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
Autism Biomarkers Consortium for Clinical Trials

Overall PI
James McPartland, Ph.D.

Administrative Core
Pt. James McPartland, Ph.D.

Project Manager: Helen Seow, Ph.D.
Scientific Coordinator: Katherine Stavropoulos, Ph.D.
Multicenter Support: Rhoda Arzoomanian, R.N., M.S.M.
Communications: Lisa Brophy

Steering Committee
(voting/ non-voting)
Pt. James McPartland, Ph.D.
Site Director: Geraldine Dawson, Ph.D.
DCC: James Dziura, Ph.D.
DAAC: Sara Webb, Ph.D.
NIH Project Scientists: Lisa Gilotty, Ph.D.
Alice Kau, Ph.D.
Margaret Grabb, Ph.D.
Deborah Hirtz, M.D.
BCPT: Linda Brady, Ph.D.
NIH Program Officer: Ann Wagner, Ph.D.

External Advisory Board
Robert Schultz, Ph.D.; Chair
Evdokia Anagnostou, M.D.
Daniel Geschwind, M.D., Ph.D.
Ami Klin, Ph.D.
James McCracken, M.D.
John Elder Robison
Alison Singer, M.B.A.
Jeremy Veenstra-Vanderweele, M.D.

Data Coordinating Core
PD: Cynthia Brandt, M.D., M.P.H.
QA: Alyssa Gateman, M.P.H., C.C.R.P.
Sub: Prometheus Research

Collaborating Implementation Sites

Duke
PD: Geraldine Dawson, Ph.D.;
Co-Director, Clinical Workgroup

Boston Children's
PD: Charles Nelson, Ph.D.;
Co-Director, EEG Workgroup

UCLA
PD: Shafali Jeste, M.D.;
Co-Director, EEG Workgroup
Co-I: Scott Johnson, Ph.D.;
Co-Director, ET Workgroup

UW
PD: Raphael Bernier, Ph.D.;
Co-Director, Clinical Workgroup

Yale
PD: James McPartland, Ph.D.
PD: Kasia Chawarska, Ph.D.

NDAR/ NIH/ NIMH Data Repositories
NIMH Repository and Genomics Resource

Oversight

Monitoring

Data

Acquisition protocols

FNIH Biomarkers Consortium
Executive Committee

James McPartland, Ph.D.; Co-chair
Linda Brady, Ph.D.; Co-chair
Geraldine Dawson, Ph.D.
Sara Webb, Ph.D.
James Dziura, Ph.D.
Catherine Sugar, Ph.D.
Ann Wagner, Ph.D.
William Potter, M.D., Ph.D.
Wendy Chung, M.D.
Gahan Pandina, Ph.D.
Declan Murphy, Ph.D.
Silvana Borges, M.D.
Peter Como, Ph.D.
Rosa Canet-Aviles, Ph.D.

FNIH Biomarkers Consortium
Project Team

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Rosa Canet-Aviles, Ph.D.
Sample characteristics:
Inclusion/exclusion criteria

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

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

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

■ TD exclusion
  ■ ASD/sibling with ASD
  ■ Genetic/neurological
  ■ Epilepsy
  ■ Sensory/motor impairment
  ■ Metabolic/mitochondrial
  ■ Misc. invalidating factors

■ Clinical score on CASI
ASD Biomarkers Project – Objectives

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
- 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
EEG: Emotional faces

- Neural response to neutral versus fearful expressions

- Discriminates ASD vs. TD in children and adults

- Association with social function
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
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
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

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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
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