Autism Biomarkers Consortium for Clinical Trials

Project Overview

James McPartland, Ph.D.
Associate Professor, Yale Child Study Center Director,
Yale Developmental Disabilities Clinic
ASD is a complex neurodevelopmental disorder of unknown etiology, characterized by:
- Difficulties with social-communication
- Restricted, repetitive behaviors and interests and/or atypical sensory responsivity

Heterogeneous clinical presentation
- Symptom profile
- Language
- Cognitive ability

Early stage evidence of social-communicative biomarkers

The ABC-CT will provide methodologically rigorous multi-site evaluation of potential biomarkers in a large sample
- Infrastructure designed to support future clinical trials
ABC-CT study design

- Multi-site, naturalistic study
  - **Administrative Core**: Yale
  - **Sites**: Duke, UCLA, UW, Boston Children’s Hospital, Yale
  - **Data Coordinating Core**: YCCI, Prometheus
  - **Data Acquisition and Analysis Core**: SCRI, Duke, Yale, BCH, SiStat
- 4 to 11 year-old-children with ASD (N = 200) and typical development (TD; N = 75) with IQ 50-150
  - Feasibility study (25 ASD, 25 TD)
  - Three time points (Baseline, 6 weeks, 24 weeks)
- Potential biomarkers of social-communicative function
  - Eye tracking (~EU-AIMS)
  - EEG (~EU-AIMS)
  - Lab-based measures
- Commonly used clinician and caregiver assessments
- Blood draw for participant and parents
Sample characteristics:
Inclusion/exclusion criteria

**ASD inclusion**
- ADOS, ADI, DSM-5
- IQ 50-150
- Medication stable 8 weeks

**ASD exclusion**
- Genetic/neurological
- Epilepsy
- Sensory/motor impairment
- Metabolic/mitochondrial
- Pre/perinatal
- Environmental
- Misc. invalidating factors

**TD inclusion**
- IQ 50-150
- Medication stable 8 weeks

**TD exclusion**
- ASD/sibling with ASD
- Genetic/neurological
- Epilepsy
- Sensory/motor impairment
- Metabolic/mitochondrial
- Misc. invalidating factors
- Clinical score on CASI
1. Compare sensitivity of objective indicators of social communicative function to conventional clinician and caregiver assessments with respect to clinical status
   - Correlations with clinical status at each time point and across time points

2. Evaluate potential utility of these measures, individually or in combination, as biomarkers for use in clinical trials
   - Feasibility of implementation; Construct validity; Test-retest reliability, consistency, and stability; Discriminant validity; Convergent validity; Sensitivity to change; Adequate variability within and between groups

3. Collect DNA samples for future genomic analyses and other potential analyses from all subjects, including parents of ASD subjects, to create a **community resource** of raw, processed, and analyzed data across modalities
EEG Paradigms
EEG: Resting state

- Videos of non-social, abstract moving images
- Resting spectral power
  - Connectivity and coherence
  - Hemispheric asymmetry
  - Multiscale entropy
- Baseline for event-related EEG measures
- Discriminates ASD vs. TD in infants, children, adults
- Association with language ability
EEG: Visual evoked potentials

- Checkerboards reversing phase
- Low level visual processing
  - Functional integrity of visual pathway
  - Baseline for more complex (social) visual perceptual tasks

- Discriminates ASD vs. TD in infants
EEG: Biological motion

- Neural response to point light displays of human motion
  - Bio. motion
  - Scrambled

- Discriminates ASD vs. TD in school-aged children
  - Data collected across four study sites
EEG: Face processing

- EU-AIMS task
- Neural response to faces (vs. houses), inversion effect
- Discriminates ASD vs. TD in HR infants, children, and adults
- Association with social and communicative function
- Sensitive to change in response to treatment

The Autism Biomarkers Consortium for Clinical Trials | www.asdbiomarkers.org
EEG: Emotional faces

- Neural response to neutral versus fearful expressions
- Discriminates ASD vs. TD in children and adults
- Association with social function

The Autism Biomarkers Consortium for Clinical Trials | www.asdbiomarkers.org
EEG: Social scenes

- EU-AIMS task
- Neural response to social and non-social dynamic scenes
- Discriminates ASD vs. TD in infants
Eye-tracking Paradigms
ET: Biological motion

- Overlap with EU-AIMS task
- Preferential attention to human motion

- Discriminates ASD vs. TD in toddlers through adults
- Collected across two study sites

The Autism Biomarkers Consortium for Clinical Trials | www.asdbiomarkers.org
ET: Spontaneous social orienting

- Response to bids for dyadic engagement, joint attention
- Discriminates ASD vs. TD in infants through preschool
- Stratification by developmental trajectory
- Associates with social function
ET: Activity monitoring

- Attention to shared social activity versus background distracters
- Discriminates ASD vs. TD in toddlers through adults
- Associates with social function
- Collected across two study sites

The Autism Biomarkers Consortium for Clinical Trials | www.asdbiomarkers.org
ET: Interactive social task

- Attention to naturalistic social activities between child partners

- Discriminates ASD vs. TD in school-aged children
ET: Dynamic naturalistic scenes

- Scanning patterns towards complex, dynamic social scenes
- Discriminates ASD vs. TD in school-aged children
- Scan patterns stratify children by social impairment
- Collected across two study sites

The Autism Biomarkers Consortium for Clinical Trials | www.asdbiomarkers.org
ET: Pupillary light reflex

- EU-AIMS task
- Central fixation on black background flashes white for 75ms
  - Interspersed video clips induce saccades
- Discriminates
  - ASD vs. TD in infants, children, and adults
ET: Gap overlap task

- EU-AIMS task
- Attention shifting and flexibility

- Discriminates ASD vs. TD in infants, children, adults
ET: Visual search/Static images

- EU-AIMS task
- Salience of social stimuli among distracters
- Discriminates ASD vs. TD in children
Lab-based Measures
Lab-based measures: Video Tracking

- Proximity seeking during free play
Lab-based measures: Video Tracking

- Social avoidance correlates with social-communicative impairment
Lab-based measures: LENA

- Language ENvironment Analysis
  - Conversational turns
  - Vocalizations
- Data collected in lab and at home
- Associated with social communicative function in Duke clinical trial

The Autism Biomarkers Consortium for Clinical Trials | www.asdbiomarkers.org
Lab-based measures: Face and affect recognition

- Affect recognition
  - NEPSY-II
    - Administer to all
    - Normed 3-11

- Face recognition
  - Kaufman Assessment Battery for Children
    - Administer to age 4
    - Normed 3-6
  - NEPSY-II
    - Administer to all
    - Normed 5-11
Clinician/caregiver assessments

**Clinician administered**
- Autism Diagnostic Observation Schedule
- Autism Diagnostic Interview – Revised
- Vineland Adaptive Behavior Scales
- Differential Ability Scales
- Clinical Global Impression Scale

**Caregiver report**
- Aberrant Behavior Checklist
- Autism Impact Measure
- Behavior Assessment System for Children – Second Edition
- Pervasive Developmental Disorder Behavior Inventory
- Social Opportunities Questionnaire
- Social Skills Improvement System
- Social Responsiveness Scale – Second Edition
- Child and Adolescent Symptom Inventory
- Pediatric Quality of Life
- Caregiver Strain Questionnaire
- ACE Family/Medical History
- Intervention History
- Demographics/Screening
Biospecimens

- Blood draw
  - Proband and available biological parent(s)
  - Simons Foundation SPARK
    - 1 EDTA for DNA extraction and sequencing
  - NIMH Repository
    - 1 LCL/ACD tube for generation of cell lines
    - 1 EDTA
- Genetic feedback to families via SPARK
Planned Interim and Final Data Analyses

- Assess technical and biological viability of the measures as potential biomarkers:
  - Identify EEG and eye tracking biomarkers and lab-based measurement variables with good performance metrics
  - Examine the relationship and sensitivity among EEG and eye tracking biomarkers, lab-based measures, clinician/caregiver assessments, and independent measures of clinical status
  - Evaluate longitudinal change in eye tracking, EEG, and lab-based measures to identify if they will be sensitive tools for intervention trials

- Use multivariate methods to find meaningful groups of individuals or variables
  - Cluster analysis to identify homogenous subgroups based on these variables and check for their correspondence with known/observed patterns of heterogeneity in ASD symptoms and behaviors
  - Multidimensional scaling to identify composites by capturing heterogeneity in the sample across measures
Expected Outcomes

- The ABC-CT is an early stage biomarker validation effort
  - Determine if biomarkers are robust enough to be used for subject selection of school-aged ASD subjects for clinical trials
  - Assess technical and biological variability of the measures in pre-school and school-aged children
  - Assess the utility of investigator-administered assessments of domains of social impairment as predictors of clinical outcomes

- A public data resource
  - An integrated data set of EEG, eye tracking, lab-based, and clinical measures from pre-school and school-age ASD subjects, as well as blood samples from ASD subjects and their parents for future genomic analyses
  - All data and analyses made publicly available through the National Database for Autism Research
Status and timeline

Current status

- Complete
  - Protocol review by External Advisory Board
  - In-person protocol finalization meeting with SC and BCPT
  - Experimental paradigms and clinical protocols
  - Hardware configuration and standardization
  - Study-wide and site-specific trainings
  - Electronic case report forms and data management infrastructure
  - Site visits by DCC and DAAC
- Feasibility study enrollment commenced December 8
- Feasibility analyses ongoing
- Three month goal for feasibility study completion
  - Presentation to Biomarkers Consortium Executive Committee

Timeline

- Three year data collection period
- Finalization of analyses and publication in Year 4

The Autism Biomarkers Consortium for Clinical Trials | www.asdbiomarkers.org