Biomarkers in Autism Spectrum Disorder

PI: James McPartland, Ph.D.
Yale Child Study Center
Overview

- State of biomarker science in autism
- Rationale for ABC-CT
- Study design
- Preliminary results
- Ongoing activities
Autism spectrum disorder (ASD)

- ASD is a behaviorally defined neurodevelopmental condition of unknown etiology
  - Social-communicative deficits
  - Restricted, repetitive behavior or interests

- Heterogeneity in clinical phenotype
  - Core social features
  - Associated features (e.g., cognitive function)

- Gold standard for quantifying symptoms (clinical, research)
  - Clinician-rated behavioral assessment and parent interview
  - Caregiver and self-report questionnaires

- No established biomarkers for any context of use
State of the Science: ASD Biomarkers

- Promise of EEG and eye-tracking
  - Viable in population
  - Economical, accessible
- Multiple candidate markers
  - Mechanism
  - Symptom domain
- Suggestive evidence
  - Sensitivity to diagnostic status
  - Association with symptoms
- Limited evidence
  - Test-retest reliability
  - Stability over development
  - Sensitivity to clinical change
  - Influence of methodological variation
Autism Biomarkers Consortium for Clinical Trials

- Test well-evidenced biomarkers
- Acquired via practical assays
- Large sample (including TD)
- Deep phenotyping
- Longitudinal design
- Methodological rigor
ABC-CT Objectives

1. Evaluate candidate biomarkers for clinical trials
   - Feasibility of implementation
   - Reliability across sites
   - Construct validity
   - Discrimination between ASD and TD
   - Stratification within ASD
   - Developmental stability/Sensitivity to change
   - Predictive of course

2. Compare to conventional clinician and caregiver assessments

3. Create a community resource spanning genetics, biomarkers, and clinical and behavioral information

4. Develop infrastructure viable for clinical trials
ABC-CT Study Design

- Multi-site, naturalistic study
  - **Administrative Core**: Yale Center for Clinical Investigation
  - **Sites**: Duke, UCLA, UW, Boston Children’s Hospital, Yale
  - **Data Coordinating Core**: YCCI/YC Analytical Sciences, Prometheus
  - **Data Acquisition and Analysis Core**: SCRI, SiStat, Duke, Yale, BCH, Penn
- Feasibility study: 25 children with ASD and 25 with typical development
- Main study: 200 children with ASD and 75 with TD
  - Three time points (Baseline, 6 weeks, 24 weeks)
- Biomarkers of social-communicative function
  - Harmonized with EU-AIMS consortium
- Commonly used clinician and caregiver assessments
- Blood draw for participants with ASD and biological parents
- Integrative governance (U19 mechanism)
ABC-CT Study Design

- Sample characteristics
  - Age 6-11
  - IQ 60-150
  - Medication stable 8 weeks

- EEG
  - Resting EEG
  - Visual evoked potentials
  - Biological motion
  - N170 ERP to faces*

- Eye-tracking
  - Activity monitoring
  - Interactive social task
  - Static social scenes*
  - Biological motion*
  - Pupillary light reflex*

- Blood draw
  - Probands, biological parents

* EU-AIMS paradigm
ABC-CT Study Design

- 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
  - Pervasive Developmental Disorder Behavior Inventory
  - Social Responsiveness Scale
  - Child and Adolescent Symptom Inventory
  - ACE Family/Medical History
  - Intervention/Medication History
  - Demographics/Screening
ABC-CT Rigor

- Weekly calls within and across cores
- Biomarker data
  - Identical biomarker acquisition hardware and protocols at sites
  - DAAC staff performed on-site setup and training
  - Manuals of Procedures
    - Biomarker acquisition, room setup, behavioral management
  - QC and feedback to data collection sites within 72 hours
  - Centralized processing and analysis
- Regulatory
  - Administered according to Good Clinical Practice guidelines
- Statistical
  - Pre-designated directional hypothesis for primary DV from primary assay within each data modality
ABC-CT Enrollment

- Enrollment: N = 399 (ASD = 280, TD = 119)
- Completion: N = 374 (ASD = 260, TD = 114)
ABC-CT Biomarker Acquisition

- EEG neural response to faces (N170)
  - ASD: 74% across time points
  - TD: 92-94% across time points
- Eye-tracking composite
  - ASD: 97-99% across time points
  - TD: 98-100% across time points
- Blood draw
  - Proband: 76.8%
  - One or both parents: 85.0%
Primary EEG Biomarker: N170 Latency

- N170 event-related potential
  - Neural index of early stage face processing
  - Activity in superior temporal sulcus, fusiform gyrus
  - Delayed in children through adults with ASD
- Experiment
  - Faces, inverted faces, houses
  - EU-AIMS harmonized assay
- Prediction
  - Increased N170 latency to upright faces at right posterior temporal electrode cluster
# Primary EEG Biomarker: N170 Latency

<table>
<thead>
<tr>
<th></th>
<th>Whole sample (N=179)</th>
<th>TD (N=59)</th>
<th>ASD (N=120)</th>
<th>Test TD vs ASD</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Mean</strong></td>
<td>204.8</td>
<td>194.3</td>
<td>209.2</td>
<td>F(1,201)=10.7</td>
<td>&lt;.01</td>
</tr>
<tr>
<td><strong>SD</strong></td>
<td>30.2</td>
<td>26.8</td>
<td>30.6</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Note:** Faster latency indicates a shorter latency time for N170 to upright faces.
Primary EEG Biomarker: N170 Latency

Time 1 (Baseline)  Time 2 (6 weeks)  Time 3 (6 months)

ASD  TD  ASD  TD  ASD  TD

Faster latency  Frequency  Frequency  Frequency  Frequency  Frequency
Primary EEG Biomarker: N170 Latency

<table>
<thead>
<tr>
<th>ICC</th>
<th>All</th>
<th>ASD</th>
<th>TD</th>
</tr>
</thead>
<tbody>
<tr>
<td>T1,T2,T3</td>
<td>.62</td>
<td>.53</td>
<td>.75</td>
</tr>
<tr>
<td>T1,T2</td>
<td>.68</td>
<td>.67</td>
<td>.67</td>
</tr>
<tr>
<td>T1,T3</td>
<td>.58</td>
<td>.45</td>
<td>.78</td>
</tr>
<tr>
<td>T2,T3</td>
<td>.62</td>
<td>.49</td>
<td>.78</td>
</tr>
</tbody>
</table>
Primary ET Biomarker: Social Composite

- Eye-tracking social composite
  - Visual attention to onscreen faces and heads
  - Modulated by amygdala and superior temporal sulcus
  - Reduced attention to faces in ASD
- Experiments
  - Two classes of videos
  - Images of social interactions
- Prediction
  - Reduced proportion of looking time to faces in ASD
## Primary ET Biomarker: Social Composite

<table>
<thead>
<tr>
<th></th>
<th>Whole sample (N=222)</th>
<th>TD (N=64)</th>
<th>ASD (N=158)</th>
<th>Test TD vs ASD</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Mean</strong></td>
<td>.236</td>
<td>.290</td>
<td>.214</td>
<td>F(1,220)=51.5</td>
<td>&lt;.01</td>
</tr>
<tr>
<td><strong>SD</strong></td>
<td>.079</td>
<td>.073</td>
<td>.070</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

- **Test TD vs ASD**: F(1,220)=51.5, p < .01

**Chart**: 
- **Title**: ET Composite
- **Axes**: 
  - X-axis: Frequency
  - Y-axis: ET Composite
- **Diagnosis**: TD, ASD
- **Legend**: Less looking at social information

---

The Autism Biomarkers Consortium for Clinical Trials | www.asdbiomarkers.org
Primary ET Biomarker: Social Composite

Time 1 (Baseline)        Time 2 (6 weeks)        Time 3 (6 months)

ASD       TD          ASD       TD          ASD       TD

Less looking at social information

Frequency  Frequency  Frequency  Frequency  Frequency  Frequency
### Primary ET Biomarker: Social Composite

<table>
<thead>
<tr>
<th>ICC</th>
<th>All</th>
<th>ASD</th>
<th>TD</th>
</tr>
</thead>
<tbody>
<tr>
<td>T1, T2, T3</td>
<td>.83</td>
<td>.80</td>
<td>.78</td>
</tr>
<tr>
<td>T1, T2</td>
<td>.83</td>
<td>.79</td>
<td>.82</td>
</tr>
<tr>
<td>T1, T3</td>
<td>.83</td>
<td>.80</td>
<td>.77</td>
</tr>
<tr>
<td>T2, T3</td>
<td>.83</td>
<td>.81</td>
<td>.75</td>
</tr>
</tbody>
</table>
N170 Latency: Biomarker Qualification

- BQ LOI submitted November, 2018
- Accepted May, 2019
- Proposed context of use
  - Biologically homogeneous subgroup
  - Enrich clinical trials by reducing heterogeneity

Considerations
- Refining COU
- Determining cut point
- Functional differentiation of subgroup
- Processing and equipment
- Development of BQP ongoing
  - FDA DDT grant awarded September, 2019

![Graph showing N170 Latency to Upright Faces](chart.png)

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

21
ABC-CT: Ongoing Work

- ET LOI submission in preparation
- Preparing data for final analyses (NCE through June 2020)
  - Primary analyses
    - Relationship to clinical characteristics
    - Sensitivity to change in clinical status
  - Data-driven methods and composites
- Scientific questions raised
  - Replicability
    - Age groups
    - IQ ranges
  - Measuring sensitivity to change