Developing Biological Markers to Improve Clinical Care in Autism

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Overview

• What is autism, and why do we need biological markers?

• Biomarkers
  • What is a biomarker?
  • In what ways could biomarkers improve care?
  • What makes a good biomarker? What makes a good autism biomarker?
  • What does progress look like?
  • What’s the goal?

• Innovations
  • Using biomarkers to develop new treatments
  • Including the full spectrum in biomarker science
Autism

- Developmental condition impacting
  - Social-communicative function
  - Interests and behavioral flexibility
  - Sensory perception and response

Multiple causes and mechanisms

Centrality of social-communication

Reliance on behavior

Need to harness biology
FDA 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, 2020
Uses for Biomarkers in Autism

• Presence of autism (diagnostic)
• Likelihood of developing (screening)
• Developmental course (prognosis)
• Treatment selection (prediction)
• Measuring outcome (treatment response)
• Subgroups (stratification)

Loth et al., 2015
General Considerations for Biomarkers

• Replicable
• Reliable
• Tolerable for autistic people and children
• Cost effective
• Accessible
Autism-specific Considerations for Biomarkers

- Different in autistic and non-autistic people
- Associated with social-communication
  - Specifically associated
- Relevant in children and adults
- Sensitive to clinical improvement

*Not all attributes needed to be useful*

*Different attributes important for different purposes*

*Walsh, Elsabbagh, Bolton, Singh, 2011; Loth et al., 2015; McPartland, 2016*
Autism-specific Considerations for Biomarkers

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Diagnosis

*Walsh, Elsabbagh, Bolton, Singh, 2011; Loth et al., 2015; McPartland, 2016*
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Treatment Response

Walsh, Elsabbagh, Bolton, Singh, 2011; Loth et al., 2015; McPartland, 2016
Electroencephalography (EEG)

- Electrical brain activity recorded directly from scalp
- Viable across ages and levels of function
  - Non-invasive
  - Movement tolerant
- Practical
  - Cost effective
  - Accessible
- Informative about social-communication
N170 is Slower in Autism

N170 is different in autistic and non-autistic adolescents and adults

McPartland, Dawson, Webb, Panagiotides & Carver, 2004
N170 is Associated with Social Function

- Standardized tests of face recognition
  - Increased errors among adolescents and adults with autism
  - Errors correlated with N170

N170 is related to social-communication

McPartland, Dawson, Webb, Panagiotides & Carver, 2004
N170 Specificity

- Are N170 differences particular to social information?
- Are differences observed in children?
N170 Differences Observed in Younger Children

- Lower face recognition scores in autism
- Slower face processing (N170) in autism

N170 differences consistent across children, adolescents, and adults

McPartland, Wu, Bailey, Mayes, Schultz & Klin, 2011
N170 Differences are Specific to Social Information

- Average reading scores
- Brain response to letters comparable to non-autistic children
  - Enhanced amplitude
- Comparable speed

N170 differences specific to social-communication

N170 is Sensitive to Clinical Improvement

- Pivotal Response Treatment
  - Naturalistic behavioral intervention
  - Preschool-aged children received 14-week course of treatment
  - Measured N170 before and after treatment
- Increased N170 speed after treatment

Changes in N170 speed parallel changes in social-communication

Kala et al., 2021; Dawson et al., 2012; Ventola et al., 2013
Autism-specific Considerations for Biomarkers: Evidence for the N170

- Different in autistic and non-autistic people
- Associated with social-communication
  - Specifically associated
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The Next Step: Qualifying Biomarkers

- Evaluate most promising biomarkers
- Large groups of children
- Confirm consistency across laboratories
- Multiple time points to understand stability
- Stringent scientific standards
- Cost-effective, accessible methods
ABC-CT Study Design

• Phase 1 (2015-2020)
  • 280 school-aged children with ASD and 119 with TD
  • Baseline, 6 weeks, 24 weeks

• Phase 2 (2020-2025)
  • Long term follow-up with Phase 1 cohort (~3-4 years)
  • Replication sample of 200 ASD and 200 TD children
  • Evaluate feasibility in preschool-aged children

• Measures
  • Comprehensive clinician and caregiver reports
  • Four EEG and five eye-tracking biomarkers
    • Including N170 latency
ABC-CT Progress: N170

• Replication of N170 delay in autistic children
  • Across all four time points (6 weeks to approximately 4 years)

• Replication of relationship with social function (face memory, $r = -.21$)
• Stable in children over:
  • 6 weeks (ICCs = .66-.75)
  • 24 weeks (ICCs = .56-.75)

Webb et al., 2022
ABC-CT: Biomarker Qualification

- Letter of Intent submitted to the FDA Biomarker Qualification Program
  - Accepted in May 2019
  - First biomarker for a psychiatric condition
- Proposed purpose: Subgrouping (stratification)
  - Biologically defined subgroup
  - Improve clinical trials by reducing variability
- Ongoing development of qualification plan with FDA
- Challenges
  - How to define the subgroup?
  - How to validate subgroup?
  - How to measure what it means for treatment?
  - How easily can this approach be applied in other settings?
Translating Biomarkers to Care

• N170 linked to function of specific brain region (STS)
  • Involved in social perception and thinking
  • Observed to change during behavioral treatments
• Could we use the N170 as a guide to boost function in this area?
  • Would it enhance social-communication?
Translating Biomarkers to Care

- Proof of concept in neurotypical adults
- Faster N170 latency after stimulation
Increasing Inclusivity of Biomarker Research

- Individuals with ASD and intellectual disability excluded from most neuroscience research
  - 38% of those with autism
  - 1% of neuroscience studies
- Failure to meet the needs of those in most significant need of support
Increasing Inclusivity of Biomarker Research

- Innovative strategy
- Laboratory setup
- Behavioral protocol
- Experimental approach
Increasing Inclusivity of Biomarker Research

- High success rate in ASD+ID (IQ ~31)
- Valid response patterns
- Replication of N170 findings
Thank you to the individuals and families that partner with us in research!

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You can help!!!

Research Participation
• Aged 3 – Adult
• With or without ASD or ID
• Clinical report
• Up to $300

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Do you have a child between 6 and 18 years of age?

They can play an important role in research by participating in our study to help us learn about brain development.

The McPartland Lab at the Yale School of Medicine is seeking children with autism spectrum disorder, intellectual disability, and typically developing children. Participants will receive a clinical evaluation and report, as well as compensation up to $300.

To learn more, contact our study team at autism@yale.edu or (203) 787-3439.