4. Which Treatments and Interventions Will Help?

- **When should treatments or interventions be started?**
- **What are the medical issues I need to know about?**
- **How do I know that treatments are both safe and effective?**

What do we know?

Although autism is defined and diagnosed by deficits in core behaviors, accumulating evidence suggests that the breadth of this disorder extends well beyond the behavioral diagnosis. There is increasing recognition that the multiple systemic issues in children with ASD may influence vulnerability, onset, and severity of symptoms and behaviors. The systemic component of autism supports the possibility that both the core behaviors and medical issues have a convergent mechanistic basis that if identified, could provide new insights into treatment targets, candidate genes, and strategies for prevention.

A wide range of treatment and intervention options are available for children and adults with ASD that can target core symptoms, ameliorate associated symptoms, and prevent further disability. For example, interventions such as speech therapy facilitate language development, pragmatic communication and social interaction. Occupational therapy can improve functioning in everyday activities (e.g., eating, bathing, and learning) as well as sensory integration. Both types of therapy can promote the development of life skills, which help people with ASD to gain more independence. People with ASD can benefit from adaptive technologies, such as the use of keyboards and computers that promote expressive communication skills, and visual representation tools such as the Picture Exchange Communication System (PECS) that assist those with little or no language to communicate more effectively. For pre-school and school age children, public school systems and private schools can provide essential interventions including curricula that are individualized to the child, testing for cognitive and academic strengths and weaknesses, and special education services with lower teacher to student ratios, to name a few. For all of these interventions, there is a range of improvement, with some people making profound gains and others showing little response. We do not know how to predict which people will benefit from any of the available treatments.

Of the numerous behavioral interventions currently in use, little scientific evidence from randomized controlled trials (RCT) supports their efficacy. Behavioral therapies, such as Applied Behavior Analysis (ABA) based therapies, which use the principles of reinforcement and repetition, have been used since the 1960s and have been studied most extensively. Controlled trials have shown ABA to be effective for improving social skills and language when provided for at least 25-40 hours per week for 2 years (Lord & McGee, 2001). Efficacy is greatest when behavioral interventions are used early, but improved skills have been reported with adolescents and adults (McClannahan, MacDuff, & Krantz, 2002; Weiss & Harris, 2001).

Medications to improve some of the symptoms associated with autism have been studied. However, thus far, no medication has been shown in controlled trials to enhance social behavior or communication. In 2006, risperidone became the first Food and Drug Administration (FDA)-approved pharmacologic therapy for certain symptoms of autism. First introduced in 1993 as medication used to treat symptoms of schizophrenia, risperidone has now been shown to be effective as a treatment of irritability and aggression seen in some children with ASD. Selective serotonin reuptake inhibitors have had mixed results in decreasing certain repetitive and stereotyped behaviors (Kolevzon, Mathewson, & Hollander, 2006; King et al., 2009). Other biological and pharmacological treatments that have been investigated in small studies and may warrant fuller attention include omega-3 fatty acids, memantine, oxytocin, and pioglitazone (Ammiger et al., 2007; Chez et al., 2007; Hollander et al., 2007; Boris et al., 2007).

There are other treatments in wide use that have not been studied in randomized controlled trials. These include nutritional supplements and diets (e.g., probiotics, mitochondrial cocktails, CoQ10, carnitine, and gluten-casein free diets), and chelation. One such treatment, the neuropeptide secretin, that had been reported to improve symptoms of ASD, was studied in a placebo-controlled trial and found to be ineffective (Esch & Carr, 2004). Some parents and therapists suggest that these treatments are effective, that recovery is possible, and that further studies are needed. Others are concerned that these treatments involve more than minimal risks and urge caution before recommending large-scale studies.

What do we need?

Safe and effective interventions are needed across the lifespan, from early development shortly after the detection of risk or diagnosis, through childhood, school age, adolescent, adult, and senior phases of life. Going forward, research needs to be balanced between two poles. On the one hand, we need novel, targeted interventions based on an understanding of the molecular mechanisms of ASD. These interventions, analogous to ongoing efforts in cancer and cardiovascular research, will require a successful commitment to earlier elements of this Strategic Plan. On the other hand, we need rigorous studies to develop and safely test the efficacy of current interventions, identifying which elements are most effective in reducing or ameliorating symptoms for which persons. Intervention research should collect information about the mode of delivery, intensity, duration, and dose as well as unique characteristics of the people with ASD (e.g., behavioral, biological, genetic) in an effort to develop more personalized interventions, treatments, services and supports, and help inform basic research about additional targets for study. This research will require large-scale multidisciplinary randomized controlled trials.

The identification of biomarkers, for instance, in plasma, saliva, cerebrospinal fluid (CSF), or tissue is necessary to provide insights into targeted treatment strategies designed to improve or reverse autistic symptoms as well as insights into preventive measures. Further, if biomarkers present in children with ASD are found to be present in infants and toddlers at high risk of developing autism, targeted

intervention strategies to normalize these biomarkers could be tested for potential to arrest or reverse the symptoms and progression of autism.

Decision makers (people with ASD, families, clinicians, and payors) frequently lack critical information about which treatment is best for an individual person. While there are many interventions in wide use, the field lacks comparative studies of their value or how these various interventions should be staged or combined. Comparative effectiveness research yields information from head to head comparisons of interventions or policies that, when combined with a personalized approach, can inform decision makers about health care choices. This approach, already helpful for cardiovascular and cancer research, needs to be developed to inform ASD interventions.

Special attention is needed on treatment of co-occurring medical issues, developing pharmacological treatments, and testing interventions that are in wide use, (e.g., nutritional supplements) but for which little rigorous efficacy data exist (Levy & Hyman, 2003). Medical issues, such as gastrointestinal symptoms and sleep disorders, may influence the effectiveness of interventions designed to affect the core symptoms of ASD. Similarly, interventions that focus on medical issues may also affect or reduce core symptoms. Animal models and/or cell lines relevant to autism are needed to develop new or test existing pharmacological agents for ASD, understand the mechanisms of action, and serve as a first-step in testing drug safety. Such model systems research may be crucial in leveraging the pharmaceutical industry to develop medications that target the core symptoms of ASD.

While some people with ASD have been reported to show marked improvement, little is known about the characteristics of these people or the types of interventions they have received that may help to explain these changes. Studies of these people may provide an opportunity for discovering important clues with regard to risk factors and intervention strategies for specific ASD subgroups.

***ASPIRATIONAL GOAL*: INTERVENTIONS WILL BE DEVELOPED 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.**

Research Opportunities

- Large scale studies that directly compare interventions and combinations of interventions (e.g., pharmaceutical, educational, and behavioral interventions) to identify what works best for which people and how much it will cost.
    - Best practice models that are being used in community-based ASD intervention programs.
    - Clinical trials that assess the safety and efficacy of widely used interventions that have not been rigorously studied for use in ASD populations.
    - Studies in diverse populations.
- Interventions that improve functioning and quality of life for people with ASD across the lifespan, including older children, adolescents, and adults with ASD.
- Early interventions that aim to prevent the development of ASD in very young "at risk" children and reduce family burden.
- Innovative treatments that specifically target core symptom clusters unique to ASD.
- Development of emerging technologies, such as assisted communication, that provide opportunities for people with ASD to become more engaged in the community.
- Animal models and/or cellular lines that can be used to test efficacy and/or safety of ASD interventions and treatments.
- Strategies that facilitate rapid translation of promising basic scientific discoveries and community practices into clinical research and trials.
- Methods of treating co-existing medical or psychiatric conditions and assess how such treatments affect ASD symptoms and severity.
- Interventions that may enhance neural plasticity and adaptive brain reorganization in children, adolescents, and adults with ASD thereby promoting significant improvement of ASD.
- Outcome studies of the effectiveness of behavioral, developmental, and cognitive therapies and approaches.
- Methods for measuring changes in core symptoms of ASD from treatment.
- Dissemination research (coordinated with subsequent goals) to ensure that evidence-based interventions are implemented in diverse communities with fidelity and efficiency.
- Investigation of the use of medications to control challenging behaviors in people with ASD, particularly adults.

Short-Term Objectives

A. Support at least three randomized controlled trials that address co-occurring medical conditions associated with ASD by 2010. *IACC Recommended Budget: $13,400,000 over 3 years.*

B. Standardize and validate at least 20 model systems (e.g. cellular and/or animal) that replicate features of ASD and will allow identification of specific molecular targets or neural circuits amenable to existing or new interventions by 2012. *IACC Recommended Budget: $75,000,000 over 5 years.*

C. Test safety and efficacy of at least five widely used interventions (e.g., nutrition, medications, assisted technologies, sensory integration, medical procedures) that have not been rigorously studied for use in ASD by 2012. *IACC Recommended Budget: $27,800,000 over 5 years.*

D. Complete two multi-site randomized controlled trials of comprehensive early intervention that address core symptoms, family functioning and community involvement by 2013. *IACC Recommended Budget: $16,700,000 over 5 years.*

New Objective

E. Convene a workshop to advance the understanding of clinical subtypes and treatment personalization (i.e. what are the core symptoms to target for treatment studies) by 2011. *IACC Recommended Budget: $50,000.*

New Objective

F. Launch five randomized controlled trials of interventions including biological signatures and other measures to predict response, and monitor quality of life and functional outcomes, in each of the following groups:

- Five trials in infants and toddlers by 2013. *IACC Recommended Budget: $30,000,000 over 5 years.*
- Three randomized controlled trials of interventions for school-aged children and/or adolescents by 2013. *IACC Recommended Budget: $18,000,000 over 5 years.*
- Three trials for adults by 2014. *IACC Recommended Budget: $18,000,000 over 5 years.*

Long-Term Objectives

A. Complete at least three randomized controlled trials on medications targeting core symptoms in people with ASD of all ages by 2014. *IACC Recommended Budget: $22,200,000 over 5 years.*

B. Develop interventions for siblings of people with ASD with the goal of reducing risk recurrence by at least 30% by 2014. *IACC Recommended Budget: $6,700,000 over 5 years.*

New Objective

C. Conduct at least one study to evaluate the safety and effectiveness of medications commonly used in the treatment of co-occurring conditions or specific behavioral issues in people with ASD by 2015. *IACC Recommended Budget: $10,000,000 over 5 years*.

What Progress is Being Made in Fulfilling the Objectives?

(Please provide 1-2 paragraphs to summarize progress.)

***Note:** Objectives labeled "New Objective" are either entirely new additions to the 2010 Strategic Plan or significantly modified objectives from the 2009 Strategic Plan. Objectives from the 2009 Strategic Plan that did not change or that have been slightly modified for clarification purposes are unmarked.*