e., fibroblast growth factor, human growth factor, stem cell therapies. (Autism Town Hall Meeting)

4C2. Novel treatments of core symptoms

Strengths:

- There exist a few promising pharmacological (e.g., oxytocin) and behavioral (affective approaches) treatments to target core symptoms of autism, such as impairments in social affiliation and social reciprocity. (Workshop 4C2)
- Work has progressed in identifying efficacious behavioral interventions that will target core symptoms. (Matrix #32)

Weaknesses:

- Until more is known about the pathophysiology of autism, it is unlikely that efficacious drug treatments will be found that target core features. (Matrix #32)

Recommendations to Address Opportunities & Gaps:

- Research in this area needs to be broadened to include behavioral, cognitive and psychosocial interventions, all of which may target core features of autism. (Matrix #32)
- There is a need to develop innovative treatment approaches that address core symptoms of autism, using pharmacologic, behavioral or other methods. Among the range of treatment approaches to be considers are assistive technologies. (Workshop 4C2, Autism Town Hall Meeting)
- The Research Matrix 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. (Matrix Additional Gaps and Opportunities)

4B3. Animal models and cellular systems for developing treatments for autism

Strengths:

- 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. (Matrix #17)

Weaknesses:

- The conceptualization of the phenotype remains underdeveloped and hampers this area. (Matrix #17)

Recommendations for Addressing Opportunities & Gaps:

- Developing models that are better characterized and sufficiently sensitive to assess change and manipulation is critical in addressing the essential need to understand the causes of ASD and to produce effective treatments. (Workshop 4B3)
- The Research Matrix Panel identified the development of model systems, particularly animal models, and possibly also cellular and circuitry models, to be an overall research need and opportunity. (Matrix Additional Research Needs and Opportunities).
- The potential role of candidate genes on the phenotype must be assessed in model systems, such as genetically altered animal models. (Workshop 4B3)
- Other animal models with known behavioral defects that map onto the behavioral impairments of autism may provide insight into the genetic alterations in certain forms of autism. (Workshop 4B3)
- Cellular systems, such as stem cells derived from individuals with autism, may also be a valuable resource for evaluating metabolic, genetic and functional alternations associated with autism. (Workshop 4B3)

4B4. Fast track mechanisms to facilitate translational treatment research

Strengths:

- Various basic science investigations using animal models are identifying novel therapeutic targets in different model systems on an ongoing basis. (Workshop 4B4)
- There are existing basic science discoveries that have not yet been translated into therapies. (Workshop 4B4)
- There are also existing collaborative treatment networks that are poised to test approaches including pharmacologic, behavioral, or other interventions. (Workshop 4B4)

Weaknesses:

- Currently, there is a large, temporal gap between basic science discoveries and therapeutic application to clinical populations, particularly to large scale clinical trials that are necessary to test safety and efficacy. (Workshop 4B4)

Recommendations to Address Opportunities & Gaps:

- Prior to large scale clinical trials, require collaboration between basic and clinical researchers to gather pilot data to evaluate new treatments and approaches in clinical populations. (Workshop 4B4)

Q5. Where Can I Turn for Services?
5A1. State of the States for individuals with ASD

Strengths:

- There is an annual report, "The State of the States in Developmental Disabilities" by Braddock et al., which is considered by many to be the single, most useful document available for policy and advocacy, and for system reform. (Workshop 5A1)

Weaknesses:

- There is a lack of information on existing programs, supports, unmet needs, resource utilization, and favored intervention models for ASD. (Workshop 5A1)
- Great variability exists in terms of states' service paradigms, utilization, funding streams, identification and labeling practices, eligibility criteria, and resource levels. (Workshop 5A1)
- Indeed, the strongest predictor of whether a person/family gets any services/supports, as well as what kind and at what intensity, is the state in which the person resides. (Workshop 5A1)
- The nation needs a regular update on "counts and amounts" of services and their costs. A state-by-state annual report containing such information is needed for families, policy makers, and researchers. (Workshop 5A1)
- Differences among states' Medicaid waiver programs limit the ability of families to move across state lines for employment or for other purposes. (Autism Town Hall Meeting)

Recommendations for Addressing Opportunities & Gaps:

- Conduct a survey to create a "State of the States for ASD", updated and published annually. (Workshop 5A1)
- The report should include analysis of "unmet needs." (Workshop 5A1)
- Research is needed to identify the unique needs of high functioning individuals with ASD and to develop appropriate interventions for them. (Autism Town Hall Meeting)

5A2. Identify and evaluate models of effective dissemination of evidence-based practices (EBP) into community programs

Strengths:

- 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 important topic. (Matrix #24)
- There is some evidence of dissemination through personnel preparation and in-service training. (Matrix #27)

Weaknesses:

- There is a lack of availability and access to evidence based practices in community programs. (Workshop 5A2)
- There is a need to enhance, support, and create effective, sustainable programs in the community. (Workshop 5A2)
- There is a need for scientific information to inform policy for use of evidence based practices in the community (Workshop 5A2)
- There is little evidence of support for interventions at the middle and secondary school levels, and this gap needs to be addressed. (Matrix #27, Autism Town Hall Meeting)

Recommendations for Addressing Opportunities & Gaps:

- The Research Matrix Panel discussed a number of additional research opportunities and gap areas. This included 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. (Matrix Overall Recommendations on Opportunities & Gaps)
- Studies to evaluate the feasibility, impact, and cost of different models of dissemination of evidence based programs for the provision of services, including assessment, diagnosis, and treatment (medical and psychosocial) to diverse communities. (Workshop 5A2)

5A4. Cost-outcome studies of intervention models for people with ASD

Strengths:

- Responsible public funding requires information to balance the cost of services against anticipated outcomes. (Workshop 5A4)
- Good data are needed to find maximally productive intervention approaches. (Workshop 5A4)
- It is important to know "what works" and "at what cost". (Workshop 5A4)

Weaknesses:

- There is a lack of information on costs of various ASD intervention models, and the expected outcomes of those interventions. (Workshop 5A4)
- Lifetime estimates of services/supports as "investments" are needed to support public funding. (Workshop 5A4)
- Estimates of the cost of non-treatment, including the burdens on families, are needed. (Workshop 5A4)

Recommendations for Addressing Opportunities & Gaps:

- Environmental Scan (literature review) on cost-outcome studies (particularly from developmental disabilities) should be conducted. This information should be compared to prospective data collected via collaboration with existing evaluation or outcome project(s) to add a valid and reliable assessment of costs. (Workshop 5A4)

1B2. Characterizing and improving the diagnostic process in the community

Strengths:

- A number of screening tools have been developed for detecting autism, including: 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). (Matrix #15)
- Current 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. (Matrix #15)
- Some of screening 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. (Matrix #15)
- The CDC has funded specific research evaluating the effectiveness of various strategies for implementing screening into community practice settings. (Matrix #9)

Weaknesses:

- There is a lack of information on the sensitivity and specificity of screening measures. (Matrix Overall Recommendations for Screening)
- Lack of parental follow-though may be an important barrier to early diagnosis and treatment in population based early diagnosis studies. (Matrix #9)

Recommendations to Address Opportunities & Gaps:

- 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. (Matrix Overall Recommendations for Screening)
- 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. (Matrix Overall Recommendations for Screening)
- 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. (Matrix Overall Recommendations for Screening)
- Studies involving general population screening will need to identify effective strategies for optimizing parental follow-through for recommended follow-up exams and treatment. (Matrix Overall Recommendations for Screening)
- 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. (Matrix #15)

- More focus is required on studying barriers to use of existing screening measures. (Matrix #15)
- 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. (Matrix #15)
- While there are some population-based studies underway, more are needed using varied research methodologies. (Matrix #9)
- Parental follow-through needs to be targeted for research regarding screening and referral practices that optimize parental adherence. (Matrix #9)
- Utilization of existing large-scale, population-based studies will allow for cost-efficient investigations of the impact of early identification procedures. (Matrix #9)

6B1. Enhanced tracking of ASD prevalence in children and adolescents

Strengths:

- There are multiple efforts currently underway to develop first generation community-based prevalence studies. These include: The Autism and Developmental Disabilities Monitoring (ADDM) Network, which is implementing community-based prevalence studies in 10 states, and 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. (Matrix #28)
- CDC is currently conducting a clinical validation study to examine the validity of using expert clinical review of records based information. (Matrix #28)
- 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. (Matrix #28)
- First generation prevalence studies have been successfully developed and implemented. (Workshop 6B1)

Weaknesses:

- There have been limited opportunities to compare and develop alternate and complementary methods of characterizing the ASD population over time. (Workshop 6B1)
- With the exception of the MADDSP, little work is being done on intensive community-based prevalence studies that include clinical evaluations. (Matrix #38)

Recommendations to Address Opportunities & Gaps:

- There are a number of gaps in prevalence studies including: continued estimation of prevalence in the same population over time; evaluation of prevalence in the same population over time, assessment of ASD prevalence in the context of other neurodevelopmental disorders; comprehensive confirmation of case-status; collection of data beyond core ASD symptoms, including genetic data; and, expansion of studies across ages. (Workshop 6B1)
- Develop systems to assess time trends in the prevalence of ASD in the context of trends of other neurodevelopmental disorders, in populations of children and adolescents. (Workshop 6B1)
- The Autism Matrix Evaluation 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. (Overall Matrix Recommendations on 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? (Overall Matrix Recommendations on Epidemiology)
- More emphasis should be placed on conducting clinical assessments that can determine the extent of misclassification among those designated as having autism (false positives). (Overall Matrix Recommendations on Epidemiology)
- More prevalence studies using varied methodologies are needed to ensure that the estimates derived from the ADDM methodology are accurate. (Overall Matrix Recommendations on Epidemiology)
- Greater emphasis needs to be placed on direct clinical evaluations in prevalence studies. (Matrix #28)
- 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). (Matrix #28)
- Changes in prevalence estimates over time should be examined by following up earlier prevalence studies, such as Brick Township, using the same population, approach, and measures. (Matrix #28)

Q6. What Does the Future Hold?
6A1. Understanding developmental trajectories of children and families affected by ASD

Strengths:

- NICHD and Autism Speaks/National Alliance for Autism Research (NAAR) formed a consortium of researchers focused on studying infant sibs of children with autism to help identify early features and distinguishing characteristics of autism. (Matrix #25)
- Studies are underway to examine subsequent pregnancies of women with autistic children. (Matrix #25)
- 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. (Matrix #22)
- The Simons' Collection has selected 11 centers to collect genetic samples from up to 2,000 simplex families in two years. (Matrix #3)
- There is good evidence from other psychopathologies that information on developmental trajectories informed diagnosis and treatment in helpful ways. Advances in statistical methods and procedures also make this more readily achievable. (Workshop 6A1)

Weaknesses:

- The specificity of neuropathological features to autism has not yet been established for any brain structure. The cerebellum, for example, while clearly pathological in autism, also appears to exhibit pathology in a variety of other neurodevelopmental disorders. (Matrix #22)
- 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. (Matrix #1)
- 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. (Matrix #1)

Recommendations to Address Opportunities & Gaps:

- More comparative studies are needed across neurodevelopmental disorders. We need much better control material and clinical contrast material to do these types of comparisons. (Matrix #22)
- “Risk profiles” that incorporate both biological and behavioral measures should be developed. (Matrix #1)
- Research aimed at identifying prenatal biological markers is needed. (Matrix #1)
- 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. (Matrix #33)

- 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. (Matrix #23)
- Longitudinal and/ or prospective, hypothesis-driven studies are needed, in which multiple domains of development, and family and social context are simultaneously characterized. These studies should include biomarkers when possible, including genetic biomarkers, and they should include regression as a type of trajectory. (Workshop 6A1)

6A2. Improved identification and characterization of autism in adulthood

Strengths:

Weaknesses:

- There is a lack of evidence about prevalence and course of autism in adults. (Workshop 6A2)
- There is inadequate policy and service development and for adults with autism a lack of coordination across those services that do exist. (Workshop 6A2)

Recommendations to Address Opportunities & Gaps:

- Develop feasible methods for ascertaining and diagnosing autism in adults. (Workshop 6A2, Autism Town Hall Meeting)
- Conduct longitudinal studies of prevalence and functional outcomes in existing adolescent cohorts, as well as de novo adult prevalence studies. (Workshop 6A2)
- Address diagnostic issues (co-morbidities, tracking developmental changes) that coincide with transitions from adolescence to adulthood, including functional outcomes (school-to-work, independent living, access to healthcare, etc.). (Workshop 6A2)
- Promote greater independence and a better quality of life for adults with autism. (Workshop 6A2)
- Improve clinicians' ability to describe and foresee possible outcomes to parents of children with autism. (Workshop 6A2)
- More treatments need to be developed for school-age children, adolescents transitioning to adulthood, and adults with autism. (Overall Matrix Recommendations on Specific Treatments)
- There should be increased focus on adolescents' transition to work, as well as middle-aged and senior adults who are working. It is important to develop interventions that will support more fulfilling vocational experiences and recreational and social lives. (Overall Matrix Recommendations on School and Community Interventions, Autism Town Hall Meeting)
- 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. (Matrix #29)
- Develop improved quality-of-life (QOL) measures for adults with ASD that assess indicators beyond IQ and language skill. (Autism Town Hall Meeting)
- Determine the prevalence of ASD within the criminal justice system. Assess the impact of incarceration on individuals and families. (Autism Town Hall Meeting)

6C1. Merging and analyzing administrative databases relevant to diagnosis, course, interventions, and long-term outcomes

Strengths:

- Methods for merging administrative databases and linking investigator-recruited samples to these merged databases has been demonstrated feasible in other populations and in specific locales. For example, such efforts have been effectively employed to evaluate child welfare programs. (Workshop 6C1)

Weaknesses:

- There are poorly developed methods for characterizing intervention history, including disparities in access and utilization. (Workshop 6C1)

Recommendations to Address Opportunities & Gaps:

- There are untapped opportunities for merging and analyzing administrative databases (e.g., medical, educational, social services, Medicaid) to study the impact of timely diagnosis, entry to intervention, course of intervention, and course of development. (Workshop 6C1)
- Develop methods for linking administrative databases that allow for tracking the involvement of people with ASD and developmental delay in health care, education, and social services over time. (Workshop 6C1)
- Develop methods for linking of investigator-recruited samples with merged administrative databases. (Workshop 6C1)
- Fund studies that make use of merged databases to examine diagnosis, course, and phenotypic variation. (Workshop 6C1)
- Increase the inclusion of individuals with ASD in research priority setting. (Autism Town Hall Meeting)

6C2. Develop resources to coordinate large population-based ASD initiatives (NDAR, CDC, NIH, IAN, State Registries)

Strengths:

- CHARGE has enrolled 700 subject, and characterization and analysis has begun using medical data, biological specimens, immunological features and genomic profiles. (Matrix #10)
- 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. (Matrix #10)
- 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. (Matrix #10)

Weaknesses:

- Policies on data sharing need to be established. (Matrix #10)
- There is insufficient recognition of the National Database for Autism Research (NDAR) and the Phenome Project among autism researchers. (Matrix #10, #4)
- Collections such as the CPEA/STAART, CHARGE, NICHD/Autism Speaks/NAAR, Simons' Collection, and the Norwegian studies are not making the best use of the latest techniques in genetic research, and the phenotypic characterization is not being advanced. (Matrix #3)

Recommendations to Address Opportunities & Gaps:

- There is a need to increase data sharing and address data storage issues, and to publicize for existing resources. (Matrix Overall Recommendations on Characterization)
- Goal of NICHD/Autism Speaks/National Alliance for Autism Research partnership is to create larger, combined samples of the infant sibs/high-risk pop for multi-site studies. (Matrix #25)
- The National Database for Autism Research (NDAR), currently under development at NIH, is designated as a major resource for the phenome project. (Matrix #10)
- Form and support a U.S. Autism Epidemiology Network that would promote information-sharing and collaboration across population-based epidemiologic initiatives. Projects could include: support for conferences, web resources, integration of currently independent projects, development of new common resources—e.g., merging multiple administrative databases (child find, state disability, other state registries, Special Education)—as well as common measures in the specific context of epidemiological studies. (Workshop 6C2)