**Conference Call IACC Scientific Workshop Panel Three**
Wednesday, September 16, 2009
Strategic Plan Question III: *"What Caused This to Happen and Can It Be Prevented?"*

**Call Participants:** Dr. Story Landis (Co-Chair), Mr. Lee Grossman (Co-Chair), Dr. Robin Hansen, Dr. Susan Swedo, Dr. Craig Newschaffer, Dr. Matthew State, Dr. Lars Perner, and Mr. Jeffrey Sell: Dr. Della Hann and Dr. Susan Daniels (OARC Staff)

**Summary:**

Dr. Landis welcomed the panelists addressing Question III of the Strategic Plan: "What Caused This to Happen and Can It Be Prevented?" and described their goal. The panelists are asked to identify gaps, opportunities, and research priorities around risk factor and prevention research, to be taken into consideration during the update to the IACC Strategic Plan. These recommendations will be presented in a 30-minute Powerpoint presentation during the Scientific Workshop held September 30 – October 1.

The panelist introduced themselves to the group and asked for an update on NIH funding for ASD research in FY 2009. Dr. Hann said that information about grants supported by the American Recovery and Reinvestment Act (ARRA) would be presented during the Scientific Workshop. NIMH, in collaboration with four participating NIH Institutes, has allocated an additional $60 million in Recovery Act funds to solicit applications for research relevant to understanding the variation in causes, symptoms, and characteristics of ASD. However, information about total NIH funding for ASD research in FY 2009 will not be available until a later date.

Dr. Landis said that she was confident that the research being funded through ARRA would include a significant amount of support for genetic research and gene-environment interaction studies. The panel will be better able to assess how well the goals of the 2009 Strategic Plan are being met after receiving information about ARRA funding, she said. The panel agreed that without the most recent funding information, the best way to proceed was to review progress more generally and identify gaps and strengths of the current plan.

Mr. Grossman said that he felt that the Question III objectives needed to be made more immediately relevant to people with ASD and their families by identifying environmental risk factors and implementing early interventions for people at risk for these environmental exposures. Dr. Hansen stated the importance of identifying the multiple pathways and differing developmental trajectories that lead to ASD. Due to the heterogeneous nature of ASD, careful phenotyping is important and to this end, researchers must look beyond behavioral indicators and investigate biomarkers, neural networks, and processing markers associated with ASD, she said.

Dr. State said that in recent genetic research similar genetic abnormalities (or genetic lesions) have been implicated in a range of psychiatric disorders, in addition to ASD. People with these rare recurrent genetic abnormalities, such as the deletions and duplications seen at 16p11, lead to a diverse array of

outcomes: some people with the variant develop ASD, while others experience developmental delays without social disability. Other people may develop a range of neuropsychiatric disorders, while some may develop typically. Because similar genetic lesions lead to a range of outcomes, Dr. State said that it may be valuable to collect a group of people with the genetic abnormality and study them longitudinally, rather than to rely on a DSM-IV diagnosis.

Dr. Hansen recommended looking at individual markers of susceptibility to identify separate phenotypes. By stratifying subgroups, researchers may be better able to identify mechanisms and preventative measures that may only be applicable to certain subgroups. Dr. Perner stated the importance of addressing aggregation bias in ASD research, which occurs when disparate subgroups are combined into one set, obscuring relevant results for a particular subset. He recommended reexamining the results of past studies of vulnerability for aggregation bias.

Dr. Swedo said that the Autism Treatment Networks (ATN) and Autism Centers of Excellence (ACE) networks which feed data into the National Database for Autism Research (NDAR) represent opportunities for in-depth phenotype research. She said that macular degeneration was a good model for a disease where genetic studies drove the identification of risk factors.

Dr. Landis stated that while genetic research has been given significant funding, ASD research using phenotyping, dysmorphology, and family history has not been explored as extensively. The group discussed the numerous ways phenotype could be measured and discussed the phenotyping study being conducted by the Simons foundation. Dr. State recommended moving away from clinically-ascertained samples in favor of epidemiologically-acquired ones, in order to create a more realistic picture of common genetic variation and outcomes. Dr. Swedo said that, in practice, the samples from the two sources were the same because of overlapping participants.

Dr. Landis said that the panelists should be sensitive to the ideas of a group of people at the most functional end of spectrum when discussing prevention research. There is a contingent of people with ASD who feel that prevention of ASD is not necessary or appropriate because people with ASD represent a natural neurodiversity within the population that should be respected and preserved. Instead, they feel that risk factor research should focus on maximizing the potential of every person with ASD in order to improve his or her quality of life. The panelists suggested focusing on prevention of disability associated with ASD, and on identification of protective and resilient factors as opportunities in the plan.

The panelists discussed expanding the common measures taken in ASD studies to aid phenotype research and recommended decreasing the amount of time between NDAR data submission and the time when it is available for analysis by others. (Currently, researchers funded by NIH are required to contribute data, including a set of common measures, to NDAR.)

The panelists then discussed gaps and opportunities for environmental research. Dr. Landis reported that NINDS was currently funding a long-term study, not reflected in the panel's funding information, on the effects of ultrasound on fetal neuronal migration in non-human primates. Mr. Grossman said that the ASD community felt that there were many gaps in environmental risk factors research. Dr. Swedo

pointed out the difficulty in identifying which environmental factors to study because of the thousands of potential environmental toxicants, and viral and bacterial agents. Dr. Hansen recommended undertaking long-term prospective studies of pregnant mothers who have previously given birth to a child with ASD, in order to study how genetic susceptibility interacts with environmental risk factors.

Dr. Swedo spoke about the current studies of baby siblings in the United States, Norway, and Denmark. She said that the National Children's Study represented an opportunity to prospectively study environmental risk factors, but that it would be difficult to study something so vast without specific hypotheses. Dr. Landis said that the biological samples taken from the Norway studies could be analyzed to try to identify biological risk factors.

Dr. Landis mentioned that one study funded through ARRA could have broad implications for ASD research. The study will investigate proteomics in cerebrospinal fluid (CSF). The diseases targeted in the study do not include ASD, but the research methodology could be applied to ASD research. Dr. Hansen said that the inability to collect CSF for comparative material from typically-developing children was a huge obstacle to that line of research. The panelists discussed the possibility that biomaterial from induced pluripotent stem cells (iPSC) could be derived from blood and hair follicles in the future.

Dr. State discussed the need for an easily accessible diagnostic instrument to collect the large sample needed for an effective epidemiologic study.

Mr. Sell stated that many members of the public still called for a comparative study of vaccinated and unvaccinated children to investigate health outcomes. Dr. Landis noted that an increasing number of children were going unvaccinated or receiving alternate vaccination schedules, increasing their risk of preventable childhood diseases. Mr. Sell indentified the need to ensure and optimize vaccine safety, identify people at higher risk of vaccine injury, and prevent unnecessary overexposure in all U.S. infants. Dr. Landis recommended focusing a study of vaccinated/unvaccinated children to measure a range of health outcomes, including preventable childhood diseases. Mr. Sell said that studies investigating mitochondrial disorders and gastrointestinal involvement should also be undertaken and that these issues were not receiving adequate funding. Dr. Landis reported that NINDS was funding an ARRA grant on mitochondrial disorders, although the study was not specific to ASD.

Dr. Swedo said that designing a vaccinated/unvaccinated study would be problematic because of the ethical issues surrounding the random assignment of children to an unvaccinated group. Conducting an observational study of people who choose not to vaccinate their children creates selection bias, because this population varies in unknown ways. Dr. Hansen recommended looking at real-time behavioral and immunologic responses to vaccination in children with ASD. These studies could help to identify the small subgroup of children with ASD who could potentially be injured by vaccines, a group that would be lost in a large-scale epidemiologic study.

Dr. Newschaffer discussed the benefits of light phenotyping for epidemiologic studies, but cautioned not to disregard comprehensive phenotyping in order to identify etiologically distinct subtypes. He discussed selection issues with a vaccinated/unvaccinated study and the need for large numbers to conduct a

study with confidence. Dr. Newschaffer said that studies of immune and symptom response in cohorts of high-risk siblings would be the best way to identify highly susceptible subgroups. In addition, post-vaccine immune response in all children should be studied.

Dr. Landis asked if studying communities with a large population opting out of vaccinations would reduce selection bias. Dr. Swedo said she felt that this regional selection would actually increase bias. The panel discussed amplifying the current baby siblings effort to increase the power of the study and its result reliability. Dr. State recommended enlisting the help of a broader group of researchers to develop diagnostic assessments that consider social traits and overall social competence. Dr. Newschaffer called for research to define and explore other markers of quantitative phenotypes and discussed the danger of misclassification as a result of using quick categorical screeners. Dr. State emphasized the need to communicate the results of risk factor research in a responsible manner and to underscore the limitations of early studies to the public.

Dr. Landis said that she would develop a draft slide presentation incorporating the points discussed by the panel during the call and asked members to continue to think about gaps, opportunities, and priorities for the next call on Wednesday, September 23rd from 11:00 a.m. to 1:00 p.m.

**Action Items:**

- Refine gaps and opportunities
- Identify new opportunities
- Draft suggestions for the next call via e-mail
- First draft of slides to be sent to the panelists by Dr. Landis