Redefining Autism: A new framing for more effective early childhood interventions and policy

Alliance for Early Success: Every Child, Every State
Virtual, May 19, 2021

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Alliance for Early Success
Every Child. Every State.

Marcus Autism Center
NIH Autism Center of Excellence
Thanks & Disclosure

• Thank you - Dr. Warren Jones, my wonderful colleagues and students, and the children and families who participated in our studies over the years at Yale and at Emory.

• Dr. Klin’s research is supported by grants from the National Institute of Mental Health.

• Dr. Klin’s research is also supported by grants from the Eunice Kennedy Shriver National Institute of Child Health and Human Development, The Marcus Foundation, and The J B Whitehead Foundation, as well as contributions from the Georgia Research Alliance.

• This presentation includes research related to investigational device development.
  - Dr. Klin is an inventor and patent holder of investigational device technologies licensed in 2020 to EarliTec Diagnostics.
  - EarliTec Diagnostics is a company that develops medical technologies for early diagnosis of autism and gives revenue to support treatment of children with autism. Dr. Klin is an equity holder in EarliTec Diagnostics.
  - Dr. Klin’s external activity with EarliTec Diagnostics has been reviewed and approved by Emory University’s Conflict of Interest Review Office and by Emory University School of Medicine’s Dean’s Office.
Public Health Challenge
Autism is a Public Health Challenge

- Prevalence: 1:54 autism; more than any other complex neurodevelopmental condition
- 73,000 children born every year in the US will have autism
- Autism Societal Cost/Year in the US: $126 billion
- Autism Lifetime Cost of Care Per Child: $1.5 - 2.4 million
- Importance of early diagnosis and intervention for lifelong outcome and cost of care
- American Academy of Pediatrics recommends screening for autism at 18 and 24 months
- Autism median age of diagnosis in US: 4-0 to 5.7 years
- Not enough expert clinicians, major healthcare disparities
- 5-6 hours of evaluation, costly, not accessible, not available (gold standard used in < 6% of the population of children with ASD)

CDC, 2016, 2018, 2020; Peacock et al., 2012; Cidav et al., 2012; Mandell et al., 2015; 2009; 2013; 2014; Wang et al., 2013; Buescher et al., 2014; Wiggins et al., 2006; Shattuck et al., 2009; Honigfeld et al., 2012; Heidgerken et al., 2005; Dosreis et al., 2006; Hyman et al., 2020
The burden of intellectual disabilities (ID) in 8-year-olds with ASD

- **Ascertainment**: Rates per 1000 for White (W), Black (B) and Hispanic (H)
- **ID**: IQ <70, percentages for White (W), Black (B) and Hispanic (H)

CDC ADDM 2012, 2014, and 2016 cohorts (Christensen et al., 2016, Baio et al, 2018, and Maenner et al., 2020)

- **Ascertainment**:
  - (W): 15.5/1000; (B): 13.2/1000; (H): 10.1/1000
  - (W): 17.2/1000; (B): 16.0/1000; (H): 14.0/1000
  - (W): 18.5/1000; (B): 18.3/1000; (H): 15.4/1000

- **Burden of ID**:
  - (W): 21.3%; (B): 43.9%; (H): 24.7%
  - (W): 22.0%; (B): 44.0%; (H): 35.0%
  - (W): 27.0%; (B): 47.0%; (H): 36.0%

**Intellectual Disability Burden Among AA children is almost double that in W children**
In regards to AA children with ASD

- AA children (and Latino children) with ASD, on average, are diagnosed later, are more likely to have carried non-ASD diagnoses, have poorer access to healthcare services, and are less likely to have a medical home.


- Largest-available repository of diagnosis and phenotypic information on AA children with ASD (N=584) - Event History Calendar Interviews

- Average age of ASD diagnosis was 64.9 months (+/- 49.6), on average 42.3 months (+/- 45.1) following parents’ first concerns about their children’s development:
  - Age Parental First Concerns: 23.0 (17.9)
  - Age Parent First Shared Concerns with a Professional: 29.1 (23.1)

A “Diagnostic Odyssey”, and that’s only the beginning of the journey
Public Health Opportunity

Redefining Autism
Autism symptoms RESULT from deviations from normative socialization

Genetics → Autism

Autism symptoms RESULT from deviations from normative socialization.

Genetics → Autism

Normative Behavior & Brain Development

The beginning
Neonates preferentially orient towards stimuli that...

More Preferred
- mother, engaging
- stranger, eyes open

Less Preferred
- stranger, eyes averted
- stranger, eyes closed

...sound like caregivers.
...smell like caregivers.
...move like caregivers.
...look like caregivers.
...interact like caregivers.
Universal Principle: the Platform for Development of Social Brain

Born to Socially Orient

Reciprocal Social Interaction

Neuroplasticity

WHITE MATTER DEVELOPMENT

Preterm (6month)  Infant (4 weeks)  Adult (25 years)
Autism at 15 months
Social Interaction is the Platform for Brain Development

“Our brains become who we are.” (J LeDoux)

Brain structure and function are physical instantiations of lived experience.
What kind of world is she creating?
Quantifying social visual engagement, moment-by-moment
Derivation of Attentional Funnel
The majority of typically-developing 2-year-olds fixate on the same locations, at the same moments, during 80% of viewing time.
Objective, Quantitative Measures

Experimental Presses
Hundreds of natural experiments within a 5-minute free viewing video experiment

- In ASD: \( \approx 570 \) divergences in 5 minutes of video
- \( \approx 13,680 \) divergences in a 2-hour period of real-life social experience
- 6 hour social exposure/day results in \( \approx 15,000,000 \) divergences over the course of one year of real-life exposure to social environments

TD normative funnels = [Diagram]
ASD comparison scanpaths = [Diagram]
Scenes of Social Action

Toddlers with Autism

Typically-Developing
Scenes of Social Interaction

Toddlers with Autism

Typically-Developing Toddlers
Scenes of Social Interaction

Typically-Developing

Toddlers with Autism
Greater Access to Early Diagnostic Services
Translational Opportunities

• Objective, quantitative, & rapid measures of social adaptive & maladaptive behavior

• Leverage automated measurement technology to enable early detection

• Support a public health system that does not have enough expert clinicians
Investigational Device:
Neurodevelopmental Assessment via Eye-Tracking
Utility of our eye-tracking assays to diagnostic and developmental characterization

Moment-by-moment entrainment to socialization “hot spots”
Non-ASD data from the discovery cohort defined benchmark normative data against which all other comparisons were made.
Quantitative Indices for Assessing Presence of ASD

TD normative funnels =
ASD comparison scanpaths =
Data Harmonization: Participants N=1,059, by Reference Standard Outcome Diagnosis

**Discovery Cohort** (lab-based eye-tracking research setting)

<table>
<thead>
<tr>
<th>measure</th>
<th>ASD</th>
<th>non-ASD</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>300</td>
<td>389</td>
</tr>
<tr>
<td>age, months</td>
<td>22.5(3.6)</td>
<td>21.6(3.5)</td>
</tr>
<tr>
<td>ADOS Total score, mean(SD)</td>
<td>17.4(4.9)</td>
<td>4.5(2.5)</td>
</tr>
<tr>
<td>Mullen Verbal age equivalence</td>
<td>11.9(5.8)</td>
<td>23.1(5.7)</td>
</tr>
<tr>
<td>Mullen Nonverbal age equivalence</td>
<td>18.3(5.0)</td>
<td>22.2(4.9)</td>
</tr>
</tbody>
</table>

**Replication Cohort** (standalone investigational device in community clinic)

<table>
<thead>
<tr>
<th>measure</th>
<th>ASD</th>
<th>non-ASD</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>187</td>
<td>183</td>
</tr>
<tr>
<td>age, months</td>
<td>28.3(5.8)</td>
<td>26.0(5.9)</td>
</tr>
<tr>
<td>ADOS Total score, mean(SD)</td>
<td>19.4(5.0)</td>
<td>5.5(3.2)</td>
</tr>
<tr>
<td>Mullen Verbal age equivalence</td>
<td>14.8(7.7)</td>
<td>23.1(8.0)</td>
</tr>
<tr>
<td>Mullen Nonverbal age equivalence</td>
<td>20.7(6.8)</td>
<td>27.3(9.8)</td>
</tr>
</tbody>
</table>
Index Test Eye-Tracking Measures

Discovery cohort data collection
• Lab-based university research setting

Replication cohort data collection
• Standalone investigational eye-tracking device located in a community clinic

Naturalistic videos of peer social interaction
• 14 videos, each ~53 seconds in duration
• 12 min 26 sec of videos in total
Presence of ASD:
Diagnostic Accuracy (ASD vs non-ASD)

Discovery Cohort

N = 680

Replication Cohort

N = 361

Sensitivity 83.9 (77.8-88.6)
Specificity 82.3 (76.1-87.2)
PPV 82.5 (76.3-87.4)
NPV 83.7 (77.5-88.5)
Accuracy 83.1 (78.9-86.6)

Replication se, sp at Discovery Threshold

9 children in each cohort with insufficient data for meaningful analyses.

se ~83%, sp ~82%
### Presence of ASD: False Positives from Eye-Tracking Assays

<table>
<thead>
<tr>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>'Patient has family history of ASD. Caregivers wanted to find out if child has autism.'</td>
</tr>
<tr>
<td>'Patient presented for an evaluation following referral from SLP at Fayette who reported that'</td>
</tr>
<tr>
<td>'Patient presenting with language delays and social skills difficulties. Parents report his'</td>
</tr>
<tr>
<td>'Patient presenting with language delays, sleep concerns and behavioral issues. Family'</td>
</tr>
<tr>
<td>'Patient presenting with some language delays. Family history is significant for anxiety and'</td>
</tr>
<tr>
<td>'Child presenting with language delays. She displays good social overtures, but her eye'</td>
</tr>
<tr>
<td>'Typical - no concerns'</td>
</tr>
<tr>
<td>'Clear language delays - concerns about social communication - generally not'</td>
</tr>
<tr>
<td>'Speech delay. Mom had many more concerns that were not consistent with her'</td>
</tr>
<tr>
<td>'Clear language delay- also had some repetitive behaviors. Language repetitive (frequent'</td>
</tr>
<tr>
<td>'No ASD concerns. Did show hand-flapping and some posturing but social reciprocity'</td>
</tr>
<tr>
<td>'Did not provide a diagnosis - follow up evaluation in 1 year. Was on the fence - social'</td>
</tr>
<tr>
<td>'Patient presenting with language delays. Patient's parents also reported visual-motor'</td>
</tr>
<tr>
<td>'Patient presenting with language delays and social skill difficulties. Family history is'</td>
</tr>
<tr>
<td>'Patient presenting with variable eye contact, though displayed adequate social overtures'</td>
</tr>
<tr>
<td>'Patient was previously seen at MAC in the PNC/CAD where he received a multidisciplinary'</td>
</tr>
<tr>
<td>'Patient presents with some language delays. Family history is significant for ASD and'</td>
</tr>
<tr>
<td>'Patient's mother reports concerns with regard to her response to name and social skills.'</td>
</tr>
</tbody>
</table>
Presence of ASD: False Positives from Eye-Tracking Assays

Identification of Actionable Vulnerabilities

80% of “false positives” via eye-tracking assays were given a different clinical diagnosis:

- “language delay” or “global developmental delay” (25%),
- provisional diagnosis of “sub-threshold symptoms of ASD” (35%) or “sub-threshold communication disorder” (15%) (both with requests to return for re-evaluation within a year),
- or suspected genetic disorder (5%) (referred for genetic testing).

Half of the children given a provisionally sub-threshold diagnosis were later given an ASD diagnosis.
Quantitative Indices for Assessing Severity of ASD Symptoms

TD normative funnels =
ASD comparison scanpaths =
Quantitative Indices for Assessing Severity: Social Disability

~78% of variance in ADOS total scores
Quantitative Indices for Assessing Severity: Verbal Ability

~71% of variance in Mullen verbal age equivalents
Quantitative Indices for Assessing Severity: Nonverbal Ability

**Discovery Cohort**

\[ R^2 = 0.862, \ p = 4.97e-78 \]

**Replication Cohort**

\[ R^2 = 0.603, \ p = 1.01e-21 \]

~60% of variance in Mullen nonverbal age equivalents
Translating this science into a tool for increasing access to diagnostic services

Enrollment
- Complete: 503
- Target: 472

Cheryl Klaiman

Warren Jones

Eye-Tracking Session

MINNETRONIX MEDICAL
Accelerating Breakthroughs

Validated Cloud
Translational Opportunities

• High-throughput, low-cost, deployment of universal screening in the community

• Early detection, early intervention, optimal outcome

• Prevention or attenuation of intellectual disability in ASD
Developmental Social Neuroscience meets Public Health Opportunities

- We are genetically programmed to be social beings
- This programming is altered in autism
- But social experiences are co-created by environment
- We can engineer these experiences via parent-delivered treatment
Greater Access to Early Treatment
Caregivers’ most important role in promoting early brain development in their children
Providing the social experiences children are missing

Augmenting access to early intervention services:
parent-mediated treatment
Autism Navigator™ increases the capacity of healthcare and early intervention providers, educators, and families to improve outcomes of young children with autism spectrum disorder (ASD).

About Autism

Early Intervention Providers

Primary Care Physicians

Family Collection

Autism Navigator™ is a unique collection of web-based tools that uses extensive video footage to bridge the gap between science and community practice.

About Autism is a tool for families, professionals, or anyone interested in learning about autism spectrum disorder (ASD). It is available free of charge. Just register and login.

Launch About Autism

Our partners are helping us make an impact on community practice.

www.autismnavigator.com

www.babynavigator.com
the Community: Families, Pediatricians, Early Intervention Providers

Parent-Delivered Early Social Interaction

Wetherby et al., 2014
Teaching Strategies & Supports to Promote Active Engagement

Supports for better skills
- Model and expand language and play skills
- Extend activity, child's roles, & transitions
  - Balance demands and supports

Supports for social reciprocity
- Natural reinforcers
- Waiting for initiation and balance of turns
  - Clear message to ensure comprehension

Supports for a common agenda
- Positioning
- Follow child’s attentional focus
  - Motivating activity with clear roles & turns
<table>
<thead>
<tr>
<th>Child Behaviors</th>
<th>Parent Behaviors</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>ACTIVE ENGAGEMENT</strong></td>
<td><strong>TRANSACTIONAL SUPPORTS</strong></td>
</tr>
<tr>
<td>1. Emotional Regulation</td>
<td>1. Participation &amp; Role</td>
</tr>
<tr>
<td>2. Productivity</td>
<td>2. Make Activity Predictable</td>
</tr>
<tr>
<td>3. Social Connectedness</td>
<td>3. Follow Child’s Attention</td>
</tr>
<tr>
<td>4. Gaze to Face</td>
<td>4. Promote Initiations</td>
</tr>
<tr>
<td>5. Response to Verbal Bids</td>
<td>5. Balance of Turns</td>
</tr>
<tr>
<td>7. Flexibility</td>
<td>7. Modeling</td>
</tr>
<tr>
<td>8. Generative Ideas</td>
<td>8. Expectations &amp; Demands</td>
</tr>
</tbody>
</table>

Goals for Early Treatment:

Every waking hour in the home and in the community
### Everyday Activities

<table>
<thead>
<tr>
<th>Play with Toys</th>
<th>Play with People</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blocks, Puzzles, Sand box, Playdough, Cars and Trucks, Ball Games, Baby Dolls</td>
<td>Social Games like Peek-a-boo, Rough and Tumble, Songs &amp; Rhymes</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Meals and Snacks</th>
<th>Caregiving</th>
</tr>
</thead>
<tbody>
<tr>
<td>Preparation, Eating, Cleanup</td>
<td>Dressing, Diaper Change, Bath, Washing Hands, Brushing Teeth</td>
</tr>
</tbody>
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<table>
<thead>
<tr>
<th>Book Sharing</th>
<th>Family Chores</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>Mailbox, Laundry, Care for Pets, Plants</td>
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</tbody>
</table>
Universal design because there is only one platform for early brain development

• For children with complex genetic burden: Autism, Williams syndrome

• For children with compromising medical conditions: Extremely Preterm, Congenital Heat Disease

• For children from disadvantaged backgrounds
Pediatric Medicine of the 21st century: The criticality of Public Health considerations

• Not necessarily curing “diseases”
• BUT OPTIMIZING OUTCOMES
• Universal screening, accessing identification, increasing access to early intervention
• Cost-effective, community-viable
• Value Proposition!
5 Steps for Brain-Building
Serve and Return

Center on the Developing Child
HARVARD UNIVERSITY

Dr. Jack Shonkoff

Dr. David Willis

An Early Brain and Child Development Focus
Dr. Brenda Fitzgerald

Brain Trust 4 Babies
To make autism an issue of diversity, not of disability