

**Summary of IACC Strategic Plan Working Group 3 – Conference Call #3
December 7, 2016; 11:30 am-1:00 pm ET**

Welcome and Introductions

Working Group Members in Attendance:

David Amaral – Co-Chair

Cindy Lawler – Co-Chair

Raphael Bernier

Laurie Schieve

Dani Fallin

Stephan Sanders

Irva Hertz-Picciotto

Elaine Hsiao

Craig Newschaffer

Alycia Halladay

Working Group Members Absent:

Ruth Etzel

Alison Singer

Evan Eichler

Daniel Geschwind

Elise Robinson

Joan Scott

Discussion of Chapter Outline

- A working group member noted that the concept of genomic architecture, including how multiple genetic risk factors combine to result in phenotype, should be included in the section on genetic risk factors.
- Working group members also requested that sex differences be added to the outline under the section on genetic risk factors.
- There was general agreement that functional genomic studies would fit best under the third topic in the outline, which is on gene-environment linkages.
- A working group member asked that the outline be simplified to reflect the importance of genomic studies, which will include studies undertaking DNA sequencing or arrays.
- Working group members pointed out that although improved tools for examining the exposome are needed, it is also important to advance exposure science more generally, and apply new methods in exposure science to autism studies specifically.
- Although working group members agreed that studies of exposures individually and in combination were both important, there was interest in perhaps highlighting the benefits of leveraging an “omics” approach to examining exposure.
- Challenges related to epidemiological studies of risk factors include the difficulties of obtaining sufficient sample sizes for identifying subgroups (sex, ASD, and genetic), as well as the issue of how to differentiate risk factors from other correlates (use of anti-depression medications versus depression, for example).

- Working group members thought it would be important in the section on environmental risk factors to include studies of biomarkers of exposure, which can serve as surrogates for detecting primary environmental factors. The identification and utilization of these kinds of biomarkers are useful for developing exposure metrics (appropriate to discuss under environmental risk studies), even if they are not directly related to the pathway or mechanism of action. In addition, studies using biomarkers of exposure to help with understanding mechanisms of environment should be described under the section on gene-environment studies.
- Public health implications and communication, and the prospect of implementing exposure testing in comparison to genomic testing, should be included in the section of the chapter on environmental risk. Working group members agreed that these issues should be considered when carrying out relevant studies, even if exposure testing is very aspirational at this point.
- The application of “omics” technologies is needed to identify and interpret genetic and environmental risk factors.
- Working group members felt that the importance of working within the context of diverse, representative populations is critical to both understanding the contributions of genetic and environmental risk factors.
- After a discussion about the appropriate placement of different types of “omics” biology within the outline, it was decided that the first section would address the genome, the second section would address the exposome, and the third topic would address downstream systems, such as the transcriptome, proteome, metabolome, and epigenome.
- The working group acknowledged that large genetic studies have not done a sufficient job incorporating environmental data and vice versa; since both are important, there was interest in ensuring the Strategic Plan emphasizes that there need to be more efforts to study genetic and environmental factors together.
- The third section of the chapter, touching on linkages between genes and environment, may include mention of some of the connections between the mechanistic studies of risk factors and understanding the biology of ASD (which is the main focus of Strategic Plan Question 2).
- Working group members agreed to include studies of the integrated contributions of disparate systems (immune, endocrine, microbiome) to ASD risk within with the broader topic of genetic and environmental linkages.
- To provide more detail to the outline, it was suggested that the term “gene-environment studies” be fleshed out to emphasize the need to forge real, meaningful linkages between existing genetic and environmental studies, and that funders should incentivize true gene-environment collaborations.
- The term “animal models” should be changed in the outline to “model systems,” as this will allow for the inclusion of induced pluripotent stem cells (iPSCs) in addition to animal models.
- Working group members expressed a desire to somehow recognize the positive aspects of ASD traits. There was agreement that a discussion of these aspects of ASD should be included in the Chapter’s introduction. The outline will be edited to reflect this addition.

Discussion of Proposed Strategic Plan Objectives for Question 3

Areas highlighted on previous calls for possible consideration:

1. Strengthen understanding of genetic risk factors for ASD across a large population representing the full diversity and heterogeneity of those with ASD.

2. Understand the effects on ASD risk of individual and multiple exposures in both the pre- and postnatal environment over time, enabling development of strategies for reducing severe disability and comorbidities in ASD.

3. Expand knowledge about the functional linkages and complex relationships between environmental risk factors and specific biological mechanisms that may be involved in ASD, such as altered gene expression or immune pathways.

- Working group members noted that – as with the goal of ASD environmental studies – the ultimate goal of ASD genetic studies is to reduce disabilities and comorbidities; a phrase reflecting this should be added to the objective about genetics. A suggested revised version of the first objective is:

1. Strengthen understanding of genetic risk factors for ASD across a large population representing the full diversity and heterogeneity of those with ASD, enabling development of strategies for reducing disability and comorbidities in ASD.

- Working group members requested that the word “severe” be removed from the second proposed objective. A suggested revised version of the second objective is:

2. Understand the effects on ASD risk of individual and multiple exposures in both the pre- and postnatal environment over time, enabling development of strategies for reducing disability and comorbidities in ASD.

- There was interest in revising the third proposed objective so that it would reflect the need to understand how genetic and environmental factors act together through biological pathways. A suggested revised version of the third objective is:

3. Expand knowledge about how multiple environmental and genetic risk factors act through specific biological mechanisms that influence ASD phenotypes.

Discussion of Change to Aspirational Goal

Causes of ASD will be discovered that inform **diagnosis, **prognosis**, and **treatments** and lead to **prevention/preemption of the challenges and disabilities** ~~(severe disability and comorbidities in)~~ of ASD.**

- Working group members proposed that the word “diagnosis” be inserted after the word “inform.”
 - There was also discussion about whether the word “challenges” is too broad and should be changed to a more specific word.
 - Does the group want to consider any other changes to the aspirational goal?
- Working group members did not want the word “severe” added to the aspirational goal.
 - It was decided that the word “comorbidities” was unnecessary to add to the goal because the word “challenges” already includes this concept.
 - The revised draft version of the aspirational goal is:

Causes of ASD will be discovered that inform diagnosis, prognosis, and treatments and lead to prevention and preemption of the challenges and disabilities of ASD.

Title: What Caused This to Happen and Can It Be Prevented?

- Does the group want to consider making any changes to the Chapter's title? (On the last call, the group did not suggest changes.)
- There was interest in changing the Chapter title to align more closely with the current discussion by focusing on the concept of reducing or preventing the challenges and disabilities associated with ASD, rather than sounding as if the goal is to prevent ASD entirely.
- After a discussion of proposed modifications, a draft revised version of the title was proposed, and will be open for additional input from the Working Group and full IACC:

Title: What Causes ASD and Can Disabling Aspects of ASD Be Prevented or Preempted?

Wrap Up and Next Steps

- Dr. Daniels will be in touch with the Co-Chairs to finalize the outline, make the discussed revisions, and devise a plan for dividing the writing of the Chapter among working group members.
- The goal will be to present the draft chapter and/or objectives for discussion with the IACC at the next full committee meeting scheduled for January 13, 2017.

Adjourn