Working Group 2 – Conference Call #2
October 4, 2016; 1:00pm EDT

Welcome and Introductions

Working Group Members in Attendance:
Walter Koroshetz – Co-Chair
Louis Reichardt – Co-Chair
Graeme Davis
Christine Nordhal
James Battey
Kevin Pelphrey
Robert Ring
Elizabeth Redcay
Guoping Feng

Working Group Members Absent:
David Amaral
Nicole Williams
Katarzyna Chawarska
Heather Hazlett
Shafali Jeste
Eric Klann
Jamie McPartland
Flora Vaccarino

Follow Up from Call #1

- No specific follow-up from the first call of Working Group 2 was required.

Discussion of Themes from Public Comments Received Through Request for Public Comment

- The working group members felt that most of the public comments addressed many of the same topics that have come up in the past. There appeared to be perhaps a slight increase in the level of interest in sex and gender differences in ASD, although this topic also emerged during the development of the last Strategic Plan.
- Other topics of note highlighted in the public comments included:
    - Genetic testing, especially the importance of educating the public about its most promising uses; it will likely be more helpful for targeting individualized therapies (personalized medicine), rather than for characterizing ASD risk.
    - The need for improved dissemination of research findings to patients and families.

Discussion of Research Progress

1. What are the most notable areas of recent progress in this Question's field of research? What new opportunities have emerged?

- The working group members noted that in recent years, there has been significant progress technologically in the development of mouse, rat, and nonhuman primate models as well as the

use of stem cells to study ASD risk factors. Regarding the rodent models, there has been progress in the level of sophistication of methods used to analyze behavior.

- There are also now more objective measures of behavior in humans. The development of new mobile technologies may help enable improved behavioral measures in humans.
- Recent progress in identifying genetic risk factors of ASD has paved the way for improved studies on the neurobiology of autism, pointing to major molecular pathways such as those related to synaptic activity and chromatin modification.
- Some functional biological studies are now able to focus on understanding the underlying biology and distinct pathways of individual symptoms (e.g. repetitive behavior); the hope is that these will allow for the development of treatments of individual symptoms that can be combined, rather than attempting to tackle all of the diversity in ASD symptoms together.
- Recent research has illustrated the impact of somatic mutations in the developing organism. This suggests a "two-hit" hypothesis for neurodevelopmental disorder risks and has implications for diagnosis as well as the effects of changes in different portions of the brain.
- There has been progress in imaging studies, especially in establishing large-scale, aggregated data sets of structural MRIs, which has allowed researchers to start identifying key phenotypic differences. Imaging data is also being combined with genetic data.
- Studies in recent years have revealed that females with ASD have a greater genetic load than males with ASD. There is also emerging evidence of differential expression of autism risk genes between males and females.

2. What progress has been made in translating research into practice?
    - The working group members noted advances in eye-tracking and brain imaging and the application of these in patient populations.
    - Recent research findings suggest that the possibility of identifying brain markers to predict treatment response holds promise. However, more needs to be done to determine which treatment will work for which individuals and why some treatments do not work in some individuals.

3. What are the most significant barriers to progress in this field?
    - Currently, conclusions about how to treat co-occurring conditions in children with ASD are drawn from research in neurotypical children because there is not enough understanding of the unique aspects of these conditions when they co-occur with ASD.
    - A lack of sufficient funding for ASD research remains a significant barrier. This makes funding decisions about where to devote resources difficult.
    - It has been challenging to undertake large-scale studies involving large collaborative teams spanning from basic to translational to clinical research. More work with large data sets is needed, but standardization of the data aggregation is a problem and should be done prospectively rather than retrospectively.
    - Studies need to move from a cross-sectional focus to a longitudinal focus, especially to start learning more about developmental aspects over time. This includes continuing studies so that they also include research on ASD in later childhood, adolescence, and adulthood; however, a barrier to these kinds of studies is that patients and families often do not stay in the study location for a long period of time.
    - There remains an inability to pursue quantitative causal cell biology in vivo. This relates to a lack of the necessary technological tools for this research, and there is hope that research funded through the BRAIN Initiative will help address aspects of this challenge in the future.

- One barrier has been the difficulty of planning studies that include large sample sizes where sample collection has been planned in advance. In addition, to meaningfully investigate subgroups within the ASD population requires even larger sample sizes, which are even more difficult to obtain. It would be beneficial to find ways to obtain and link phenotypic data to the genetic data of individuals.
- A lack of accessibility to brain tissue for research remains a major barrier.
- Wandering and attention issues are important topics to address, especially for caregivers, but studies to uncover the neural basis for behavior and aspects of motivation are difficult to design.

4. What are the most pressing needs or evidence gaps that can be addressed through research?
    - The working group members cited a gap in understanding the mechanisms underlying known genetic abnormalities associated with ASD.
    - Also mentioned was an evidence gap regarding brain development and the developmental differences in neurotypical and ASD phenotypes.

5. Are there emerging areas of research that need additional support?
    - The working group identified the following emerging areas of research as those in need of additional support:
        - Characterization and determination of which animal models are robust and consistent enough to hold up across different strains and species. Well-validated models will be best to guide future studies in humans and elucidate complex biological mechanisms. In addition, more support is needed for advancing studies from rodent models to nonhuman primates.
        - Development of biomarkers other than behavioral biomarkers.
        - Integration of research by collaborative teams conducting research across the spectrum of science – from animal models, to imaging, to clinical applications.
        - Application of new technologies to investigate circuit abnormalities in the brain. Leveraging transmagnetic stimulation technology as well as the “connectome” project may help provide more data on individuals across the lifespan.
        - Advancement of genetic findings and basic research to the identification of potential druggable targets, such as ion channels, for example.
        - Systems biology to understand the complexity of associated mechanisms and move from investigating linear biological pathways to interactions between signaling pathways.
        - Investigation of the underlying causes of epilepsy in individuals with ASD.
        - Impact of somatic mutations on developmental lineages and autism, in addition to measuring gene expression at the single-cell level.
        - Understanding environmental, experiential, and sensory input impacts on the nervous system and autism, as well as the brain’s adaptive capacity and how it relates to causes versus effects of ASD.
        - Integration of molecular biology and genetics in a developmental context, through the multifaceted investigation of patient-derived stem cells.
        - Interactions between genes and environment, such as interactions between genetic risk and the immune system.
        - Understanding the function of the enteric nervous system and the microbiome GI disorders in individuals with ASD.

- Collection of more sequencing, imaging, and longitudinal data on large groups of girls with ASD to better understand sex differences.
- Determination of what is unique about co-occurring conditions in ASD versus those same conditions in neurotypical individuals in order to inform development of treatments.
- The biological basis of regression and the possibility of certain immune risk factors roles in regression.

Discussion of Services and Policy Changes

1. Are there any innovative programs or recent policy changes that have address some of the gaps or interests of this Question's research area?

- The working group members noted that there has been improved collaboration between the National Institutes of Health and nonprofit organizations, which has led to more productivity and has advanced science more quickly.
- Recent efforts to improve replicability in science, especially in studies using animal models, have been beneficial.

2. Is there new research evidence that can inform the policy agenda?

- There has been significant progress on including minimally verbal children (not only high-functioning children with ASD) as research study participants in imaging studies, and this is providing new insights that may inform future treatments and policies.

3. Are there opportunities for practice to more actively inform research?

- Automatic language processing could be developed and studied more as a potential therapy in ASD.

4. What are the most significant services needs or gaps that are not being addressed by current policies and programs?

- There is a need to support the development of large, collaborative research teams that can secure long-term funding for longitudinal studies. One avenue for accomplishing this may be to build upon the existing Autism Centers of Excellence.

5. What are the workforce and training needs in this area?

- More needs to be done to develop a workforce with engineering expertise in order to have the capability to assess behavioral issues with devices.

Discussion of Aspirational Goal

Based on the state of the field, is the **Question 2 Aspirational Goal** still appropriate?

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

- Working group members discussed the word "development" and thought the definition would need to be better articulated.

- There is a desire to revise the goal to incorporate the importance of how biology can inform society about the nature of ASD and lead to appropriate societal changes that will improve the quality of life for individuals with ASD.
- An initial, proposed draft of the new aspirational goal could be “Increase knowledge of the underlying biology of ASD across the lifespan to enable the development of targeted and personalized interventions as well as societal accommodations that will improve the quality of life for people on the autism spectrum.”

Is the chapter title still appropriate (does it still represent what consumers need with regard to basic research?)

How Can I Understand What Is Happening?

- The working group approved of the wording of the chapter title and especially liked that it was in plain language.

Wrap up and preview of next call

- On the next call, the working group will discuss the development of objectives for Chapter 2.
- 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.