

## Developing Biomarkers for Autism Spectrum Disorder

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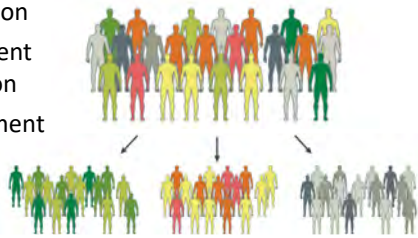
## Biomarker Definition

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.

FDA-NIH Biomarker Working Group, BEST (Biomarkers, Endpoints, and other Tools) Resource, 2017

## Biomarker Objectives

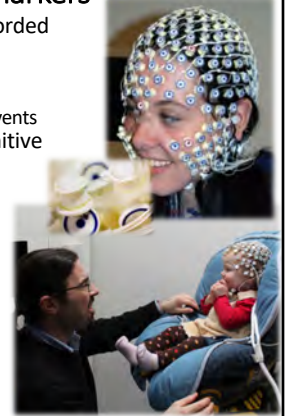
- Diagnosis/screening
- Treatment response
- Stratification
  - Treatment selection
  - Enrichment



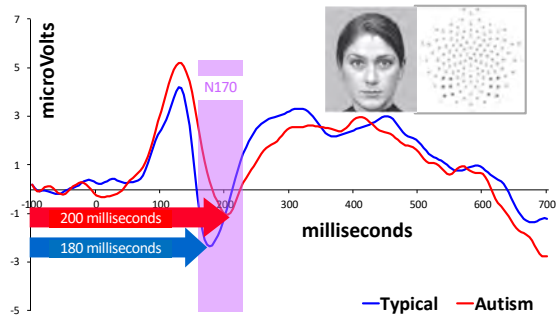
Walsh, Eisabbaq, Bolton, Singh, 2011; Loth et al., 2015; McPartland, 2016

## 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



McPartland, Dawson, Webb, Panagiotides & Carver, 2004

## N170: Viable ASD biomarker?

- ✓ 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; Valizan, 2005; Kemner et al., 2006; Webb et al., 2006, 2009, 2012; Boeschoten et al., 2007; Gurji et al., 2009; Magnee et al., 2008; Wong et al., 2008; McCleery et al., 2009; Akechi et al., 2010; Churches et al., 2010, 2012; Hillman et al., 2011; Batty et al., 2011; Apicella et al., 2013; Khorrami et al., 2013; Wagner et al., 2013; Tye et al., 2013, 2014; Golan et al., 2014; Key et al., 2014; Fojo 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; Malia et al., 2017; Kang et al., 2017; Syssoeva et al., 2018

## Remaining Challenges

- Promising evidence for many biomarkers
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  - Individual differences in face processing
  - Underpowered studies
  - Methodological inconsistencies
- Reliability/practice effects not known
- Absence of normative reference
- Critical need for more rigorous approaches to develop practicable biomarkers

McPartland et al., 2004, 2011; Grice et al., 2005; O'Connor et al., 2005, 2007; Dawson et al., 2005; Senju et al., 2005; Valizan, 2005; Kemner et al., 2006; Webb et al., 2006, 2009, 2012; Boeschoten et al., 2007; Gurji et al., 2009; Magnee et al., 2008; Wong et al., 2008; McCleery et al., 2009; Akechi et al., 2010; Churches et al., 2010, 2012; Hillman et al., 2011; Batty et al., 2011; Apicella et al., 2013; Khorrami et al., 2013; Wagner et al., 2013; Tye et al., 2013, 2014; Golan et al., 2014; Key et al., 2014; Fojo 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; Malia et al., 2017; Kang et al., 2017; Syssoeva 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

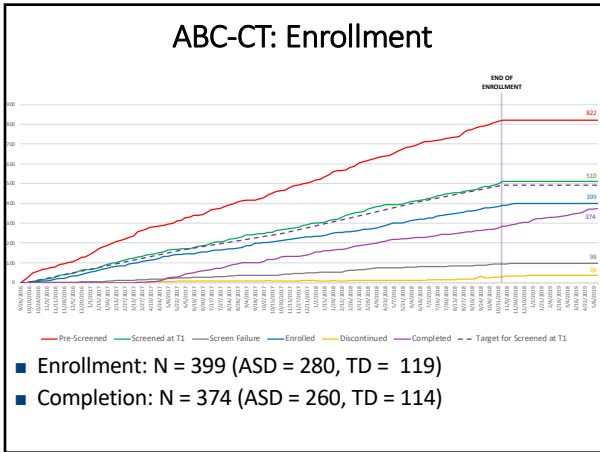
- |  |   |
|--|---|
| <ul style="list-style-type: none"> <li>• <b>EEG</b> <ul style="list-style-type: none"> <li>• Resting EEG*</li> <li>• Visual evoked potentials</li> <li>• Biological motion</li> <li>• ERPs to faces*</li> </ul> </li> <li>• <b>Blood draw</b> <ul style="list-style-type: none"> <li>• Proband</li> <li>• Both biological parents</li> </ul> </li> </ul> | <ul style="list-style-type: none"> <li>• <b>Eye-tracking</b> <ul style="list-style-type: none"> <li>• Biological motion*</li> <li>• Activity monitoring</li> <li>• Interactive social task</li> <li>• Pupillary light reflex*</li> <li>• Static social scenes*</li> </ul> </li> </ul> |
|--|---|



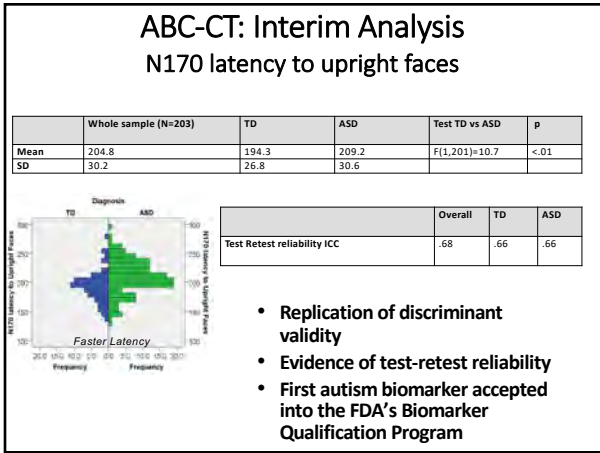
\* EU-AIMS harmonized paradigm

## ABC-CT: Clinical Measures

- |  |   |
|--|---|
| <ul style="list-style-type: none"> <li>• <b>Clinician administered</b> <ul style="list-style-type: none"> <li>• Autism Diagnostic Observation Schedule</li> <li>• Autism Diagnostic Interview – Revised</li> <li>• Vineland Adaptive Behavior Scales</li> <li>• Differential Ability Scales</li> <li>• Clinical Global Impression Scale</li> </ul> </li> </ul> | <ul style="list-style-type: none"> <li>• <b>Caregiver report</b> <ul style="list-style-type: none"> <li>• Aberrant Behavior Checklist Observation Schedule</li> <li>• Autism Impact Measure</li> <li>• Pervasive Developmental Disorder Behavior Inventory</li> <li>• Social Responsiveness Scale – Second Edition</li> <li>• Child and Adolescent Symptom Inventory</li> <li>• ACE Family/Medical History</li> <li>• Intervention History</li> <li>• Demographics/Screening</li> </ul> </li> </ul> |
|--|---|



- ### 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)



### 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

Bela Ponjevic	Kathy Koenig	Taylor Halligan
Fred Volkmar	Lynn LaValley	Simone Hasselmo
Michele Goyette-Ewing	Robert King	Estee Hamo
Pamela Ventola	David Grodberg	Kathryn McNaughton
Brianna Lewis	Roger Jou	Morgan McNair
Julie Wolf	Ela Jarzabek	Tatiana Winkelman
Elise Cummings	Kim Ellison	Dylan Stahl
Amy Barrett	Chelsea Slater	Jane Brown
Kelly Powell	Emma Lecarie	Amy Vatner
Leah Booth	Carson Kautz	Melody Altschuler
Shannon Brooke	Talena Day	Gwen Lopez-Cohen
Laura Kirby	Armen Bagdasarov	Shash Kala

**ABC-CT**  
Autism Biomarkers Consortium for Clinical Trials

PI: James McPartland  
www.asdbiomarkers.org

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