The Autism Biomarkers Consortium for Clinical Trials (ABC-CT)

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NIH SFARI SIMONS FOUNDATION AUTISM RESEARCH INITIATIVE THE biomarkers CONSORTIUM FNIH Foundation for the National Institutes of Health

Overall Objectives

- Validate objective **tools** to catalyze clinical trials of behavioral and pharmacologic interventions
  - Stratification (enrichment) biomarkers for enrollment in clinical trials – eye tracking and EEG
  - Measures of social impairment in ASD that are sensitive to change
  - Reduce subjective biases and expectancy effects
- Collect blood samples for future genomic and exploratory analyses
- Create a public community resource of data and DNA samples
  - National Database for Autism Research
  - NIMH Repository and Genomics Resource

ABC-CT:
A Public-Private, Pre-competitive Partnership

- FNIH Biomarkers Consortium, Neuroscience Steering Committee Project Team:
  - NIH Institutes: NIMH, NINDS, NICHD
  - FDA
  - SFARI
  - Janssen R&D
  - EU-AIMS

Characteristics of the Biomarkers Consortium

- Unique ability to coordinate the Project as a neutral convener to facilitate exchange of information and leverage resources among the partners
  - NIH, FDA, Clinical Research Associates/SFARI, Janssen R&D, EU-AIMS
  - The NIH Project is a pre-competitive public-private partnership
- Importance of the NSC ASD Biomarkers Work Group in developing the project concept
- Critical role in finalizing the clinical protocol for biomarker collection and the pre-specified data analyses
- Coordination with international efforts - EU-AIMS

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

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

- Biomarker validation
  - Determine if biomarkers are robust enough to be used for subject selection of school-aged ASD subjects for up to 6-month 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 objective 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
- Coordination with EU-AIMS
- Regulatory
  - Plans to pursue a request for letter of support from FDA Biomarkers Qualification Office

Comparison with EU-AIMS

- No recruitment targets by sex, age, IQ
- No DD/ID comparison group
- Single assessment battery for all participants
  - Selected for appropriateness across age, developmental, and cognitive range
  - No *a priori* designation of categorical age groupings
- No MRI
- Identical paradigms and equipment across sites
- Centralized processing and analysis
  - Firewalled from site and administrative staff

EEG paradigms

- Resting EEG
- Visual evoked potentials
- Biological motion
- ERPs to faces (EU-AIMS)
- Facial expression of emotion
- Dynamic social scenes (EU-AIMS)

Eye-tracking paradigms

- Biological motion (~EU-AIMS)
- Spontaneous social orienting
- Activity monitoring
- Interactive social task
- Dynamic naturalistic scenes (~EU-AIMS)
- Pupillary light reflex (EU-AIMS)
- Gap overlap task (EU-AIMS)
- Visual search/Static images (EU-AIMS)

Lab-based measures of social behavior

- Noldus EthoVision
- Language ENvironment Analysis (LENA)
  - Recorded during lab visits and at home
- Affect recognition (NEPSY-II)
- Face recognition (NEPSY-II; KABC-II)

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