

*Draft Autism Research Matrix Comments
Submitted to NIH, IACC by SafeMinds and the National Autism Association
January 16, 2007*

*Comments solicited by the
NIH IACC regarding the proposed Autism Research Matrix*

**Evaluating Progress on the IACC Autism Research Matrix
A draft report presented to
Interagency Autism Coordinating Committee
November 17, 2006**

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SafeMinds and the National Autism Association**

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Background

Prior to the convening of the expert panel to review and evaluate progress made to date regarding the 2003 Autism Research Matrix, representatives from SafeMinds and the National Autism Association (NAA) met with Dr. Thomas Insel and his staff concerning the proposed update. During the meeting, requests were made to expand the panel's membership to include scientists and clinicians with expertise in environmental factors and biomedical interventions, as well as and representatives from advocacy groups. Subsequent to these meetings a, SafeMinds and NAA submitted list of recommendations for environmental and biomedical treatment content areas for the panel's review. In addition, SafeMinds and NAA also requested that an external panel, comprised of scientists, clinicians, and advocates, convene at least annually to review Matrix progress and revise goals and activities as warranted in light of new research and clinical findings. We deeply appreciate the efforts of Dr. Insel and his staff for taking the time to meet with us and for reviewing our recommendations for incorporation into the process of evaluating and updating the Autism Research Matrix.

Many of our requests regarding autism research at NIH were incorporated into Senate Bill 843, the Combating Autism Act of 2006 (CAA). The amended bill, as adopted and reported out of the House of Representatives and signed into law on December 19, 2006, reauthorizes the existing Interagency Autism Coordinating Committee (IACC). The accompanying CAA report language states, *"The committee's far-reaching mandate will be to compose and annually report to Congress on a strategic plan for federal Autism activities and to make important recommendations to both Congress and the executive branch on ways to better coordinate and conduct federal autism-related activities. Further, this legislation increases the amount of public participation on the IACC from two individuals to at least six."* The report language continues by stating that *"Public participation, especially among the parents and families of those affected by autism, is necessary to emphasize the human side of autism research and to ensure that federal resources are used wisely."* CAA specifies that composition of the IACC will include no fewer than six members or one-third of the committee membership, whichever is greater, from outside the government. The act also notes that the IACC may recommend providing other formal mechanisms, such as an Autism Advisory Board, to provide public feedback and interaction. Given the passage of CAA SafeMinds and NAA respectfully request that the IACC implement the recommendations regarding the establishment of an Autism Advisory Board.

Additionally, the legislation states that *"The Director of NIH shall, subject to the availability of appropriations, expand, intensify, and coordinate the activities of the National Institutes of Health with respect to research on autism spectrum disorder, including basic and clinical research in fields including pathology, developmental neurobiology, genetics, epigenetics, pharmacology, nutrition, immunology, neuroimmunology, neurobehavioral development, endocrinology, gastroenterology, and toxicology."* Broadening the composition of the IACC committee, as well as the autism research matrix, into these areas of expertise and investigation is necessary to identify the

biological underpinnings of autism spectrum disorders. Presently, IACC membership is composed primarily of representatives from federal agencies. Expansion into these additional areas of representation will facilitate broad based research initiatives, increasing NIH's ability to positively impact the lives of those diagnosed with autism spectrum disorders.

Comments in this document are divided into three sections: 1) recommendations related to NIH guiding principles, 2) specific recommendations related to the IACC research matrix, and 3) a list of issues that serve as roadblocks to successfully implementing autism research.

Guiding Principals for Autism Research at NIH

In addition to the matrix recommendations, SafeMinds and National Autism Association have unique perspectives regarding the manner in which autism research needs to be addressed by NIH. We believe these suggestions will accelerate the pace of research, help the most autistic individuals in the fastest way possible and prevent others from succumbing to this tragic disease. Therefore, we request that these guiding principals be incorporated into each of the matrix's eight study sections to provide overall guidance from which all research originates. The following are our suggestions for guiding principals:

1. Acknowledge autism as a national emergency

In reviewing the overall autism research matrix, we sense a lack of urgency in addressing the growing epidemic of autism in our country. In 2004, the Centers for Disease Control and Prevention issued an "Autism Alert" announcing that the reported prevalence of autism spectrum disorders had risen to alarming levels, affecting approximately 1 in 166 children in the United States. Such profound numbers demand immediate attention and action from our Federal agencies. Therefore, we request that the NIH respond to autism as a ***national emergency*** and allocate the resources necessary to respond to this pervasive epidemic. Additionally, we suggest that more resources are directed into environmental studies to be launched immediately and RFA's are issued to find answers to specific questions

2. Shift research focus from genetics to environment

Acknowledgement of this epidemic demands a shift in the focus of autism research away from an exclusively genetic model to one that investigates the role of environmental factors combined with a genetic vulnerability as a potential culprit behind this otherwise unexplained epidemic. The role of the environment was recognized by the expert panel in the report as an understudied area that was given insufficient attention in the first iteration of the matrix. The absence of a well developed environmental research agenda impedes the discovery of etiologic factors responsible for the development of autism and the ability to identify effective treatment strategies. We respectfully request that a research plan specific to the environment be created and incorporated into the overall autism matrix.

3. *Develop a leveraged research agenda*

In the face of this public health crisis, we propose that the NIH develop a leveraged research agenda with a focus on identifying etiologic factors driving the epidemic of autism to prevent its occurrence and to devise effective treatments for those already afflicted with this devastating disorder. The guiding principal should be to pursue research and treatments that will impact the most lives as quickly as possible and follow clues provided by evidence-based treatments. Such an agenda would be best served by a translational research protocol where clinicians who care for children with autism advise research into the most promising areas of intervention.

4. *View autism as a dynamic disease process and amenable to treatment*

The current matrix perpetuates a belief system that autism is fixed prenatally and immutable postnatally, rather than as a condition that arises from preventable pre- or postnatal exposures and is amenable to treatment after birth. Continuation of this belief impedes research initiatives into identifying effective treatments. We are also concerned that current treatment strategies are targeted at ameliorating symptoms rather than understanding the underlying biology and pathology that is responsible for symptom manifestations. Such an approach does little to reduce the morbidity associated with autism. The latest research points to a genetic susceptibility that is environmentally triggered. As a result, the perception that autism is lifelong and incurable should be abandoned to follow the line of reasoning that autism is indeed preventable and thus, treatable. Hopeless becomes hopeful. A cure is possible in those suffering now and steps can be taken to make sure no others will become ill.

5. *Reclassify autism as a multi-organ disease*

Recent clinical investigations have identified numerous co-morbid disease states in children with autism. These include abnormal gastrointestinal function and inflammatory bowel disease, evidence of increased oxidative stress, severely disordered serum chemistries, methylation disturbances, increased body burdens of metals and microglial activation in the brain. Studies must be initiated as soon as possible to increase the focus on the identification of co-morbid disease states, since many biomedical imbalances are amenable to medical and nutritional interventions as reported by clinicians treating autism. Additional investigations into these associated disease states also offers the promise of the identification of biomarkers and more effective clinical interventions targeted on identified abnormalities.

6. *NIH to drive research agenda vs. researchers*

An area that is not addressed in the report that we feel is critical to advancing the science related to autism spectrum disorders at NIH is the way the research matrix is developed and studies are implemented. It is our understanding from discussions with staff at NIH, that the current research agenda is currently being driven by investigators, i.e. the NIH funds a research proposal and then retrofits the project into the matrix. This is best evidenced by the fact that investigations into the characterization and screening for autism are flush with research, whereas areas of research into identifying specific

treatments for those suffering with autism is severely lacking. The research goals and activities outlined in the autism research matrix would be more likely to be implemented if NIH the goals were used to set funding priorities and score proposals. Specifically, NIH should: (a) to include these activities as items to be scored when reviewing grant proposals; (b) to announce them as program project grants; and (c) to require Autism Centers of Excellence to address them as part of their center designation and to consider such project proposals when scoring center proposals.

7. Create a formal mechanism for ongoing public-private research agenda

Throughout the draft matrix, reference is made to public/private partnership regarding autism research activities. The overall research budgets for private funders are equivalent to or surpass that of our federal agencies. To enhance the potential for improving knowledge, prevent undue repetition in research activities and fill in research gaps, a formal mechanism needs to be established to coordinate and benefit from collaborative public/private efforts. Formal collaboration can be achieved with conference calls, email or in-person meetings. This mutually beneficial approach to the latest research and ideas will provide a synergistic effect and channel scarce research funds into the most critical areas.

Specific IACC Matrix Update Recommendations

The titles below are taken from the current Matrix, pages 11-22. Bulleted points are research goals and activities that should be added to the Matrix to establish a model that explores how autism is environmentally triggered and biomedically treated. In addition to enhancing the existing Environmental Factors and Treatment sections, recommendations are embedded in each of the other content sections as appropriate.

CHARACTERIZATION OF AUTISM SPECTRUM DISORDERS AND ASSOCIATED GENETICS

Goals

- The title should be changed to “Characterization of autism spectrum disorders, co-occurring conditions, associated genetics, and associated exposures”.
- Enhance the section that pertains to characterization of medical conditions. Enhance by adding science that investigates recovery and significant improvements of individuals with a previous PDD diagnosis.
 - Study autism as a dynamical process with intra-individual variability in severity that may be transient or persistent, and that may include improvement, loss of diagnosis and recovery; the mechanisms of dynamism may point toward treatment targets.

- Look for biomarkers relevant to plasticity (including brain metabolism, brain neurophysiology, and systemic metabolism as well as behavior) that could track treatment response
- Identify the environmental factors that increase risk for PDD and might give rise to subtypes within the PDDs, depending on the exposure, exposure interactions, timing, and individual genetics.
 - Identify genetic vulnerabilities to environmental exposures, for example, from the environmental genome project that would be of particular relevance to autism.
 - Special attention to detoxification pathways, including glutathione and cysteine levels, is warranted.
 - Conduct DNA methylation and epigenetics studies among autistic children.
 - Investigations into environmental triggers should not wait until the genetics of autism is characterized. Rather, these investigations can be used to inform genetics research and can be done prior to or simultaneous to genetics investigations.
 - Pre- and postnatal exposure history should be part of the medical work up and a key component of subtyping and phenotyping efforts. Exposures captured should include methylmercury, ethylmercury, mercury vapor from maternal amalgams, and small particle airborne and soil-based mercury. A study of Rh-blood type mothers who were exposed to ethylmercury from immune globulins should be part of such investigations.
 - Toxicology studies that find biomarkers in non-autistic exposed individuals or animals should be applied to autism.
 - Exposure histories among PDD individuals that identify multiple exposures that might lead to interaction effects or “double hit” effects should be used to generate hypothesis for research on such effects in autism.

Activities

- Autism phenome project defined and planned and resources established
 - Incorporate response to treatment as phenotype characteristic
 - Incorporate recovery/improvement trajectory as phenotype characteristic
 - Add exposure history to database so that phenotype and genotype can be linked to exposures, exposure interaction, and timing.
- Toxicological literature and databases are reviewed for susceptibility gene candidates and potential biomarkers.
- Using toxicological review, peripheral biomarkers are screened among well characterized ASD subgroups, with subgroups based on phenotype, genotype, or exposure history. Build on promising immune system findings to more clearly understand the role of immune alterations in ASD and how these alterations might arise from environmental exposures, both chemical and viral.
- Toxicologically-relevant susceptibility genes are screened among ASD subgroups.
- Animal models are developed using exposures relevant to the ASD population based on exposure history, factoring in susceptibility genes as appropriate.

- Longitudinal study of baby siblings is amended to add an exposure history; identify differences in exposure between siblings developing autism and those developing normally, and identify any differences in autism subtype based on differences in exposures.
- Pre-natal exposures can be captured via medical records, maternal surveys, and cord blood examinations.
- Databases of phenotype characteristics should cover not just behaviors and core deficits but also a comprehensive list of co-occurring medical and psychiatric conditions and systems alterations including CNS, sensory/perceptual, metabolic, immune, renal, and gastrointestinal. Metabolic alterations should include detoxification pathways, cell signaling, methylation, apoptosis, growth factors, and porphyrin profiles. How these characteristics change over time should be captured.

SCREENING

Goals

- Include physiologically meaningful exposure measures and intermediary metabolism measures (e.g. measures from body compartments and with laboratory measures sensitive to chronic or persistent as well as acute exposures) that could inform identification of biomarkers and development of biomarker profiles that will aid in screening.
- Gain a better understanding of the degree to which those with “early signs” progress to an actual ASD diagnosis, the reasons for progressing/not progressing, and whether progression varies by exposure history.
- Modify wording of current Matrix so that the goal to prevent autism is not to find “effective techniques for detecting autism as early as possible”, but rather to find “effective techniques for detecting the early signs that might indicate an infant susceptible to a later ASD diagnosis and determine the exposures that might be prevented or the interventions that might be employed to avert the early signs from evolving into ASD.”

Activities

- Screening tools – modify so that screening tools detect “at risk” signs and not just predict a subsequent ASD diagnosis.
- Longitudinal cohort for research – modify so that the cohort can be used to track exposures and subtype based on early signs that progress to ASD compared to early signs that resolve. Ensure that educational modules cover reduction in potentially harmful environmental exposures to at-risk infants.
- Biological and behavioral markers to develop indices of risk for ASD: modify goal to include environmental factors research along with genetic, neurobiological, and molecular biology research. Include environmental exposures and immune system molecules in the list of possible markers.

EARLY INTERVENTION

Goals

- Remove the emphasis on early intervention before age 3. While it is recognized that the earliest intervention is a lower risk and shorter term goal, it should not mean that the goal should be weakened for older individuals, only that intervention in older individuals may take longer to achieve and there is less research to support a positive outcome.
- The goal should recognize that treatments may be educational, therapeutic, or biomedical, and that the latter might include nutritional, dietary, and detoxification approaches as well as pharmaceutical ones.

Activities

- Develop intervention methods for older individuals with autism.
- Prevent 25% of autism cases: modify this goal so that the prevention of cases is set at 75%. If environmental factors play a key role in the majority of ASD cases, then eliminating or reducing exposures should prevent the majority of cases.

SPECIFIC TREATMENTS

Goals

- Overall, research should shift from a focus on “damage” towards a focus on “plasticity”, or what can be corrected or modified to achieve recovery or gain of function.
- Treatment research should be viewed as urgent and the goal should be to find effective treatments for as many individuals as possible as quickly as possible.
- Modify the goal so that it is recognized that studies on effectiveness are conducted among meaningful subgroups, as certain interventions may work among some but not others.
- Modify the goals to recognize that complex, combined interventions and not single interventions may work best for ASD, and clinical trial methodologies must be developed that can accurately ascertain effectiveness for such regimens.
- The goals should recognize that treatments may be educational, therapeutic, or biomedical, and that the latter might include nutritional, dietary, and detoxification approaches as well as pharmaceutical ones.
- Treatment databases should be established that can link effectiveness of a given regimen on a given outcome (e.g. speech, anxiety) with patient information such as phenotype, genotype, and exposure history. Such learning can be used to understand pathways and mechanisms, which in turn can be used to develop more effective interventions.

Activities

- Develop biological outcome measures, such as intermediary metabolism measures in blood, urine or cerebrospinal fluid; electrophysiology; brain perfusion; and metabolic

markers. These can be employed in clinical trials and in development of a treatment algorithm.

- Create a linked database that can be used by clinicians to record patient information, treatments tried, and outcomes, for use in research on interventions from which hypotheses can be generated for the most promising treatments and optimal subgroups for randomized clinical trials.
- Develop arrays related to intermediary metabolism that may underpin environmental vulnerabilities; these do not have to be specific to autism, just implicated in the pathophysiology.
- Efficacious drug treatments that target core symptoms: include other promising interventions besides pharmacology, and indicate that treatment may encompass complex regimens.

ROLE OF THE ENVIRONMENT IN AUTISM

Goals

- Rigorous and independent studies on historical autism prevalence rates over time and across geographies will aid in determining the extent of the autism epidemic, the role of changes in diagnostic practices, the extent to which environmental factors play a causal role in any increase, and what future services might be needed given the true increase in autism rates.
- Study environmental factors not only in relation to direct measures of exposure but also in relation to metabolic impacts to aid in developing potential treatments. Investigations of differential sensitivity, metabolic alteration, and pharmacokinetics to toxicants and other xenobiotics among ASD cases compared to controls would help in identifying toxicants, mechanisms, and doses of relevance.
- Research is showing that cumulative and synergistic effects of multiple exposures can have a far greater impact than a single exposure. Investigations of “multiple hits” are warranted.
- Other goals and activities listed in other sections of this document.

Activities

- Conduct a prevalence study comparing rates of autism and ASDs among school age children age 8 to 18.
- Conduct a study in a well defined population of autism rates before and after documented removal of thimerosal from infant vaccines.
- Retain twin registry; specify collection of complete pre- and postnatal exposure history including vaccines and other medical products.
- Implement a study of the rate and severity of ASD outcomes in vaccinated compared to unvaccinated populations.
- Conduct studies of the rate and severity of ASDs by geography, and link these geographic areas to databases of pollutants.
- As listed above, add exposure component to baby sibling longitudinal study.

- Conduct cell culture studies among autistic and control lymphocytes after exposure to thimerosal and other relevant chemicals. Look at pathways and gene expression that are differentially altered such as apoptosis, detoxification, methionine, etc.
- Create animal models based on single exposures, multiple exposures, and multiple exposures over time, both pre- and postnatally, to substances and viruses that ASD children have been exposed to in the doses to which they were exposed. Use these animal models to understand genetic susceptibility, pharmacokinetics, mechanisms (including effects at the cellular level and systems level such as GI, immune, and brain), retention and localization of body burden, and response to potential treatments. Toxicants studies should include methylmercury, ethylmercury, mercury vapor from maternal amalgams, and small particle airborne mercury. Viruses should include measles and chicken pox.

NEUROSCIENCE

Goals

- Neuroinflammation and immune system effects on brain development should be added to the list of areas to be studied. An understanding of how toxicants alter brain function during various stages of development is needed, especially if linked to examination of autism brains and how they are different from controls. Investigations on how the brain “repairs” itself would aid in treatment approaches.

Activities

- Study not only brain regional changes but pervasive volumetric changes
- Study classes of tissue changes such as inflammation, microglial activation, oxidative stress, and hypoperfusion, and the effect these might have at varying stages of development.
- Study neuromodulator alterations that could be associated with plasticity and that could be altered by treatments.
- Study dynamic features of brain function (e.g. with EEG, MEG, fMRI or SPECT) that may show alterations that might be caused by toxicants and track function that may improve with treatment.
- Examine post mortem brain tissue for direct and indirect indications of environmental exposures. Brains must be made available for such investigations.

SCHOOL AND COMMUNITY INTERVENTIONS

Goals

- Several clinical investigations have documented that children with autism spectrum disorders are particularly vulnerable to environmental toxins secondary to disordered or impaired body chemistries. Therefore, additional efforts should be made in school and community environments to reduce or eliminate unnecessary exposure to environmental toxicants.

Activities

- Add environmental interventions such as reducing pesticide and other chemical use in schools, service settings, and homes, as well as sale of low-nutrient, high-additive junk food in schools, where vulnerable children experience reduction in level of function in relation to such exposures.
- Educate school, institutional and community personnel about accommodating and supporting restrictive or prescriptive biomedical interventions including nutritional approaches.
- Expand definition of intervention in this section to include biomedical as well as behavioral/educational approaches.

EPIDEMIOLOGY

Goals

- Autism spectrum disorders have reached epidemic levels in our country and arguments that the increase in prevalence has resulted from changes in case definitions or ascertainment have not been supported by the data. Additional epidemiological investigations in may provide clues to pathogenesis or sub-types of autism spectrum disorders.

Activities

- Studies have shown that the largest increase in autism rates occurred in the late 1980s and early to mi-1990s. Epidemiology should investigate these birth cohorts and not just prospective cohorts.
- See other sections for additional epidemiology recommendations.

COMMUNICATION & COLLABORATION

Goals

- Recent investigations have documented that children diagnosed with autism spectrum disorders may also suffer with multiple co-morbid conditions including immune system abnormalities, gastrointestinal pathology, disordered serum chemistries and nutritional deficiencies. These physical abnormalities are amenable to medical treatment and have been reported to result in marked improvement in both function and behavior.

Activities

- Institute CME courses in autism treatment nationwide.
- Create standards of care for autism treatment.
- Create capacity for randomized clinical trials, including studies of complex regimens that may or may not be pharmacological.
- Ensure that biological collections are open resources, and expand available resources.

- Encourage collaboration among clinical practices and medical institutions on database development and autism registries.

Roadblocks to Research

- Inadequate funding for autism research and lack of a sense of urgency given the magnitude of the emergency.
- Lack of support and standards for clinicians working in the area of biomedical interventions for autism.
- Insufficient numbers of scientists with toxicological and environmental health expertise working in the field of autism.
- Rigorous and high quality epidemiology that retrospectively tracks trends in prevalence and addresses causal factors in addition to counting.
- Restricted access by credentialed researchers to medical databases that could advance understanding of causal factors.
- Insufficient numbers of post-mortem brains for research and lack of access to existing brains for legitimate research.
- In general, an incomplete commitment to open resources, whether biological repositories or databases.
- Lack of systematic collection of exposure history data among autistic individuals and matched controls, and incomplete medical examination of ASD individuals that might detect past, persistent, or ongoing exposures.
- Lack of rigorous sub-grouping that can indicate what treatments are most likely to be effective in a given individual.
- Unwillingness by NIH and scientists to investigate environmental factors in autism, including those that relate to vaccines and vaccine components.
- Advancement of animal models that represent environmental exposures and can elucidate complex environmental factor interaction and gene-environment interaction. Incipient animal models exist but they need to be expanded.

Thank you for the opportunity to comment on the proposed changes to the IACC matrix. We hope that our observations and suggestions related to reshaping guiding principles, improving the matrix and eliminating roadblocks will assist the NIH in its important work focused on improving the health outcomes for those suffering from autism.