**2013 IACC Strategic Plan Update – Question 4 Draft**

**"Which Treatments and Interventions Will Help?" - Volunteer drafter – Tom Insel**

**Introduction**

The aspirational goal for question 4 is development of interventions that are effective for reducing both core and associated symptoms, for building adaptive skills, and for maximizing quality of life and health for people with ASD. A review of the state of the science in 2009 noted that many treatments were in use but little rigorous evidence existed to support their safety or efficacy. At that point, the committee identified intervention research needs from two quite different approaches. One approach, dependent on progress in Questions 2 and 3, called for novel, targeted interventions based on an understanding of the molecular mechanisms of ASD. The other approach, related to Questions 5 and 6, called for rigorous studies to test the efficacy and safety of current interventions in wide use.

The 2009 Strategic Plan, including revisions in 2010 and 2011, described 12 objectives, each with many parts. Altogether the Plan recommended 37 clinical studies (including 19 randomized clinical trials), 20 model system studies to identify targets, and one workshop. The total recommended budget was $283.2M across all 12 objectives.

**Progress**

The 2011-2012 Portfolio Analysis reviewed projects funded by both government agencies and private foundations from 2008 – 2012. Based on this analysis, the cumulative investment from 2008 – 2012 was $309M. Focusing on 2009 – 2012, the period after publishing the 2009 plan, the total investment was $255M. On average, the yearly investment was 18% higher than in 2008 ($54M). From 2009 – 2012, roughly 90% of the investments assigned to Question 4 were aligned with one of the 12 objectives.

Because most clinical trials require several years for completion, the snapshot of 2012 may be helpful for assessing the current portfolio. There were 269 projects funded in 2012 at a cost of $64M, with 29 projects ($3.9M) not assigned to any objective. In 2012, there were projects funded in each of the 12 objective categories.

In terms of specific objectives, 4 were considered to have met the recommended budget and number of projects, including randomized control trials addressing co-occuring medical conditions, development of model systems, early intervention trials, and studies on interventions for non-verbal individuals. Eight were considered partially met in terms of funding including testing safety and efficacy of interventions, investigating biological signatures, health promotion, medication trials, interventions to prevent recurrence in siblings, medications to treat co-occurring conditions, and community studies evaluating intervention effectiveness, and a workshop on clinical subtypes and treatment personalization (partial because a workshop that took place only partially met the objective). What was most surprising from the portfolio review was the number of projects relative to the costs. As noted above, the Strategic Plan called for 37 clinical studies and 20 model system projects, yet in 2012 alone there were 269 projects, 175 related to interventions and 94 related to model systems.

There were two concerns from this mismatch between the Strategic Plan and the portfolio of projects. First, the large number of clinical studies with very small budgets suggests that much of the current portfolio is under-powered and will not be informative for either efficacy or safety. This appears to be equally true reviewing the trials of psychosocial, behavioral, and biomedical interventions. While some of these projects are exploratory, reflecting the early stage of this research field, the absence of therapeutic targets or consensus outcome measures calls into question how either positive or negative results can be interpreted from this large number of studies.

A second concern was the balance between the various objectives. Again, reflecting the very early stage of intervention development for ASD, it is perhaps not surprising that nearly one-third of the budget was invested in one objective: the standardization and validation of model systems to identify molecular targets or circuits for treatment development. However, several objectives of the plan that addressed the assessment of current treatments, received less investment. In particular, testing the safety and efficacy of widely-used treatments ($1.3M in 2012) and studies of interventions for either secondary conditions ($1M in 2012) or co-occurring conditions (less than $1M in 2012) received relatively little investment. Interventions for non-verbal autism received more funding and more projects than originally proposed.

These two concerns notwithstanding, the assessment is that there has been considerable activity on Question 4 since the publication of the Strategic Plan in 2009. While the overall investment, in terms of dollars, roughly matches and, in many areas, exceeds the recommendations of the Plan, it is too early to assess the impact of these investments, as clinical trials require several years for completion, analysis, and reporting. Preclinical studies, which have a shorter delivery time, have yielded some remarkable insights, especially for mice with mutations that model syndromic forms of ASD, such as Fragile X or Rett. In affected mice, treatments reverse the syndrome not only in development, but in adulthood. While these studies give hope, the relationship of syndromic autism to sporadic autism is not clear. Furthermore, in many areas of neuroscience, efficacy in mice has not translated into efficacy in human patients.

The clinical research agenda is very much a work in progress. The development of the Autism Treatment Network and the entry of industry into this area are both promising changes. ClinicalTrials.gov lists 92 intervention trials currently recruiting subjects in the U.S., including pharmacological studies of core symptoms. Early behavioral intervention trials have demonstrated efficacy for significantly improving cognitive, language, and social abilities, as well as adaptive behavior. One study demonstrated that early intensive behavioral intervention is associated with positive change in EEG activity associated with improvements in social behavior. Other trials are providing insights into managing the associated conditions, from sleep to ADHD to gastrointestinal disturbances. In 2012, the Autism Intervention Research Network for Physical Health and the Autism Treatment Network published empirically-validated physician guidelines for the assessment and treatment of GI, sleep, and ADHD symptoms in children with ASD. In addition, the American Academy of Pediatrics published guidelines for treatments of core symptoms, associated symptoms, and the use of complementary and alternative treatments.

Some clinical trials of interventions have been completed in last 5 years with some notable successes. The Early Start Denver Model (ESDM) has been shown to be effective in improving

cognitive and adaptive behavior as well as in reducing the severity of ASD diagnosis. This represents an improvement over community services, however, due to the time intensive nature of this intervention it may not be feasible in many communities. Another trial of a low intensity and brief intervention called JASPER (Joint Attention Symbolic Play Engagement and Regulation) did show an improvement over community treatment and could be widely implemented. Intensive early intervention is important, which could mean 25 hours a week of active engagement for preschoolers and 15-20 hours a week for toddlers.

Progress is also being made in educational intervention research. A recent comparative study of the LEAP (Learning Experiences and Alternative Program for Preschoolers and their Parents), TEACCH (Treatment and Education of Autistic and Related Communication Handicapped Children) and non-model specific special education intervention approaches showed that in high quality special education classrooms, all approaches were effective in improving symptom severity, and social, behavioral and communication skills. An interesting finding is that the quality of the classroom was the most important indicator, rather than the particular method, in how much the child's symptoms will improve with comprehensive special education interventions.

While as many as 50% of children will respond well to behavioral interventions, there is still a lack of good predictors of response. Clinical trials in ASD remain challenged by the absence of biomarkers for stratifying the population or for serving as surrogates of response. This remains a young field, without consensus outcome measures that are both robust and sensitive to change. In spite of the successes of genetics and neurobiological studies, there are still few molecular, cellular, and systems targets for interventions. Without some way to measure target engagement, negative results from either pharmacological or behavioral interventions will be difficult to interpret and positive results may not be able to define the requisite dose or duration of treatment.

Relatively little work has been done to validate or invalidate the many treatments currently in use. Current treatments, including complementary and alternative treatments are in wide use but there have been insufficient attempts to collect information about which interventions work and for whom they are successful. The "practice to research" movement, which collects information from large health care systems or from registries, could prove useful for assessing current interventions, but this approach has not been fully developed for ASD. Likewise, the wisdom of providers and families has not been "crowd sourced" adequately.

New technologies, including devices to serve as social prosthetics or tools for communication assistance, are exciting opportunities for the next generation of interventions in ASD. The combinations of devices, behavioral interventions, and medications will be a profound challenge for research design and regulatory approval, but may prove most useful for children and adults with complex needs.

**Progress towards the Aspirational Goal**

Before it will be possible to ensure interventions that are effective for reducing both core and associated symptoms, for building adaptive skills, and for maximizing quality of life and health for people with ASD, we need to know more about ASD. This aspirational goal will need a better foundation from the preceding Strategic Plan Questions; in particular, stratification of the

heterogeneity of ASD (so that interventions can be tailored) and a deeper understanding of the biology of ASD (so that interventions can be effective) will be critically important. Many of the interventions for other neuropsychiatric disorders have been found via serendipity without a deep understanding of the biology of the disorder. While serendipity from insightful clinical observations from may prove useful for finding interventions for ASD, investing in research to identify biological and cognitive targets for treatment development and developing preventive interventions for infants at highest risk are essential to ensure progress.

Progress on reducing core symptoms has been most evident with early behavioral interventions. The efficacy of these treatments is powerful evidence that ASD core symptoms can be treated, even if medications or devices which might be more rapid and more accessible have yet to be developed. There are now several medications in randomized clinical trials that should report results in 2014 or 2015. Whether via behavioral, biomedical, or combined approaches, early intervention to restore a normal developmental trajectory must be a high priority.

Associated symptoms are already being treated effectively, with both medications and behavioral interventions. Recent guidelines on the management of these associated symptoms is a clear sign of progress for families and providers. In addition, ongoing trials are testing the efficacy of new treatments for sleep disturbances (especially sleep maintenance) and hyperactivity (with or without irritability).

Building adaptive skills and maximizing quality of life remain aspirational goals that remind us of how far we need to go. Much of the treatment development effort has focused on children, yet the number of adults with ASD may outnumber affected children. Future studies will need to include treatment development for adults, for non-verbal individuals, and for individuals from diverse communities.