Summary of Working Group 3 – Conference Call #2
October 12, 2016; 2:00pm EDT

Welcome and Introductions

Working Group Members in Attendance:
David Amaral – Co-Chair
Cindy Lawler – Co-Chair
Ruth Etzel
Raphael Bernier
Alycia Halladay
Irva Hertz-Picciotto
Elaine Hsiao
Craig Newschaffer
Joan Scott

Working Group Members Absent:
Alison Singer
Evan Eichler
Dani Fallin
Daniel Geschwind
Elise Robinson
Stephan Sanders

Follow Up from Call #1

In the first conference call, concerns were raised regarding the projects included in the Gene-Environment subcategory. After the call, OARC provided the working group members with a detailed definition of the Gene-Environment subcategory as well as the list of project abstracts included in the 2013 Gene-Environment subcategory. It was clarified that the definition of the Gene-Environment subcategory is not limited to gene-environment interaction studies, but includes projects examining both genetic and environmental factors. Also, the definition of "environmental factors" is broad and is not limited to chemical exposures. Given the small size of the portfolio, grouping projects that address factors related broadly to both environmental and genetic risk factors together is more helpful than creation of a large number of narrow, finely differentiated subcategories.

Discussion of Public Comments received through Request for Information

- Working group members mentioned the variety of perspectives on pursuing risk factors to prevent ASD. Self-advocates often emphasized that finding a prevention should not be a research priority, while family members of individuals that have more severe medical comorbidities differed in opinion. Members agreed the focus should not be on preventing ASD but on reducing the risk of severe medical comorbidities and disability associated with ASD.
- The working group members agreed with public comments on continuing to build the research on the microbiome as well as epigenetics.

Discussion of Research Progress and Policy Issues

1. What are the most notable areas of recent progress in research on risk factors for ASD?

- In recent years there have been significant advances in microbiome research associated with ASD. Both animal studies and human studies on the microbiome have added to the field of research. While the research is still elementary, research on the microbiome and its possible association with ASD should continue to be a priority, as well as looking at the long-term changes in the microbiome.
- There have been advances in the identification of risk genes and genetic events which have led to increased confidence in determining the number of genes associated with ASD. These advances have allowed us to think more clearly about genetically defined subgroups, gene x environment interactions, and etiologic pathways.
- There has been progress in understanding females with autism. While this area often falls under Question 2 (Biology), there have been hypotheses surrounding protective genes and sex-dependent factors of exposures.
- The environmental exposure field has seen progress in epigenetics, environmental influences on the microbiome (ex: c-section), and adrenal studies. However, while there has been more research in these areas it does not mean there has been equal advances in outcomes from the environmental exposure field. As this research field progresses, it would be important to include techniques to assess the overlap of exposures of interest and outcomes of interest. An approach that was highlighted was higher dimensional assessment.

2. What new opportunities have emerged?
    - While research has focused on the prenatal environment, it is important to also keep in mind the early life course factors that could be playing a role in the postnatal environment. Often, exposures do not happen at one point in time, so it is necessary to assess ongoing exposures as well.
    - We are at a point in the environmental research field that we can look at environmental factors as mechanistic by linking the environment to changing gene expression or immune pathways instead of just linking environment to outcome and ignoring other factors. Researchers are in a position to take on more complex issues regarding a combination of factors and promote new methods and approaches.
    - Animal models have seen major developments; therefore, it would be beneficial to have the field start interrogating some of these more complex areas since animal models are quicker to assess than human models.

3. What are the most significant barriers to progress in this field?
    - Working group members cited several barriers to performing quality environmental epidemiology studies:
        - Difficulty obtaining a sufficiently large sample size
        - Exposure assessment in the prenatal period and for biomarkers
        - Gathering biospecimens during the prenatal period
        - Difficulty obtaining a female ASD subpopulation for substantial analyses
        - A lack of tools to perform uncharted analysis; need more usable tools
    - While the genetics field has done a great job gaining large genomic datasets, there are challenges in trying to find ways to incorporate environmental exposure factors in these projects. There is a need to capitalize on collecting exposures data and incorporate it into large genetic collections. There are opportunities for geneticists to standardize the collection information on environmental factors through self-report or blood; if this was made a priority it would help advance progress in the field.

4. What are the most pressing needs or evidence gaps that can be addressed through research?
    - Some working group members mentioned research on the treatment and associations of social impairment would be beneficial to understand because social impairments can be debilitating.
    - Working group members discussed that researchers need to keep in mind that behavioral impairments should be seen as continuous traits as opposed to dichotomous categories. There is a spectrum of impairment that relates to a spectrum of outcomes for individuals with ASD.
    - While the topic of addressing common variation in genetics came up, working group members agreed the priority at the moment is to fully understand rare variant interactions before addressing common variation. For example, CHD8 is being looked at in human and animal models. It is important to understand and provide prototypes as to what leads to autism and focus on proximal kinds of progress.
    - Based on the mixed findings on folic acid supplementation it is important to prioritize research on this topic.

5. Is there new knowledge about risk factors that is ready to be translated to clinical practice?
    - Within several large studies there have been robust findings on diabetes and autism. More recently, there have been smaller studies looking at the relationship between diabetes and autism. While more evidence is still needed, blood sugar control in pregnancy may be a potential public health recommendation for prevention of ASD.

6. Is there any new research evidence that should be influencing policy?
    - The NIH has recently launched a seven-year initiative called the Environmental influences on Child Health Outcomes (ECHO) program. Working group members emphasized this as an important opportunity to address the dimensions of ASD in a large population study which could provide information on how risk factors relate to outcomes of interest.

7. Have there been any recent changes with regard to how risk is communicated to members of the autism community, and are any changes needed?
    - Working group members discussed how researchers should be translating findings into public health messages that provide more benefits than harm. It is important that researchers do not add to the confusion but craft the right messages for the public.
    - The difficulty of communicating genetic risks to a family was mentioned, however working group members that were present on the call agreed they needed absent working group members who are experts in this area to comment further.

8. What are the research workforce needs in this area?
    - Working group members agreed there is an inadequate workforce across all ASD research, however there were several approaches mentioned to enhance the needs of the workforce for risk factors of ASD, these include:
        - New analytic techniques and analysis of new strategies to identify DNA and the exposome
        - New investigators that are pushed to investigate multidisciplinary approaches
        - Cross-disciplinary opportunities
        - Training in gene x environment interaction for trainees and early career investigators

9. What are the provider workforce needs in this area?

- There is a need for better connections between clinicians, epidemiologists, and researchers.

Discussion of Aspirational Goal

Based on the state of the field, is the **Question 3 Aspirational Goal** still appropriate?
Causes of ASD will be discovered that inform prognosis and treatments and lead to prevention/preemption of the challenges and disabilities of ASD.

- A working group member thought the word "challenges" might be too broad and suggested the members think of more specific wording.
- Also, it was mentioned to add the word diagnosis after inform - so that it reads, "…inform **diagnosis**, prognosis, and treatments…"
- Working group members thought they might need more time to think about this and would address it further on the next call.

Is the title of the chapter still appropriate?
"What Caused This to Happen and Can It Be Prevented?"

- Some working group members voiced they believed the title of the chapter was appropriate, emphasizing whether ASD could be prevented, not whether it should be prevented. The title will also be discussed on the next call to allow the working group members time to think if any changes are necessary.

Wrap up and preview of next call

- On the next call the working group will discuss new objectives for Question 3 that capture the key ways the field can move forward in identifying risk factors.
- In the meantime, the Chairs of the working group will start to develop an outline for the chapter, and solicit help from working members to begin drafting sections.