Comments solicited by the NIH IACC for Strategic Planning for Autism Research
(NIH Notice Number: NOT-MH-08-003)

Submitted by
SafeMinds and the National Autism Association

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Introduction

As national advocacy organizations, SafeMinds and the National Autism Association have unique perspectives regarding the manner in which autism research needs to be planned, funded, and undertaken by NIH which are based upon our personal experience as stakeholders and from our constituents. We believe the guiding principles outlined below, our list of specific research recommendations, and identification of research obstacles will accelerate the pace of research, help the most autistic individuals in the fastest way possible and prevent others from succumbing to this tragic disorder. Therefore, we request that these elements be considered during the workshop deliberations and guide the development of the strategic plan.

Founded in 2000, SafeMinds is a research and advocacy think tank. Its central mission is to raise money, fund research, produce critical analyses, and advocate for policies designed to examine and reduce the risks of adverse impacts such as autism from mercury and other environmental toxins. NAA is a national membership organization founded in 2004. Its mission is to support families affected by autism through research, education, training, services, and advocacy. Both at the grassroots and through their leadership, both Safeminds and NAA were instrumental in obtaining passage of the CAA, including its mandates for an enhanced IACC, strategic planning, and subject-oriented research funding, including an expanded focus on environmental triggers (especially vaccines) and biomedical treatments.

Guiding Principles for Autism Research at NIH

1. Acknowledge autism as a national emergency

In reviewing the previous autism research matrix developed in 2004 by NIH, we sensed a lack of urgency in addressing the growing epidemic of autism. In 2007, the CDC announced that the reported prevalence of autism spectrum disorders had risen to alarming levels, affecting approximately 1 in 150 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 epidemic. The direct and indirect costs

to society in general, government programs, and those affected are massive and growing with every new case. The effectiveness of treatments appears to be inversely related to age. These two facets of the ASD epidemic must drive sufficient investment in determining cause, treatment, and prevention with all deliberate speed.

1.5 Recognize that ASD is in fact an epidemic and not simply a relabeling of disorders that have a consistent incidence throughout history

While the number of new cases may to some small degree include cases not previously labeled as ASD or relabeled from other conditions, the CDC-reported data plus anecdotal observations unquestionably demonstrate an epidemic of very recent origin. The burden of proof must be placed on those who would deny such an epidemic to demonstrate with verifiable data (as opposed to consclusory assertions, wishful thinking, and rank speculation) any falsification of the epidemic revealed by the published data. The reality of the ASD epidemic is a threshold issue that drives many downstream decisions. Since there cannot be a gene-only epidemic, acceptance that the epidemic is real means that there must be environmental triggers, thus justifying an intensified search for such causes, appropriate treatments, and, obviously, their elimination as the key to reducing or eliminating new cases. Until proven otherwise, policy must be based upon the reality of the epidemic.

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 heritability 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 NIH in 2007 as an understudied area that was given insufficient attention in the first iteration of the NIH autism research matrix. More recently, the Institute of Medicine convened a workshop in April, 2007 *"Autism and the Environment: Challenges and Opportunities for Research"* which contains an extensive and detailed index of scientific opportunities for ASD research. 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. At least of equal importance as a policy matter, underinvestment in research relating to environmental factors frustrates the policy goal of eliminating new cases. The research recommendations outlined in the published workshop proceedings (summarized in an appendix) available at http://www.iom.edu/?id=47795 must be incorporated into all areas of NIH research - biology, risk factors, diagnosis, and treatment.

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 reduce and eventually eliminate new cases, 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 paradigm prevalent in NIH funded research is 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. Current treatment strategies are targeted at ameliorating symptoms rather than understanding the underlying biology and pathology that is responsible for these symptoms. Funding driven by this outmoded paradigm does little to reduce the morbidity associated with autism. But for the small number of ASD diagnoses (Rett, Fragile X, etc.) truly determined by a single gene mutation, 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 both preventable and treatable.

5. Reclassify autism as a multi-organ disease of the whole body rather than as simply a psychiatric syndrome

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 immediately 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. Broaden disciplines conducting autism research

P.L. 109-416, The Combating Autism Act, signed into law in December of 2006, states that *"NIH shall expand, intensify, and coordinate activities 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."* Therefore, broadening the scope of autism research into these areas that have in the past received little attention (neuroimmunology, gastroenterology, endocrinology and toxicology) and expanding the focus of research into the identification of co-morbid disease states associated with autism will serve to aid in not only the identification of the biological underpinnings of autism spectrum disorders but also effective treatment strategies.

7. NIH to drive research agenda vs. researchers and require accountability

An area that is critical to advancing the science related to autism spectrum disorders at NIH is the way the research is developed and studies are implemented. The current

research agenda is driven predominately by investigator-initiated proposals, i.e. the NIH funds a research proposal and then retrofits the project into the research matrix. This is best evidenced by the recent review of the NIH autism research matrix where investigations into the characterization and screening for autism were flush with research, whereas areas of research into identifying specific treatments for those suffering with autism was severely lacking. Therefore, research goals and activities identified and adopted in the strategic plan would be more likely implemented if NIH: (a) included these activities as items to be scored when reviewing grant proposals; (b) announced them as program announcements; and (c) required Autism Centers of Excellence to address them as part of their center designation and to consider such project proposals when scoring center proposals. Funding must be driven by and evaluated against the plan rather than essentially random funded projects being cobbled together and mislabeled as a "plan." Funded projects should be compared at frequent intervals to the strategic plan – quarterly through the IACC or an Autism Advisory Board, and not just annually through a report to Congress. The comparison should identify whether the objectives of the plan are in fact being met; adjustments should be made accordingly.

8. Create a formal mechanism for ongoing public-private research agenda
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. Congress specifically tasked NIH with increasing opportunities for public participation in decisions relating to ASD in the CAA's reporting requirements. 42 U.S.C. 280i-2(b)(4).

9. Create a dynamic strategic planning process
Knowledge on autism is changing rapidly. The strategic plan should be modified as needed to reflect the most current thinking. A process should be put into place by NIH for review of the plan with the aim to make changes on at least an annual basis. Establishing an Autism Advisory Board that will take on continual oversight of the strategic plan and report to the IACC on its implementation and ongoing modification would be a positive step.

Specific Areas of Research

RISK FACTORS

- 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. Special attention to detoxification pathways, including glutathione and cysteine levels, is warranted.
- Identify genetic vulnerabilities to environmental exposures, for example, from the environmental genome project that would be of particular relevance to autism.

  - Review toxicological literature and databases for susceptibility gene candidates and potential biomarkers.
  - Toxicologically-relevant susceptibility genes should be screened among ASD subgroups.
- Pre- and post natal exposure history should be assessed as part of the autism diagnosis and evaluation process. Exposure and body burden assessments should form a key component of subtyping and phenotyping efforts.
  - Exposure/body burden can be extended to post-mortem brain studies and other biosamples, for example, determining the levels of mercury in autism brains and other organs.
- Research is showing that cumulative and synergistic effects of multiple exposures, whether of toxicants or microbes, can have a far greater impact than a single exposure. Exposure and body burden assessments should factor in "multiple hits".
- Exposures may be directly measured or indirectly through intermediate biomarkers. Techniques should be developed to identify these biomarkers and their validity to autism. An example is altered porphyrin profiles and mercury exposure. Many markers already exist in microbiology and immunology but need to be applied to autism. Transcriptomics, proteomics, and animal models should be used to discover markers for exposure to heavy metals, PCBs, PBDEs, and other plausible candidates identified biologically or epidemiologically.
- Conduct a prevalence study comparing rates of autism and ASDs among school age children age 8 to 18 to determine if the rate of autism is really rising and not just due to diagnostic changes.
  - Conduct a prevalence study among adults, using current diagnostic criteria, to determine if the 1 in 150 rate is recent or 'has always been there and just not noticed'.
  - Determine if the phenotype of ASD has changed over time, for example, the rate of mental retardation, the frequency of co-morbid conditions, or the proportion of classic autism, PDD-NOS, and Asperger's.
- Conduct studies of the rate and severity of ASDs by geography, and link these geographic areas to databases of pollutants.
- Add exposure history and body burden components to the baby sibling longitudinal study; add extensive autism components to large environmental epidemiology studies like the National Children's Study or the Norway Longitudinal Study.
  - Identify differences in exposure between siblings developing autism and those developing normally, and identify any differences in autism subtype based on differences in exposures.
  - Investigate exposure histories among disconcordant MZ twins; establish a twin registry.
- Capture pre-natal exposures – prospectively or retrospectively - via medical records, maternal surveys, and cord blood examinations.
- Conduct cell culture studies among autistic and control lymphocytes after exposure to thimerosal and other relevant chemicals to which autistic children are exposed. 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, small particle airborne mercury, as well as aluminum and pesticides. Viruses should include measles and chicken pox.
- Pro-actively encourage vaccine research. The legislative history of the CAA specifically calls upon NIH to perform research related to vaccines and their preservatives as a potential cause of ASD. This research is essential because it will either rule out vaccines as a cause or implicate them so that immediate corrective measures can be taken. To our knowledge, no research presently being undertaken by CDC or NIH fulfills this mandate. Indeed, CDC (perhaps predictably) seems to have designed all its presently sponsored data gathering. Apparently, the newly undertaken comprehensive child health study will not include a comparison of the health outcomes of vaccinated versus unvaccinated children. Such a comparison must be undertaken immediately to assess the effect of vaccines on ASD and other related disorders.
    - Implement a study of the rate and severity of ASD outcomes in vaccinated compared to unvaccinated populations or to alternatively vaccinated (later and fewer vaccines) populations.
    - Ensure that vaccination history is included as part of any exposure assessment.
- Encourage collaboration among clinical practices and medical institutions on database development and autism registries.

<u>TREATMENT</u>

- 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.
- Acknowledge that treatments may be educational, therapeutic, or biomedical, and that the latter might include nutritional, dietary, and detoxification approaches as well as pharmaceutical ones.
    - If toxicants and microbes play a role in onset of autism symptoms, then treatment efforts should extend to removing these substances from the child's environment, for example, through remediation or withholding of health products that contain offending substances.
- Treatment databases should be established that can link effectiveness of a given regimen, a given outcome (e.g. speech and anxiety), and patient information such as phenotype, genotype and exposure history. Such information can be used to understand pathways and mechanisms which in turn can be used to develop more effective interventions

- Conduct studies on effectiveness among meaningful subgroups, recognizing that certain interventions may work among some but not others and that complex, combined interventions and not single interventions may work best. Devise clinical trial methodologies that encompass complex regimens
- Enhance characterization of medical conditions 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.
    - Conduct a specific study on recovery, to substantiate this phenomenon, determine its frequency, and identify the characteristics that might predict a higher likelihood of occurence.
- Look for biomarkers relevant to plasticity (including brain metabolism, brain neurophysiology, and systemic metabolism as well as behavior) that could track treatment response

<u>BIOLOGY</u>

- Neuroinflammation and immune system effects on brain development should be added areas of investigation. 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.
- 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.
- 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.
- 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.
- 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.
- Study not only brain regional changes but pervasive volumetric changes
- 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.

- 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.
- Develop animal models using exposures relevant to the ASD population based on exposure history, factoring in susceptibility genes as appropriate. (See Risk Factors)
- 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.
- Conduct DNA methylation and epigenetics studies among autistic children.

DIAGNOSIS

- 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.
- Track severity of symptoms and onset of co-morbid conditions with prior exposures.
- 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.

Roadblocks to Innovative 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.
    - Invite NCAM to the IACC.
- 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; lack of banking of other tissue and biological samples given autism as a multi-organ disease.
- 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.
- Commitment to developing technologies for comprehensive body burden and exposure history assessments, for example, methods for rapid screening of multiple exposures using non-invasive tests.
- Study sections that do not have the requisite expertise for the type of research that needs to done.

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Thank you for the opportunity to suggest recommendations for NIH's strategic plan for autism research. We hope that our observations and suggestions related to reshaping guiding principles, specific research recommendations, and elimination of roadblocks will assist the NIH in its important work focused on improving the health outcomes for those suffering from autism.