Summary of IACC Strategic Plan Working Group for Question 2 – Conference Call #3
November 28, 2016; 11:00 am-12:30 pm EST

Welcome and Introductions

Working Group Members in Attendance:
Walter Koroshetz – Co-Chair
Louis Reichardt – Co-Chair
James Battey
James McPartland
Christine Nordhal
Guoping Feng
Katarzyna Chawarska
Nicole Williams
Graeme Davis
Shafali Jeste
Eric Klann

Working Group Members Absent:
David Amaral
Kevin Pelphrey
Heather Hazlett
Elizabeth Redcay
Flora Vaccarino
Robert Ring

Discussion of Chapter Outline

- Working group members noted that the chapter outline should reflect advances in understanding the basic molecular components of pathways and the underlying biology of genetic conditions.
- When studying the underlying biology of factors involved in ASD, including brain imaging studies, a key challenge is the ability to distinguish between correlation and causation. More studies should be done using both animal models and large human cohorts, as early as possible in development, to begin addressing this problem.
- There is a need to address the challenge of heterogeneity in ASD, especially in imaging studies. This could be helped by obtaining sufficiently large sample sizes and more representative samples. Working group members also thought this problem could be addressed by leveraging methods that are applicable across a range of ages and intellectual abilities (e.g. eye tracking).
- Working group members acknowledged that studies of monogenic disorders have been enlightening, because they have helped enable the understanding of fundamental mechanisms, but heterogeneity also remains a challenge in understanding these syndromes.
- There was recognition that studies need to do a better job linking genetics to heterogeneity; there is a need to understand the interactions of ASD-associated genetic variants within the context of each individual's complete genome. Working group members also cited a need to link the impact of genetic mutations on brain function and circuitry.

- Working group members pointed to the importance and value of detailed studies on postmortem tissue, as well as on induced pluripotent stem (iPS) cells.
- New methods like CRISPR hold promise for enabling future studies that can tease out the polygenic aspects of ASD.
- There is a need for studies looking at early development, including in utero, and looking for adaptive brain changes in response to developmental disturbance.
- More should be done to leverage knowledge about cell types in neurotypical brains and apply that knowledge to ASD, especially as it concerns connections between cells (i.e. at the synapse level), and chromatin remodeling.
- Working group members agreed that more molecular studies are needed to examine the effect of XX and XY chromosomes on gender differences in ASD.
- Several working group members noted that there is a need for large cohort studies and infrastructure to develop methods necessary to collect data in a systematic and consistent way; this is important for a range of study types, including genetic, imaging, behavioral, and environmental factor studies. This also ties into the importance of reproducibility and ensuring that successful, small pilot studies are replicated in large cohorts.
- Many studies on environmental factors have been limited by insufficient sample sizes. Studies on environmental influences should not only focus on the external environment but also the prenatal environment of the womb.
- Working group members also noted that there should be a move toward longitudinal studies as opposed to cross-sectional studies. Scientists should leverage the variety of existing animal models, including nonhuman primates, rats, and fish.
- Other needs identified by the working group included:
    - methods to target therapeutics specifically
    - inclusion of individuals in ASD in research studies,
    - ability to track quality of life in individuals with ASD,
    - replicability of studies,
    - support for collaborative team science,
    - strategies for building the workforce,
    - availability of brain tissue,
    - importance of incentivizing individuals with ASD to participate in research efforts, and making participation of value to individuals.

Discussion of Proposed Strategic Plan Objectives for Question 2

Areas highlighted on previous calls for possible consideration:

1. Undertake studies utilizing phenotypic and genetic data to examine the biological basis of ASD, including in systems biology and developmental contexts.

2. Understand the underlying biology of co-occurring conditions in ASD, including the unique aspects of these conditions in ASD, to identify future avenues for treatment.

3. Support integration of ASD research across the continuum of science through the formation of collaborative research teams and the involvement of individuals on the autism spectrum.

- The working group considered organizing the three objectives according to three levels of scale: cell, circuits, and organisms. Another suggestion was to have each objective represent a different trajectory (rather than category) and span from the cellular level to the human phenotype. However, because these ideas are interconnected, some members mentioned potential challenges this kind of organization may present when objectives are used for coding projects.
- There was a suggestion to include both genetic (including polygenic) and non-genetic risk data into the wording of the first objective.
- Working group members thought one of the objectives should emphasize longitudinal studies, including animal studies and studies in humans.
- At the end of the discussion about objectives, there was general agreement by the working group that the objectives should be organized into the following three key topics:
    - 1) biologic basis of systems, circuits, and cellular dysfunction in ASD
    - 2) understanding co-occurring conditions in ASD
    - 3) longitudinal studies in both animals and humans, as well as studies on subtypes in ASD
- The working group agreed to continue developing these three ideas over email.

Discussion of Change to Aspirational Goal:

Discover how ASD affects development, which will lead to targeted and personalized interventions.

- On the last call, the group suggested further clarification of the word "development" is needed.
- An initial proposed draft of the new aspirational goal is:

Discover how alterations in brain development and brain function lead to ASD in order to enable the development of effective targeted interventions and societal accommodations that improve quality of life for persons with ASD.

- Working group members thought there should be a word added that would reflect the inclusion of sensory systems. The phrase "alterations in brain development, and nervous system function" was proposed.
- A possible revised aspirational goal is:

Discover how alterations in brain development and nervous system function lead to ASD in order to enable the development of effective targeted interventions and societal accommodations that improve quality of life for people on the autism spectrum.

Title: How Can I Understand What Is Happening?

- Does the group want to consider making any changes to the chapter's title? (On the last call, the group did not see the need for changes.)

- No changes were suggested.

Wrap Up and Next Steps

- Dr. Daniels will be in touch with the Co-Chairs to finalize the outline and devise a plan for drafting the chapter.

- 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.