Developing Biomarkers for Autism Spectrum Disorder

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Biomarker Definition
A defined characteristic that is measured as an indicator of normal biological processes, pathogenic processes, or responses to an exposure or intervention, including therapeutic interventions.

Biomarker Objectives
- Diagnosis/screening
- Treatment response
- Stratification
  - Treatment selection
  - Enrichment

EEG Biomarkers
- Electrical brain activity recorded from scalp
  - At rest
  - In response to perceptual events
- Viable across range of cognitive and developmental levels
  - Non-invasive
  - Movement tolerant
- Practical
  - Cost effective
  - Accessible
- Well studied in normative social-communicative development

N170: Sensitive to Diagnostic Status
- Sensitive to diagnostic status
- Associated with symptoms
- Functionally specific
- Applicable across development
- Robust to variation in behavior
- Sensitive to change in clinical status
**Remaining Challenges**

- Promising evidence for many biomarkers
- Limited reproducibility
- Individual differences in face processing
- Underpowered studies
- Methodological inconsistencies
- Reliability/practice effects not known
- Absence of normative reference

McPartland et al., 2004, 2011; Grice et al., 2005; O'Connor et al., 2005, 2007; Dawson et al., 2005; Senju et al., 2005; Valdizan, 2005; Kemner et al., 2006; Marshall et al., 2006, 2007; Churches et al., 2010; Magnee et al., 2008; Wong et al., 2008; McCleery et al., 2009; Akechi et al., 2010; Churches et al., 2010, 2012; Hileman et al., 2011; Batty et al., 2011; Apicella et al., 2013; Khoram et al., 2013; Wagner et al., 2013; Tye et al., 2013, 2014; Cygan et al., 2014; Key et al., 2014; Faja et al., 2016; Graman et al., 2016; Neuhaus et al., 2016; Shen et al., 2016; Tavares et al., 2016; Groom et al., 2017; Luckhardt et al., 2017; Monteiro et al., 2017; Luyster et al., 2017; Malaia et al., 2017; Kang et al., 2017; Sysoeva et al., 2018

**Next Generation Biomarker Studies**

- Test well-evidenced biomarkers
- Well-characterized cohorts
- Large samples (including TD)
- Longitudinal design
- Methodological rigor
- Practical assays

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
- 200 children with ASD and 75 with TD
- Ages 6-11
- IQ 60-150
- Practical assays (EEG, Eye-tracking)
- Longitudinal design (Baseline, 6 weeks, 24 weeks)
- High level of methodological and statistical rigor

ABC-CT: Biomarker Assays

- **EEG**
  - Resting EEG*
  - Visual evoked potentials
  - Biological motion
  - ERPs to faces*
  - Blood draw
  - Proband
  - Both biological parents

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

* EU-AIMS harmonized paradigm

ABC-CT: Clinical Measures

- **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 – Second Edition
  - Child and Adolescent Symptom Inventory
  - ACE Family/Medical History
  - Intervention History
  - Demographics/Screening

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ABC-CT: Enrollment

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

ABC-CT: Interim Analysis

- Acquisition and psychometrics
  - Successful acquisition (across demographic/clinical factors)
  - EEG: 96% valid acquisition
  - Eye-tracking: 100% valid acquisition
  - Consistent results across sites
  - Appropriate distributional properties
  - Construct validity
- Viability as social-communication biomarker
  - Discrimination between ASD and TD
  - Test-retest reliability (T1-T2)

ABC-CT: Interim Analysis

N170 latency to upright faces

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<thead>
<tr>
<th>Test</th>
<th>TD</th>
<th>ASD</th>
<th>ASD vs TD</th>
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<tr>
<td>Mean</td>
<td>189.9</td>
<td>191.3</td>
<td>10.47</td>
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<td>SD</td>
<td>24.7</td>
<td>25.0</td>
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Test Re-test reliability ICC

- .79
- .74
- .54

- Replication of discriminant validity
- Evidence of test-retest reliability
- First autism biomarker accepted into the FDA’s Biomarker Qualification Program

Translating a Marker to Care

- Behavioral treatments target social brain systems
- Using transcranial magnetic stimulation to “turn on” these circuits directly

Thank you to the individuals and families that partner with us in research!

Yale Developmental Disabilities Clinic

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Jane Brown  

PI: James McPartland  
www.asdbiomarkers.org

Importance of Biomarkers

Autism Biomarkers Consortium for Clinical Trials

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Michael King  

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