Early Diagnosis & Assessment of Autism via Objective Measurements of Social Visual Engagement

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EMORY UNIVERSITY SCHOOL OF MEDICINE

Marcus AUTISM CENTER

Disclosures

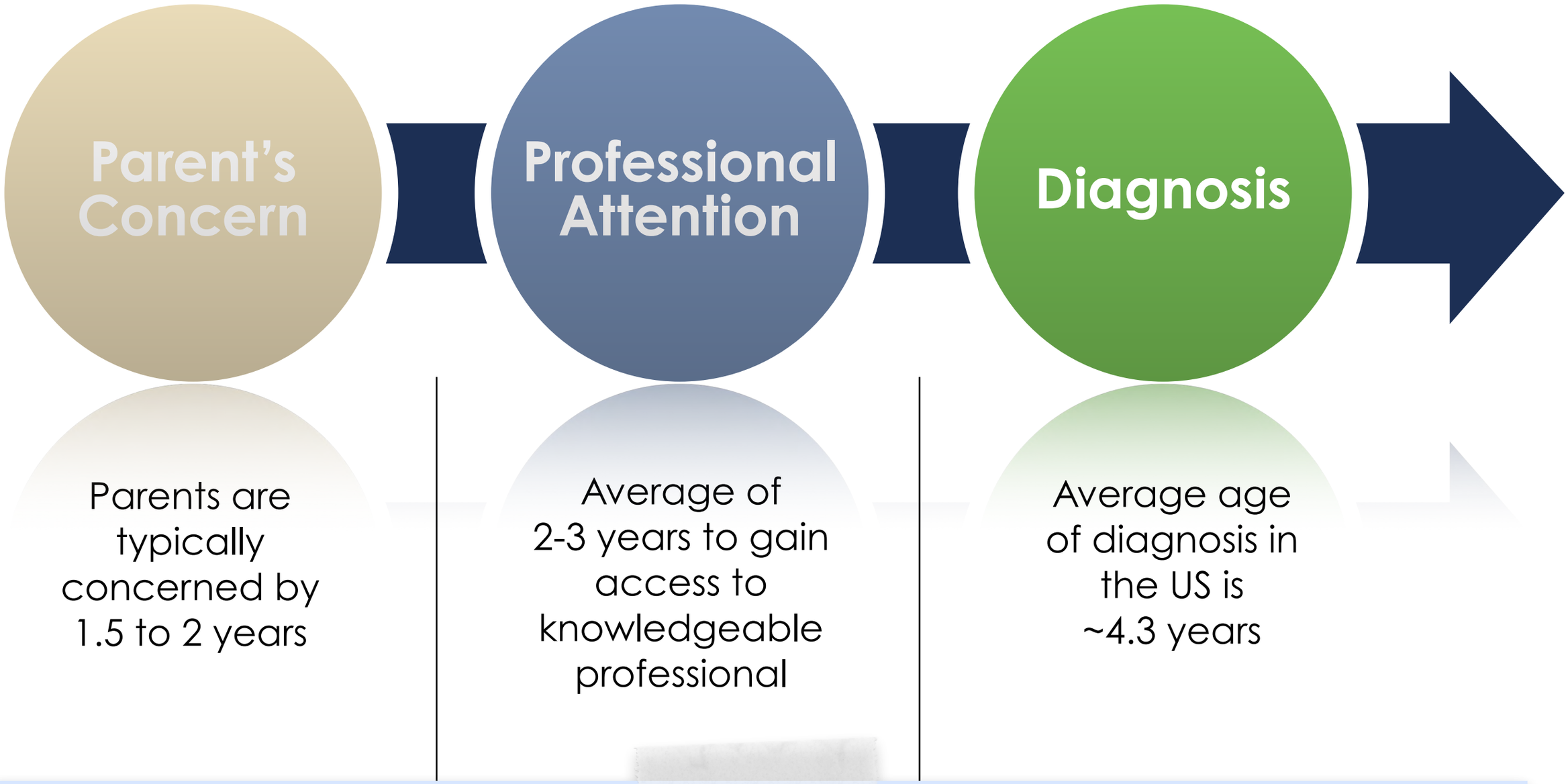
- This presentation includes research related to investigational device development.
- Dr. Jones is an inventor and patent holder of investigational device technologies licensed in 2020 to EarliTec Diagnostics.
- EarliTec Diagnostics is a company that develops medical technologies for early diagnosis and assessment of autism. Dr. Jones was a founder of and is now a consultant to and equity holder in EarliTec Diagnostics.
- Dr. Jones'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.
- Dr. Jones's research is supported by grants from NIMH, NICHD, the Marcus Foundation, and the J B Whitehead Foundation.

Autism: A Common Condition

Autism affects 1 in every 36, impacting more than 9.1 million individuals and their families in the United States alone. When we think of conditions that affect young children and their families, autism is one of the most common.

Maenner et al (2020) *MMWR Surveil Summ.* and CDC Prevalence Estimates

Current State: Obtaining an Autism Diagnosis



Parents in the US spend an average of 2-3 years between the time when they first begin to worry and the time when they finally receive a diagnosis. There are not enough expert clinicians or expert centers to meet public need. Disadvantaged families (US racial and ethnic minorities, poor, rural) wait even longer.

Chen et al (2023) *J Pediatr.*

Biomarkers Needed in Autism

- Need measures that are
  - objective
  - quantitative
  - dimensional & fine-grained
  - performance-based
  - standardized, efficient & community-viable
  - able to capture core features of social disability (i.e., have clinical validity)
  - mechanistically relevant

Social Visual Engagement

(how children look at and learn from their surrounding social environment)

Individual eye-tracking data, playback 1/2 speed, gaze location crosshair color-coded by content at gaze location.

Clinical Face Validity:

Social Visual Engagement…

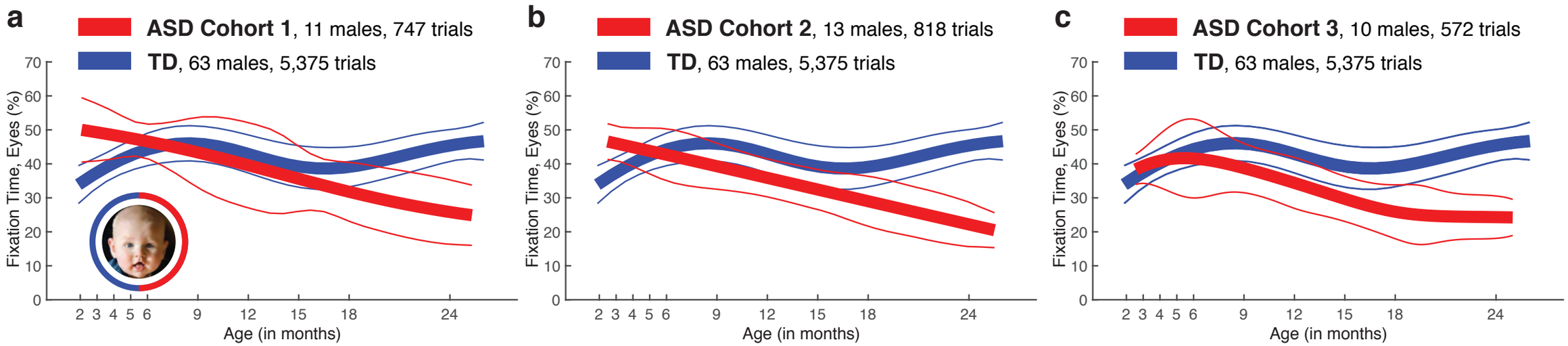


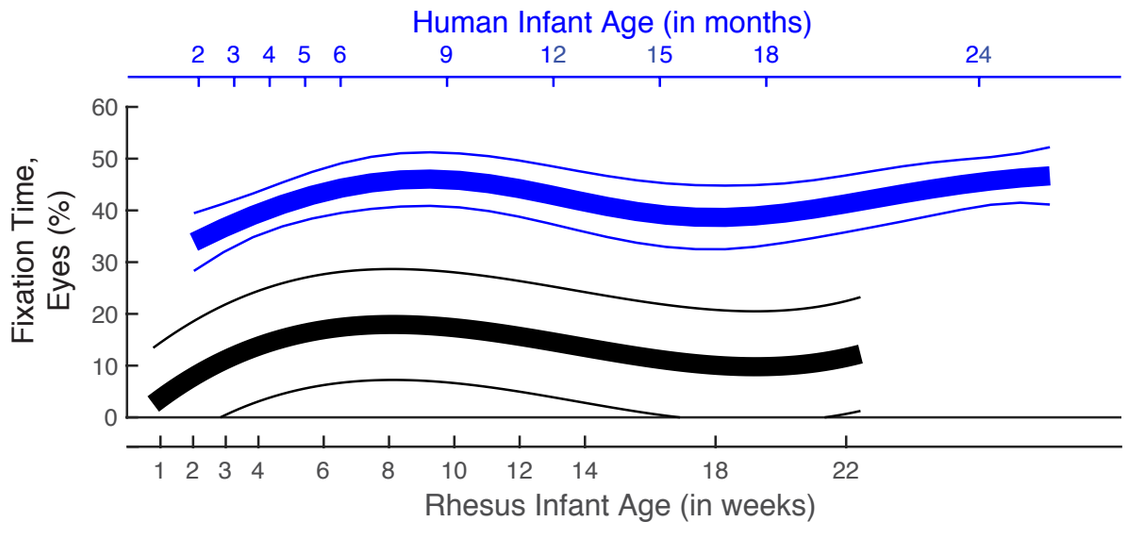
Figure 2. **Comparison of social visual engagement (eye-looking) in typically-developing infants relative to 3 independent cohorts of infants later diagnosed with ASD.** Mean levels of eye-looking from 2 until 24 months in N=63 typically-developing males (blue) compared with **(a)** cohort 1 of infants later diagnosed with ASD (in red, from Jones & Klin, *Nature*, 2013) and replication with **(b)** cohort 2 and **(c)** cohort 3 of infants later diagnosed with ASD (Olson et al, *under review*). Dark lines indicate mean growth curves, light lines indicate 95% CI. Infants later diagnosed with ASD show decline in levels of eye-looking between 2 and 24 months of life.

…reflects early-emerging differences in ASD.

(differences in ASD identifiable as early as the first 2-6 months after birth)

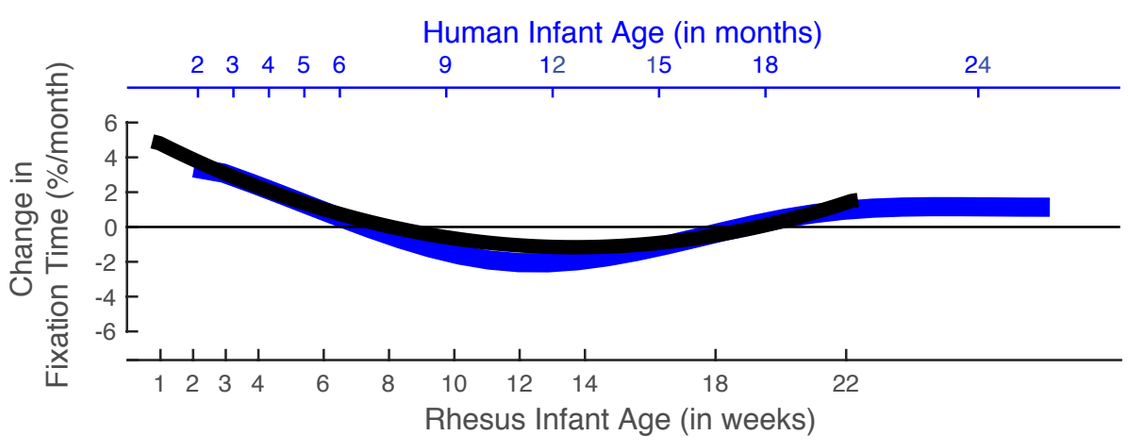
Jones & Klin. (2013) *Nature*.

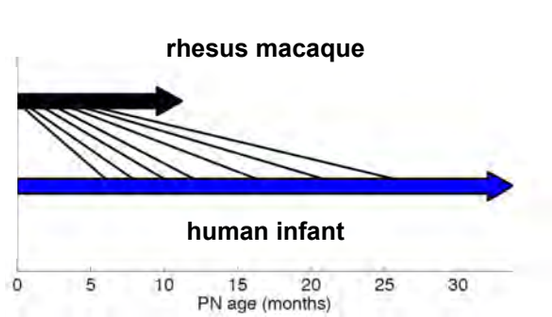
Biological Construct Validity:
Social Visual Engagement…



N=63 human infants
N=31 infant rhesus

Jocelyne Bachevalier, PhD





cross-species comparative lifespan
~4:1 human : rhesus
(Workman et al, 2013)

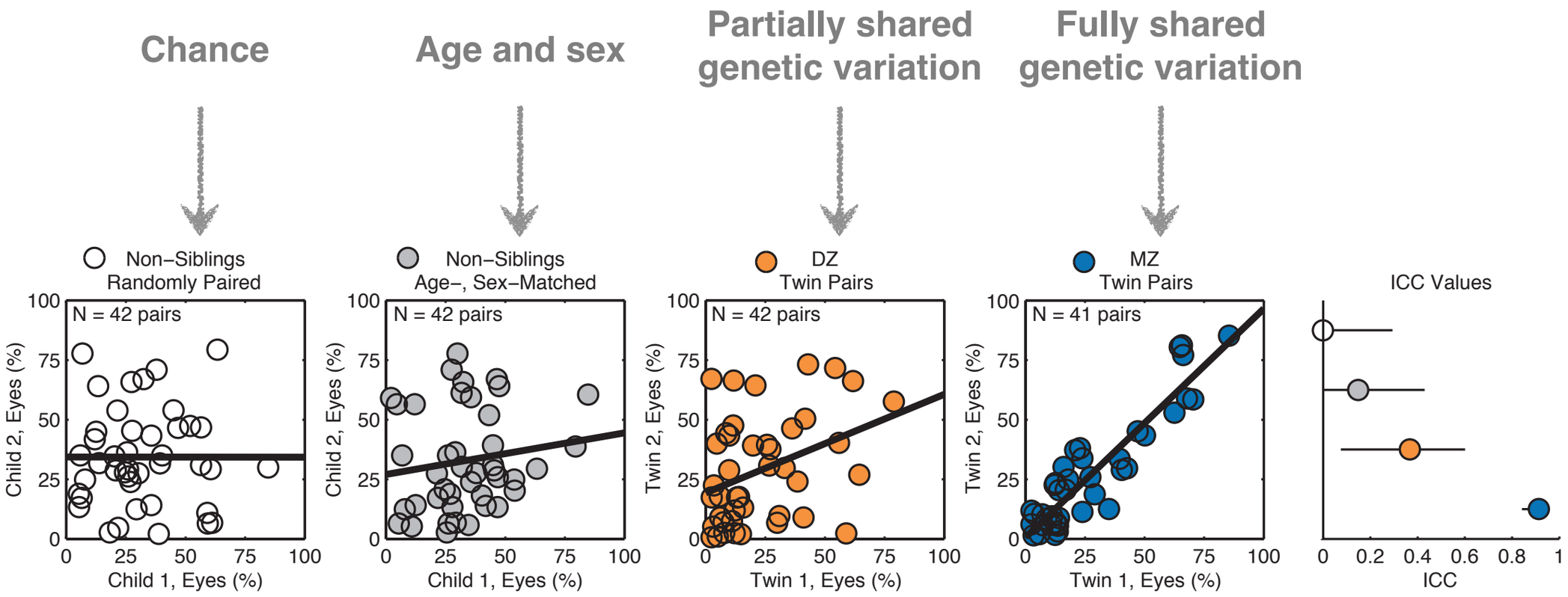
Mar Sanchez, PhD

…is highly phylogenetically-conserved.

(homologous patterns of developmental change in looking observed in human infants and infant rhesus macaques, demonstrating evolutionary importance for early social development)

Wang et al. (2020) *Dev Cogn Neurosci.*

Biological Construct Validity:
Social Visual Engagement…



…is strongly influenced by genetic variation.

(influencing millisecond timing of eye movements, with heritability of eye-looking ~0.90)

Constantino et al. (2017) *Nature*.

Basic Science to Clinical Translation

3 Studies (2 Publications)

Simultaneous publications in
JAMA & JAMA Network Open

JAMA Network | Open

Original Investigation | Psychiatry

Development and Replication of Objective Measurements of Social Visual Engagement to Aid in Early Diagnosis and Assessment of Autism

Warren Jones, PhD; Cheryl Klaiman, PhD; Shana Richardson, PhD; Meena Lambha, PhD; Morganne Reid, PhD; Taralee Hamner, PhD; Chloe Beacham, PhD; Peter Lewis, MBA; Jose Paredes, MS

Abstract

IMPORTANCE Autism spectru
condition. While 80% of parent
2 years, many children are not d

OBJECTIVE To develop an obje
assessment of autism in childre

DESIGN, SETTING, AND PART
double-blind studies, we develc
to 30 months, compared its pe
(discovery study), and then rep
Discovery and replication studie
treatment. Reference standard
specialists blind to eye-tracking
results. Children were enrolled
from March 28, 2018, to Januar

MAIN OUTCOMES AND MEAS

Research

JAMA | Original Investigation

Eye-Tracking–Based Measurement of Social Visual Engagement Compared With Expert Clinical Diagnosis of Autism

Warren Jones, PhD; Cheryl Klaiman, PhD; Shana Richardson, PhD; Christa Aoki, PhD; Christopher Smith, PhD; Mendy Minjarez, PhD; Raphael Bernier, PhD; Ernest Pedapati, MD; Somer Bishop, PhD; Whitney Ence, PhD; Allison Wainer, PhD; Jennifer Moriuchi, PhD; Sew-Wah Tay, PhD; Ami Klin, PhD

IMPORTANCE In the US, children with signs of autism often experience more than 1 year of delay before diagnosis and often experience longer delays if they are from racially, ethnically, or economically disadvantaged backgrounds. Most diagnoses are also received without use of standardized diagnostic instruments. To aid in early autism diagnosis, eye-tracking measurement of social visual engagement has shown potential as a performance-based biomarker.

OBJECTIVE To evaluate the performance of eye-tracking measurement of social visual engagement (index test) relative to expert clinical diagnosis in young children referred to specialty autism clinics.

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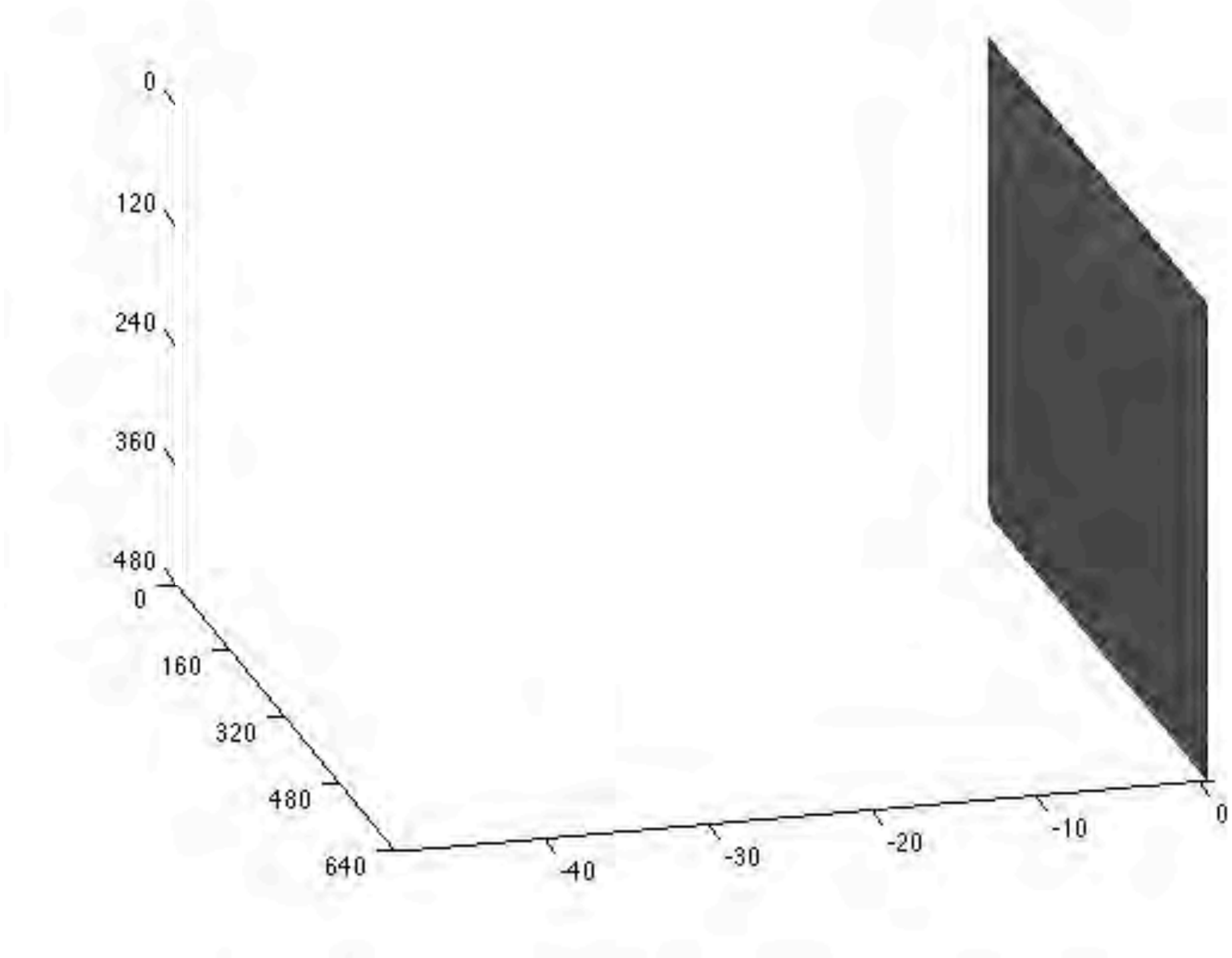
Supplemental content

Related article at jamanetworkopen.com

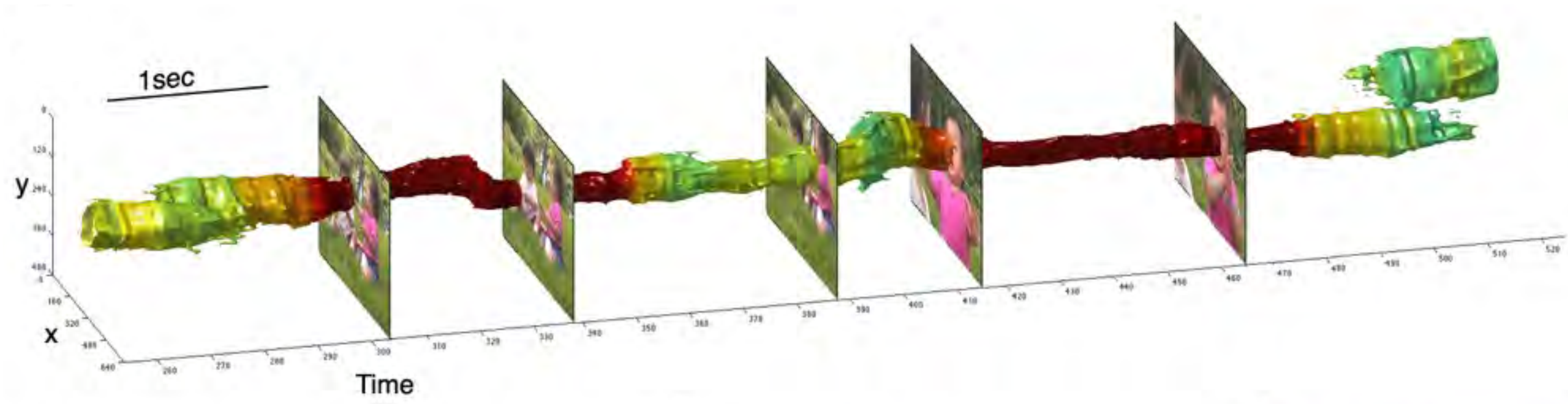
Translation to Clinical Tool:

Funnels of Attention *(at microscales of tens of milliseconds)*



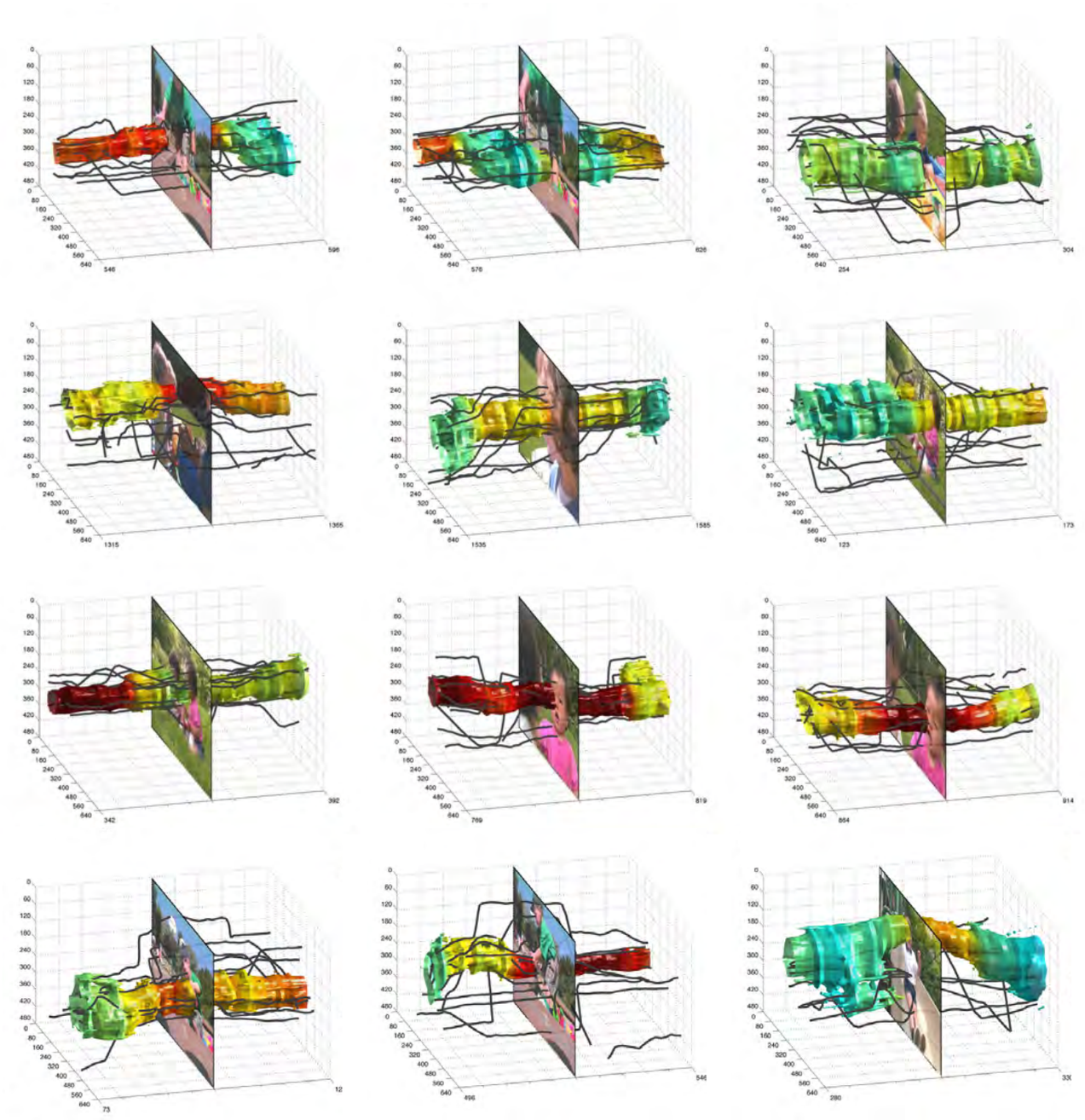
Attentional funnel denotes time-varying regions of greatest probability of fixation in typically-developing children.

Typically-Developing (TD) Toddlers Define Normative Data Model

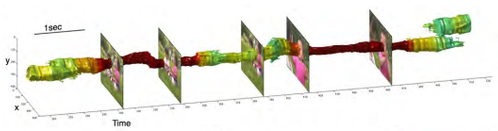


Moment-by-moment, normative benchmark data against which to compare test measurements for new children.

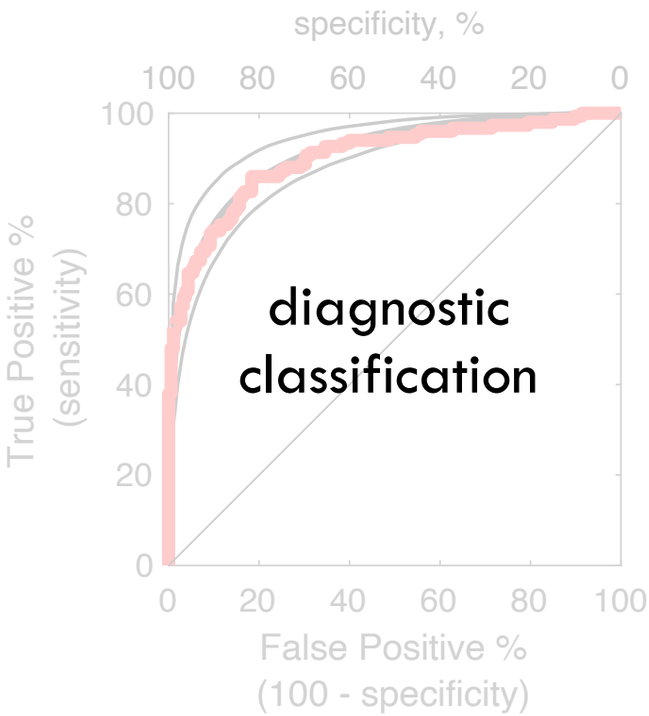
Step 1: Derive Quantitative Indices for Early Diagnostic Markers of Autism



TD normative funnels =

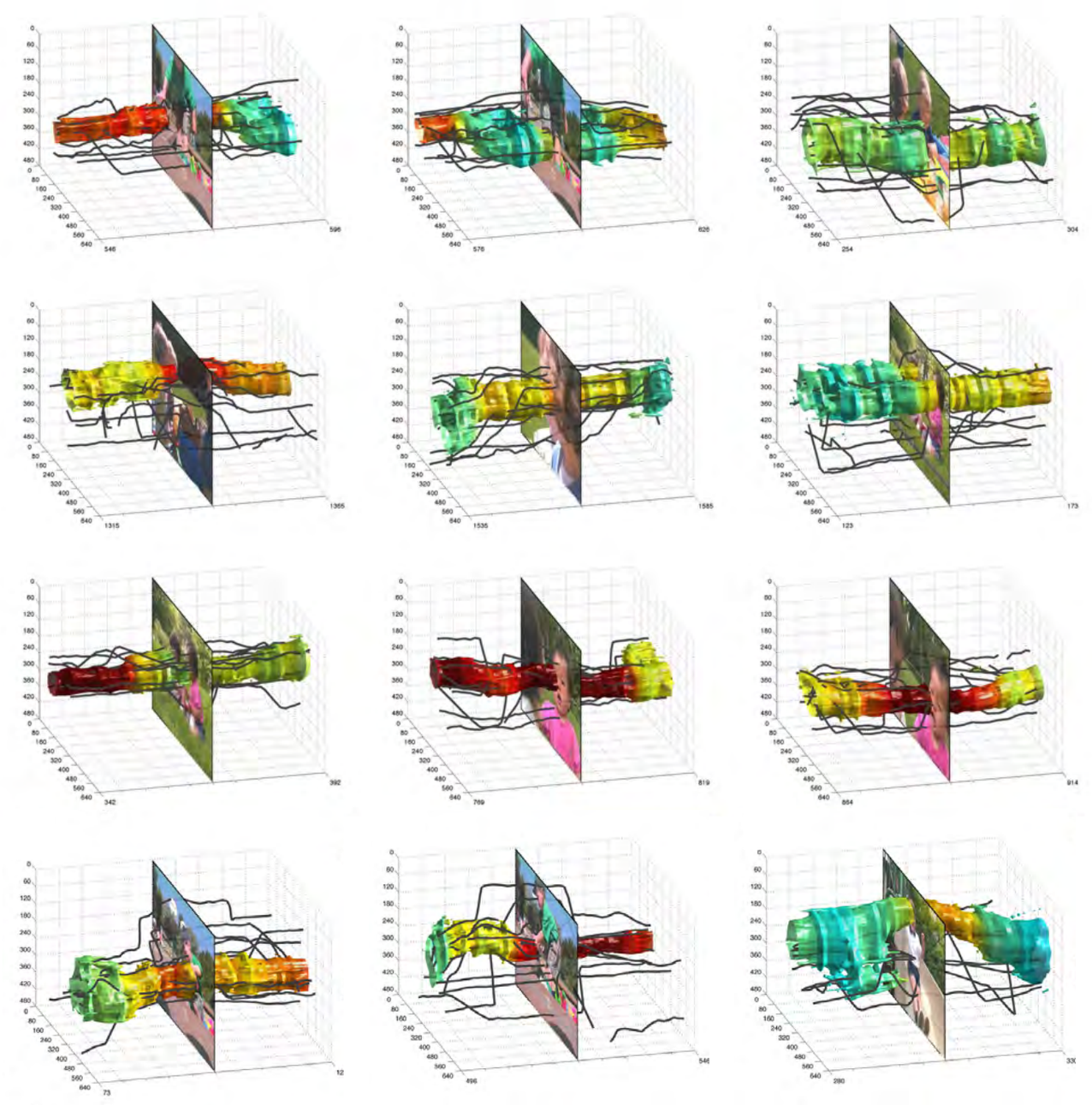


ASD comparison scanpaths =

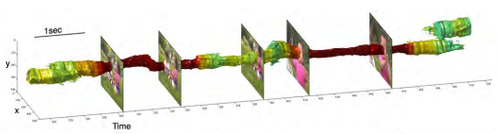


Mining 1000's of statistically significant moment-by-moment divergences from within minutes of naturalistic video viewing

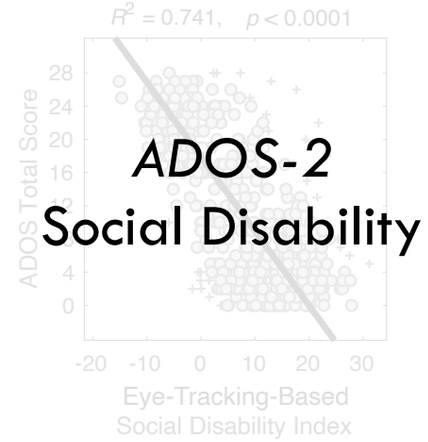
Step 2: Derive Quantitative Indices for Early Measures of Autism Symptom Severity



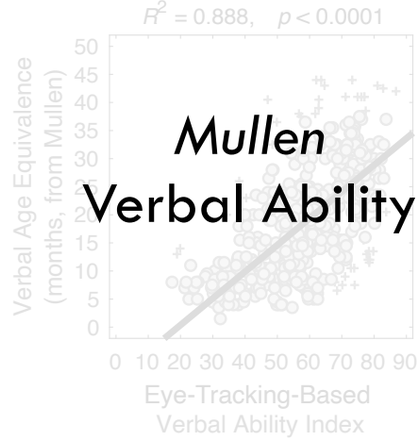
TD normative funnels =



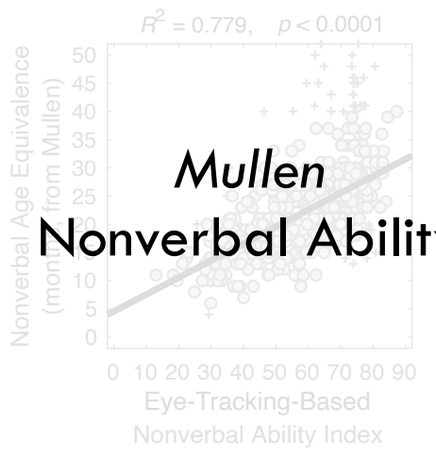
ASD comparison scanpaths =



ADOS-2
Social Disability



Mullen
Verbal Ability



Mullen
Nonverbal Ability

3 Studies (2 Publications): Discovery, Replication, & Multi-Site Trial

Goals: to test the performance of eye-tracking-based assays of social visual engagement in 16-30-month-old children to

1. accurately assess presence of ASD (se and sp relative to clinical best estimate using gold standard instruments)
2. accurately assess severity of ASD (measuring agreement with standardized measures of social disability [*ADOS-2*] and of cognitive ability [verbal and nonverbal ability, *Mullens*])

Discovery & Replication: N=1,089 toddlers (3 sites)

- N=719 Discovery Study; Marcus Autism Center (GA)
- N=370 Replication Study; Forsyth Co. (GA) and WashU (MO)

Multi-Site Trial: N=475 toddlers (6 sites)

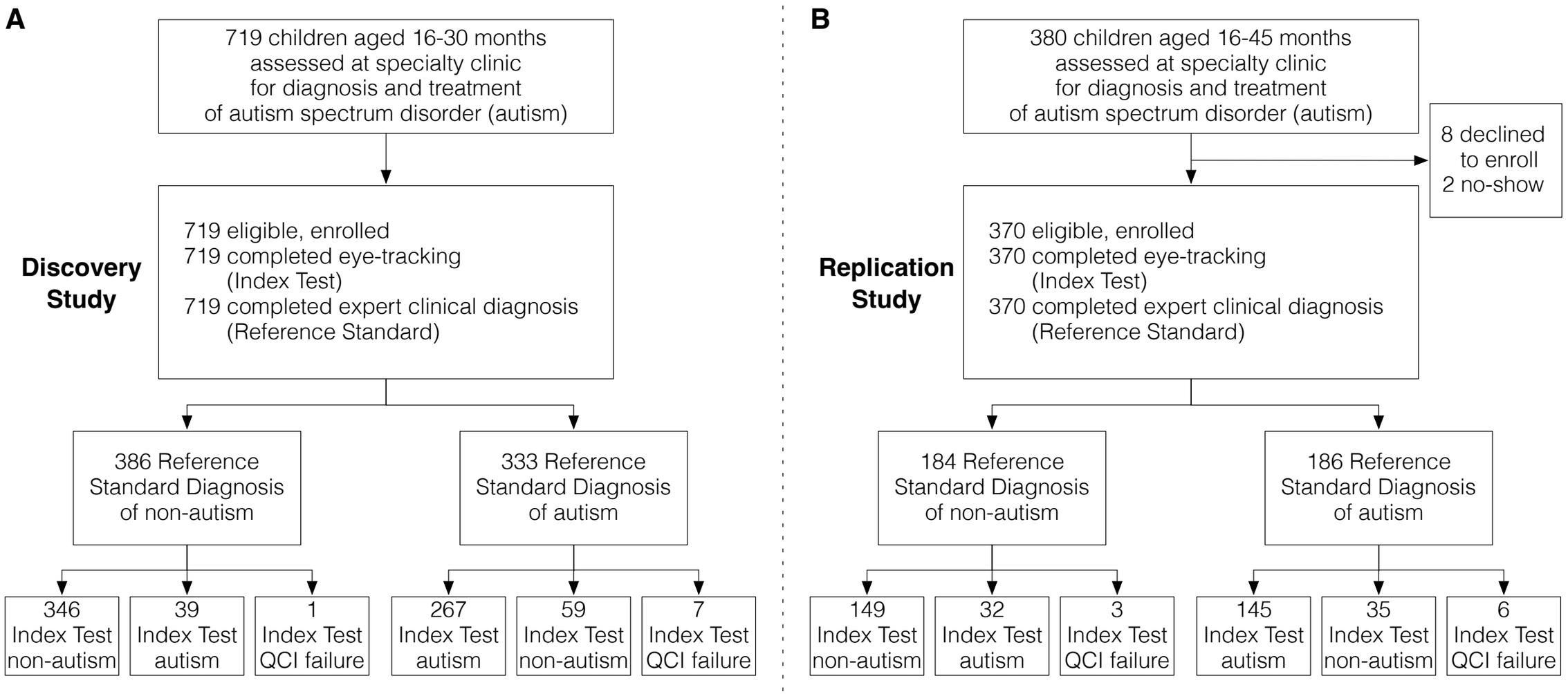
- Multi-site, nationwide clinical trial (Seattle Children's, Cincinnati Children's, UCSF, Rush, SARRC, and Emory)

Avoiding Design-Related Bias in Studies of Diagnostic Accuracy (Lijmer *et al. JAMA*, 1999)

- ☑ **Data Collection: Prospective**
  (all data collected prospectively)
- ☑ **Study Population: Broad Spectrum**
  (study samples represented full range of autism & non-autism)
- ☑ **Participant Selection: Consecutive Referrals**
  (all consecutive referrals enrolled for testing)
- ☑ **Diagnostic Verification: Complete**
  (same tests performed in all participants)
- ☑ **Collection & Analysis: Double-Blind**
  (clinical blind to eye-tracking, eye-tracking blind to clinical)

All Procedures Followed STARD Initiative (Bossuyt et al (2003) BMJ. Korevaar et al (2015). Cohen et al (2015) BMJ Open.)

Participant Flow and Outcomes



Jones et al. (2023) *JAMA Network Open*.

Participant Characterization & Demographics

Table 1. Participant Characterization & Demographics

	Discovery Study (N = 719)		Replication Study (N = 370)	
Reference Standard Diagnosis	non-autism	autism	non-autism	autism
N	386	333	184	186
Age				
months: mean (SD)	21.7 (3.4)	23.1 (3.7)	22.7 (4.9)	28.1 (5.8)
percentiles [1st, 25th, 50th, 75th, 99th]	[15, 18, 23, 24, 30]	[16, 20, 24, 26, 30]	[16, 19, 21, 25, 36]	[17, 24, 28, 31, 43]
Sex – no. (%)				
Female	154 (39.9%)	70 (21.0%)	78 (42.4%)	42 (22.6%)
Male	232 (60.1%)	263 (79.0%)	106 (57.6%)	144 (77.4%)
Race – no. (%)				
Asian	5 (1.3%)	10 (3.0%)	1 (0.5%)	23 (12.4%)
Black / African-American	21 (5.4%)	67 (20.1%)	22 (12.0%)	38 (20.4%)
Caucasian	281 (72.8%)	179 (53.8%)	139 (75.6%)	106 (57.0%)
Native Hawaiian or Pacific Islander	4 (1.0%)	3 (0.9%)	2 (1.1%)	0 (0.0%)
More than one race	28 (7.3%)	41 (12.3%)	19 (10.3%)	16 (8.6%)
Prefer not to answer / unknown	47 (12.2%)	33 (9.9%)	1 (0.5%)	3 (1.6%)
Ethnicity – no. (%)				
Hispanic	24 (6.2%)	23 (6.9%)	12 (6.5%)	20 (10.8%)
Non-Hispanic	309 (80.1%)	268 (80.5%)	166 (90.2%)	154 (82.8%)
Prefer not to answer / unknown	53 (13.7%)	41 (12.3%)	6 (3.3%)	12 (6.4%)
Income – no. (%)				
≤ $20,000	5 (1.3%)	13 (3.9%)	14 (7.6%)	2 (1.1%)
$20,001–$40,000	17 (4.4%)	29 (8.7%)	21 (11.4%)	16 (8.6%)
$40,001–$60,000	32 (8.3%)	48 (14.5%)	35 (19.0%)	42 (22.6%)
$60,001–$80,000	37 (9.6%)	51 (15.3%)	31 (16.8%)	57 (30.6%)
$80,001–$100,000	51 (13.2%)	33 (9.9%)	29 (15.8%)	29 (15.6%)
$100,001–$125,000	56 (14.5%)	26 (7.8%)	21 (11.4%)	17 (9.1%)
$125,001–$150,000	26 (6.7%)	13 (3.9%)	10 (5.5%)	11 (5.9%)

Jones et al. (2023) *JAMA Network Open*.

Participant Characterization & Demographics

$150,001–$200,000	40 (10.4%)	12 (3.6%)	8 (4.3%)	5 (2.7%)
≥ $200,000	33 (8.5%)	6 (1.8%)	5 (2.7%)	0 (0.0%)
Prefer not to answer / unknown	89 (23.1%)	102 (30.6%)	10 (5.5%)	7 (3.8%)
Maternal Education – no. (%)				
Some High School	0 (0.0%)	4 (1.2%)	1 (0.5%)	4 (2.1%)
High School or GED	8 (2.1%)	20 (6.0%)	19 (10.3%)	29 (15.6%)
Some College, No Degree	15 (3.9%)	55 (16.5%)	31 (16.8%)	21 (11.3%)
Vocational School	1 (0.3%)	12 (3.6%)	6 (3.3%)	2 (1.1%)
Associate's Degree	4 (1.0%)	14 (4.2%)	14 (7.6%)	13 (7.0%)
Bachelor's Degree	114 (29.5%)	98 (29.5%)	74 (40.2%)	76 (40.9%)
Master's Degree	135 (35.0%)	55 (16.5%)	31 (16.8%)	29 (15.6%)
Professional or Doctoral Degree	51 (13.2%)	14 (4.2%)	5 (2.7%)	8 (4.3%)
Prefer not to answer / unknown	58 (15.0%)	61 (18.3%)	3 (1.6%)	4 (2.1%)
Autism Diagnostic Observation Schedule, 2nd Ed. (ADOS-2)*				
SA Score, mean (SD)	2.3 (2.3)	13.6 (4.1)	3.1 (2.6)	13.8 (4.4)
percentiles [1st, 25th, 50th, 75th, 99th]	[0, 1, 2, 3, 11]	[5, 10, 14, 17, 20]	[0, 1, 3, 5, 11]	[6, 10, 14, 17, 21]
RRB Score, mean (SD)	1.0 (0.9)	4.3 (1.8)	2.4 (1.6)	5.6 (1.4)
percentiles [1st, 25th, 50th, 75th, 99th]	[0, 0, 1, 2, 4]	[1, 3, 4, 6, 8]	[0, 1, 2, 4, 6]	[2, 5, 6, 7, 8]
Total Score, mean (SD)	3.3 (2.6)	17.9 (5.1)	5.5 (3.2)	19.4 (5.0)
percentiles [1st, 25th, 50th, 75th, 99th]	[0, 2, 3, 5, 12]	[8, 14, 18, 22, 27]	[0, 3, 5, 7, 13]	[8, 15, 20, 24, 28]
Mullen Scales of Early Learning**				
Verbal Age Equiv., mean (SD)	24.2 (5.6)	13.0 (6.2)	23.1 (8.0)	14.8 (7.7)
percentiles [1st, 25th, 50th, 75th, 99th]	[12, 20, 24, 28, 36]	[3, 8, 12, 16, 29]	[10, 16, 23, 28, 39]	[4, 10, 12, 18, 38]
Nonverbal Age Equiv., mean (SD)	24.8 (6.1)	19.0 (5.2)	27.3 (9.8)	20.7 (6.8)
percentiles [1st, 25th, 50th, 75th, 99th]	[15, 20, 24, 29, 40]	[7, 16, 19, 23, 32]	[13, 19, 25, 32, 48]	[9, 16, 20, 24, 42]

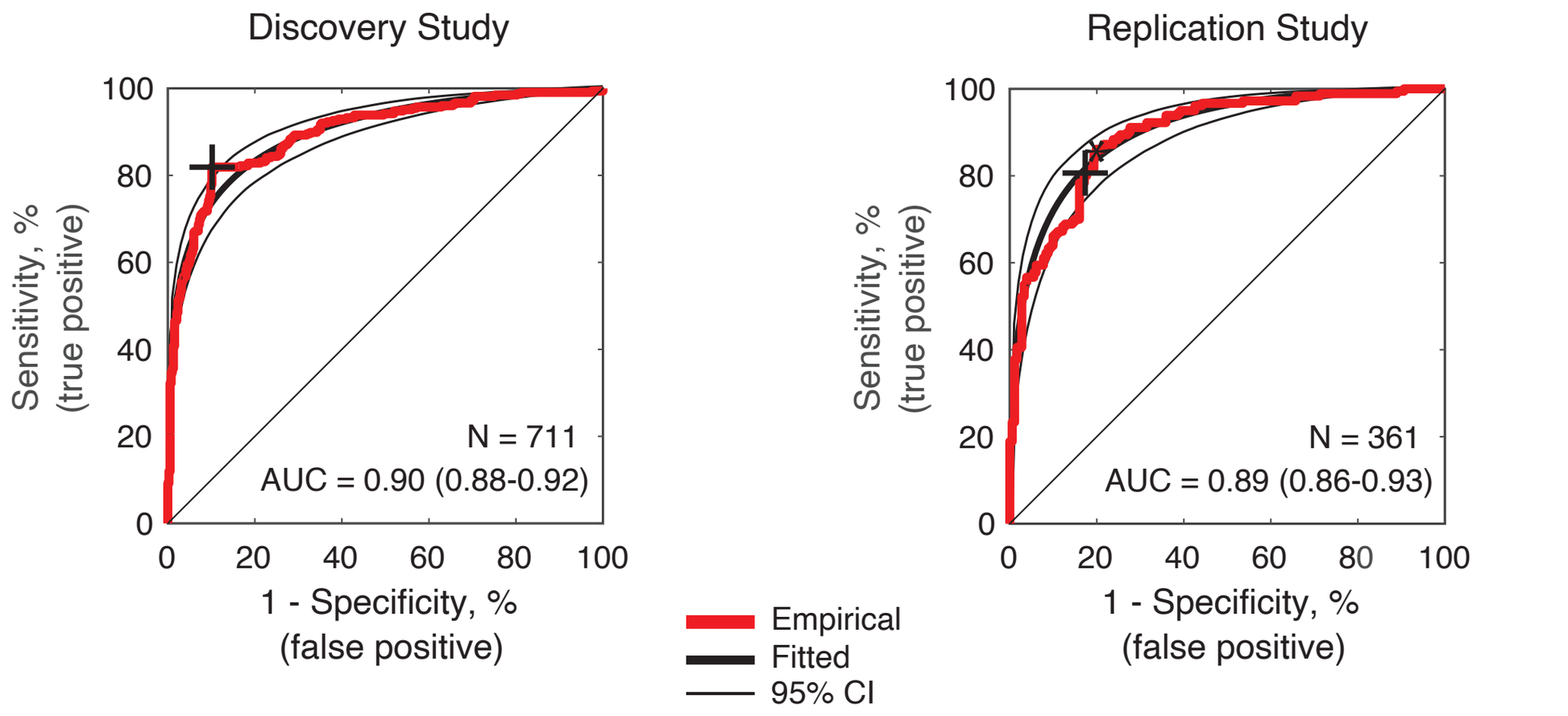
* - *Autism Diagnostic Observation Schedule 2nd Edition*, SA = Social Affect domain score; RRB = Restricted and Repetitive Behavior domain score; Discovery N_{ADOS} = 564 (333 autism, 231 non-autism), Replication N_{ADOS} = 255 (186 autism, 69 non-autism), see Supplementary Materials: Reference Standard Diagnostic Assessment Procedures.

** - *Mullen Scales of Early Learning*, Verbal Age Equiv = verbal ability age equivalent score, in months, calculated as average of expressive and receptive language age equivalent scores; Nonverbal Age Equiv = nonverbal ability age equivalent score, in months, calculated as visual reception age equivalent score; Discovery N_{Mullen} = 620 (333 autism, 287 non-autism, 10 missing nonverbal), Replication N_{Mullen} = 251 (183 autism, 68 non-autism), see Supplementary Materials: Reference Standard Diagnostic Assessment Procedures.

Jones et al. (2023) *JAMA Network Open*.

Diagnostic Performance

Eye-Tracking in Comparison with Reference Standard Expert Clinicians



	%	95% CI
Sensitivity	81.9	(77.3-85.7)
Specificity	89.9	(86.4-92.5)
PPV	87.3	(83.0-90.6)
NPV	85.4	(81.6-88.6)
Accuracy	86.2	(83.5-88.6)

	%	95% CI
Sensitivity	80.6	(74.1-85.7)
Specificity	82.3	(76.1-87.2)
PPV	81.9	(75.6-86.9)
NPV	81.0	(74.7-86.0)
Accuracy	81.4	(77.1-85.1)

Classification threshold frozen in advance on basis of Discovery Study to test in Replication Study.

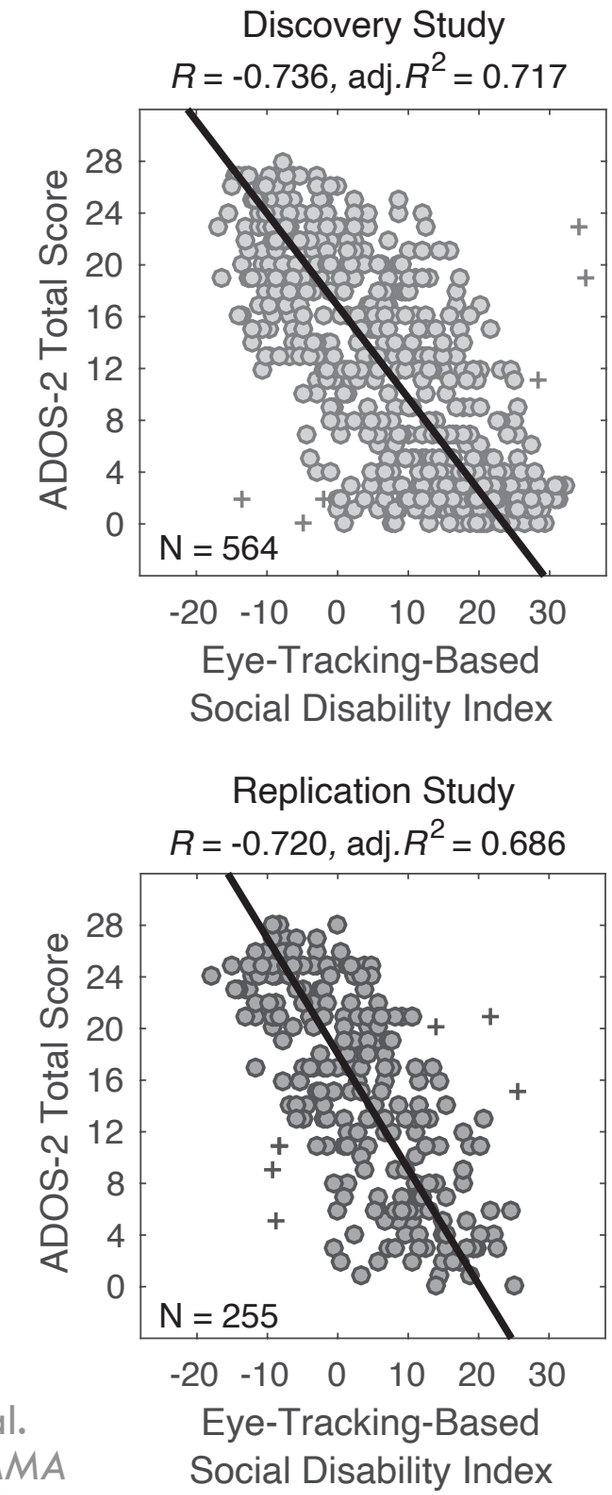
Jones et al. (2023) *JAMA Network Open.*

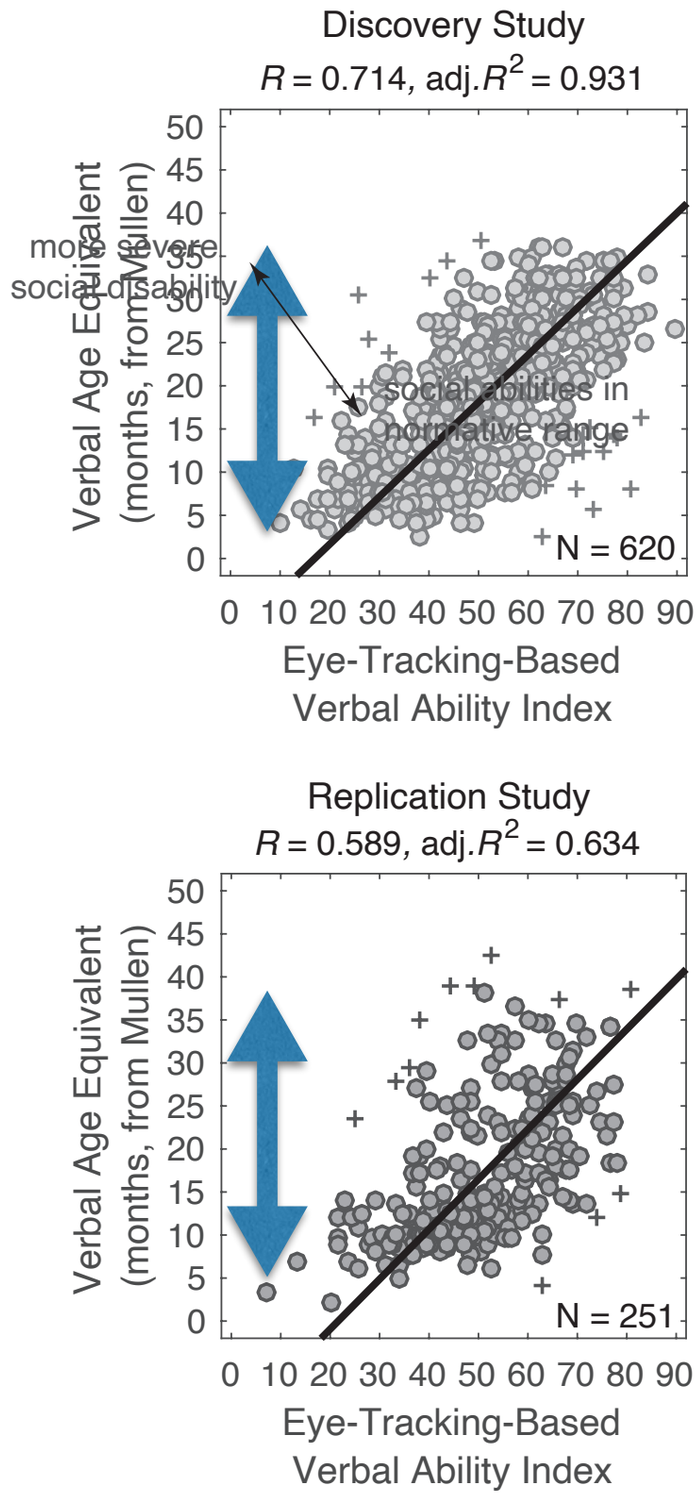
Diagnostic Performance Summary

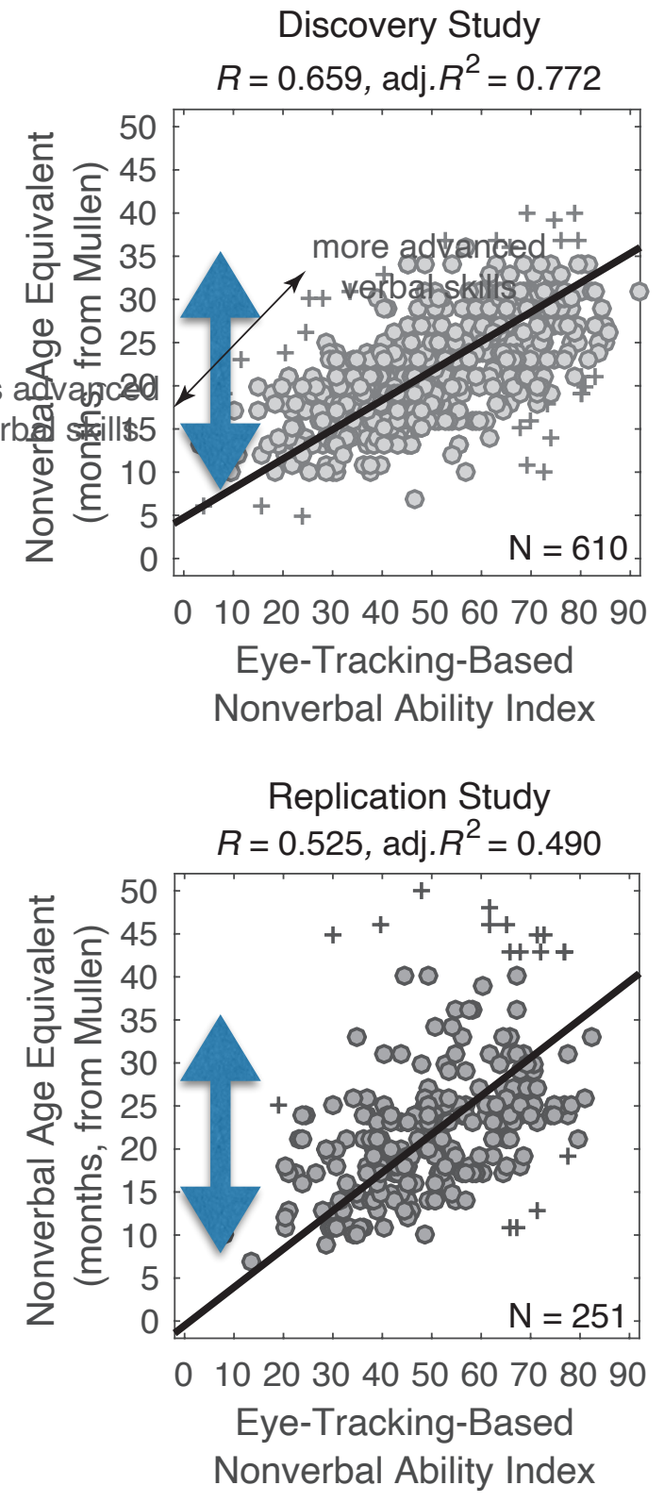
- Initial discovery study and first replication showed high sensitivity and specificity when comparing eye-tracking-based measures of social visual engagement with expert clinician diagnosis in children approximately 16-30 months old (*se* ~80%, *sp* ~80%).
  - *~5-10 minutes of video watching compared with 6-8 hours of comprehensive diagnostic and developmental evaluation conducted by a PhD- and/or MD-trained expert clinician.*
- *In current US healthcare landscape, average age of diagnosis remains ~4-5 years. Fewer than 20% of children receiving special education services in later life are currently identified by age 3 years (equivalent to very high false negative rate).*

Assessment Performance

Assessment of Individual Symptom Severity in 3 Behavioral Domains







Jones et al. (2023) *JAMA Network Open*.

Measurement Derivation

Objective, Performance-Based Measures of Children's Individual Vulnerabilities and Opportunities for Skills development

Example: Nonverbal Communication & Gestures

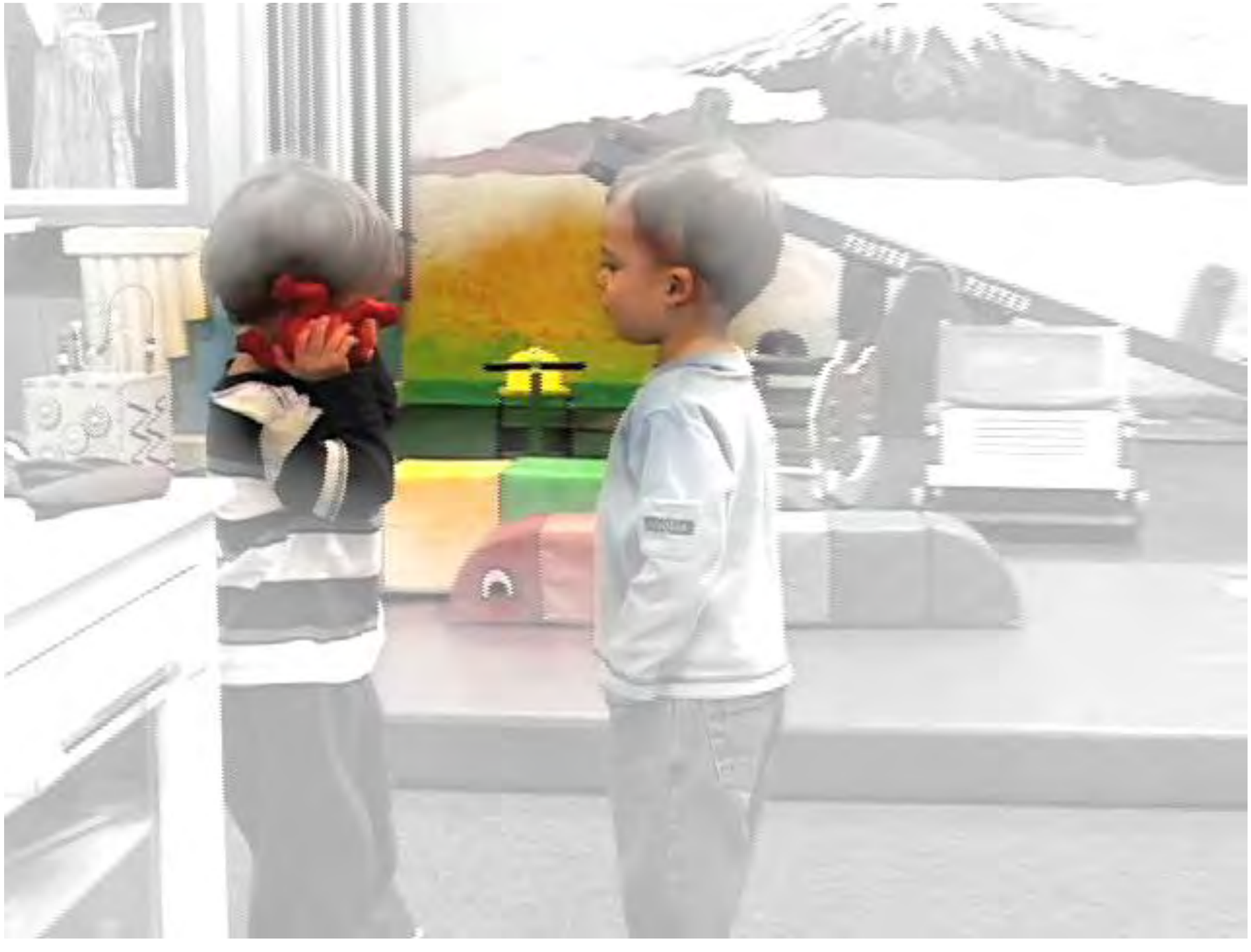
Environmental Context

Jones et al. (2023) *JAMA Network Open*.

Measurement Derivation

Objective, Performance-Based Measures of Children's Individual Vulnerabilities and Opportunities for Skills development

Example: Nonverbal Communication & Gestures



Quantitative Reference Metric: Age-Expected Social Visual Engagement

Jones et al. (2023) *JAMA Network Open*.

Measurement Derivation

Objective, Performance-Based Measures of Children's Individual Vulnerabilities and Opportunities for Skills development

Child with Autism

Jones et al. (2023) *JAMA Network Open*.

Clinical Significance

Objective, Performance-Based Measures of Children's Individual Vulnerabilities and Opportunities for Skills development

Example: Facial Affect

Environmental Context

Jones et al. (2023) *JAMA Network Open*.

Clinical Significance

Objective, Performance-Based Measures of Children's Individual Vulnerabilities and Opportunities for Skills development

Example: Facial Affect

Quantitative Reference Metric: Age-Expected Social Visual Engagement

Jones et al. (2023) *JAMA Network Open*.

Clinical Significance

Objective, Performance-Based Measures of Children's Individual Vulnerabilities and Opportunities for Skills development

Jones et al. (2023) *JAMA Network Open*.

Clinical Significance

Objective, Performance-Based Measures of Children's Individual Vulnerabilities and Opportunities for Skills development

Example: Pointing & Social Monitoring

Environmental Context

Jones et al. (2023) *JAMA Network Open*.

Clinical Significance

Objective, Performance-Based Measures of Children's Individual Vulnerabilities and Opportunities for Skills development

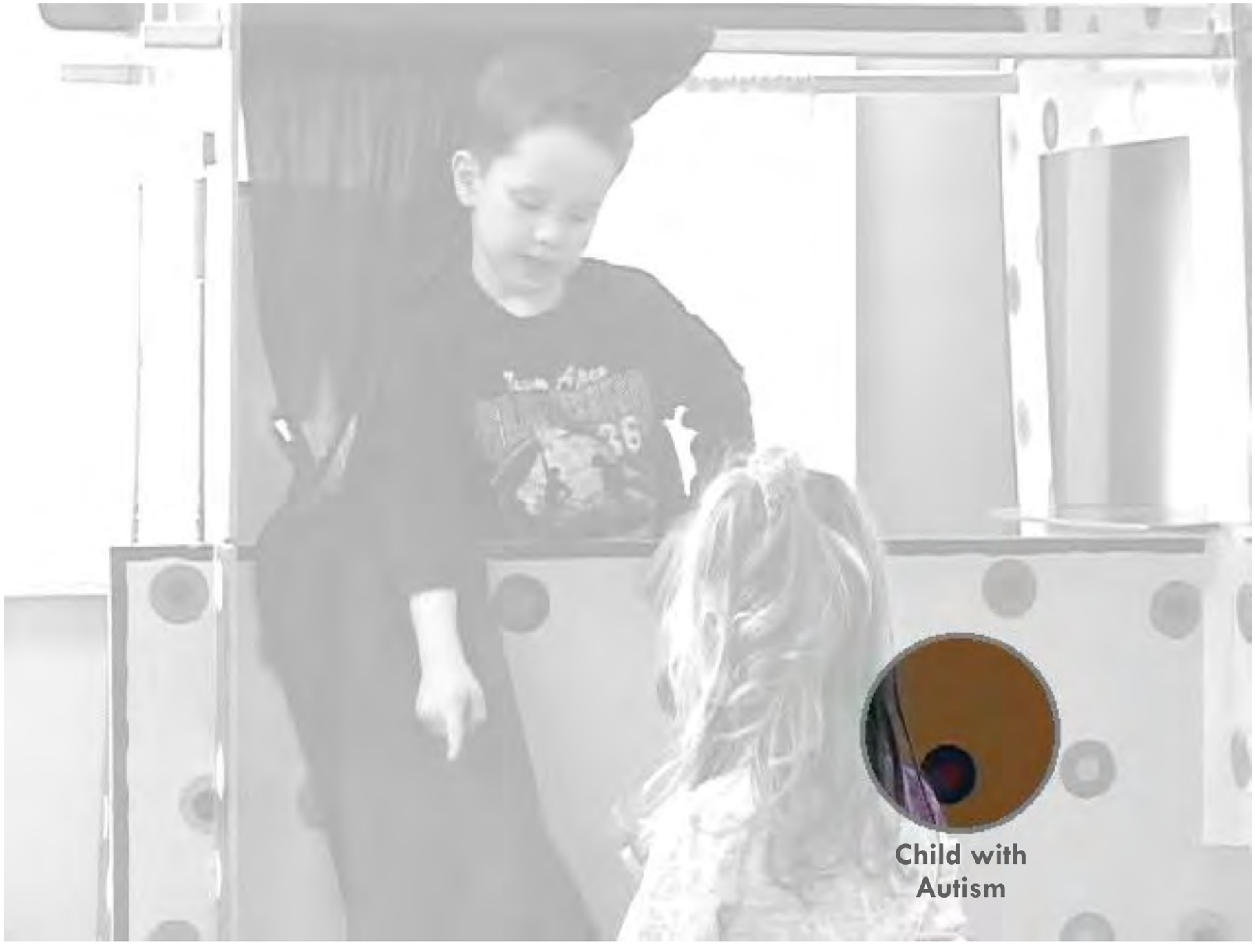
Example: Pointing & Social Monitoring

Quantitative Reference Metric: Age-Expected Social Visual Engagement

Jones et al. (2023) *JAMA Network Open.*

Clinical Significance

Objective, Performance-Based Measures of Children's Individual Vulnerabilities and Opportunities for Skills development



Child with Autism

Jones et al. (2023) *JAMA Network Open*.

Clinical Significance

Objective, Performance-Based Measures of Children's Individual Vulnerabilities and Opportunities for Skills development

Environmental Context

Quantitative Reference Metric: Age-Expected Social Visual Engagement

Child with ASD

Jones et al. (2023) *JAMA Network Open*.

Multi-Site Clinical Trial
Testing Performance at 6 Sites

Collaborating Trial Team

- ★ Southwest Autism Research & Resource Center (SARRC)
- ★ Emory University
- ★ Seattle Children's Hospital
- ★ Cincinnati Children's Hospital
- ★ UC-San Francisco
- ★ Rush University Medical Center

(https://clinicaltrials.gov/ct2/show/NCT03469986)

Avoiding Design-Related Bias in Studies of Diagnostic Accuracy (Lijmer *et al. JAMA*, 1999)

- ☑ **Data Collection: Prospective**
  (all data collected prospectively)
- ☑ **Study Population: Broad Spectrum**
  (study samples represented full range of autism & non-autism)
- ☑ **Participant Selection: Consecutive Referrals**
  (all consecutive referrals enrolled for testing)
- ☑ **Diagnostic Verification: Complete**
  (same tests performed in all participants)
- ☑ **Collection & Analysis: Double-Blind**
  (clinical blind to eye-tracking, eye-tracking blind to clinical)

All Procedures Followed STARD Initiative (Bossuyt et al (2003) BMJ. Korevaar et al (2015). Cohen et al (2015) BMJ Open.

Participant Flow and Outcomes

505 children aged 16-30 months
assessed at specialty clinics
for diagnosis and treatment
of autism spectrum disorder (autism)

6 ineligible or withdrew
- 3: ineligible, met exclusion criteria
  - 2: vision impairments
  - 1: specific criterion not recorded by site
- 3: withdrew

499 eligible, enrolled

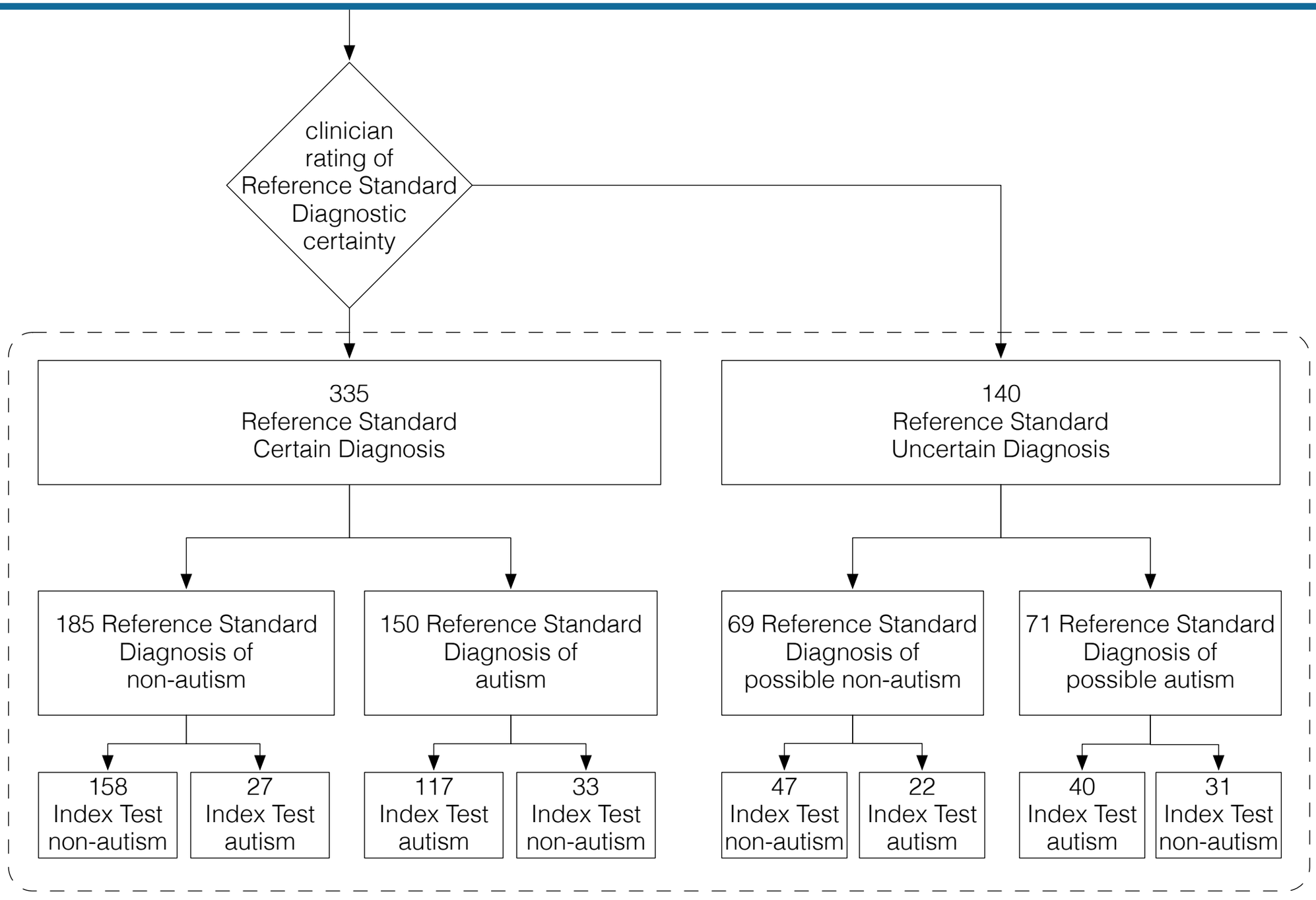
24 missing Index Test data
- 11: failed automated eye-tracking quality control indicators
- 8: children unwilling to sit
- 5: device malfunction

475 completed eye-tracking measurement of social visual engagement (Index Test)
475 completed expert clinical diagnosis (Reference Standard)
475 with rating of expert diagnostic certainty

McDonnell et al (2019) *JADD*. *Clinicians uncertain of autism diagnosis in 40% of clinic cases.*

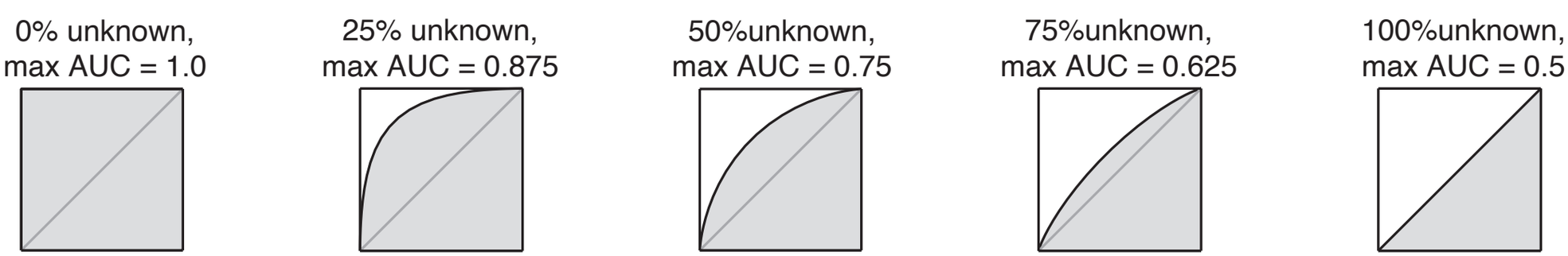
Jones et al. (2023) *JAMA*.

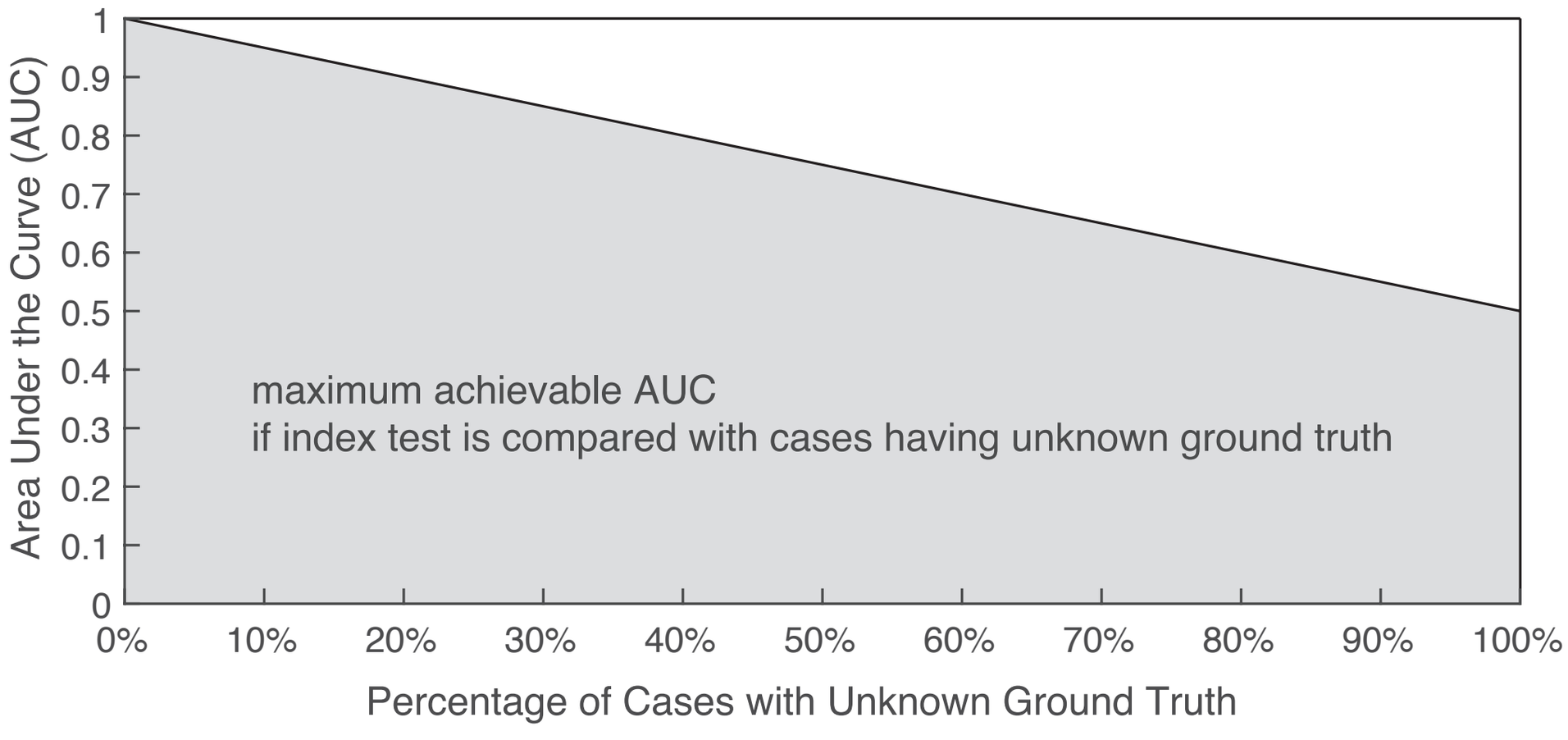
Participant Flow and Outcomes



Jones et al. (2023) *JAMA*.

Effects of Unknown Reference Standard on Index Test Performance Metrics





Jones et al.
(2023) *JAMA*.

Participant Characterization & Demographics

Table 1. Participant Characterization & Demographics

	N = 475 All Participants [a]		N = 335 Certain Diagnosis	
Reference Standard Diagnosis	non-autism or possible non-autism	autism or possible autism	non-autism	autism
N	254	221	185	150
Age, months				
mean (SD)	23.4 (4.5)	24.9 (4.2)	23.4 (4.6)	24.9 (4.1)
median (q1, q3)	24 (19, 27)	26 (21, 29)	24 (19, 28)	26 (22, 29)
Sex – no. (%)				
Female	127 (50.0%)	57 (25.8%)	102 (55.1%)	38 (25.3%)
Male	127 (50.0%)	164 (74.2%)	83 (44.9%)	112 (74.7%)
Race – no. (%) [b]				
Asian	17 (6.7%)	21 (9.5%)	10 (5.4%)	14 (9.3%)
Black / African-American	15 (5.9%)	22 (9.9%)	11 (5.9%)	16 (10.7%)
Caucasian	203 (79.9%)	149 (67.4%)	147 (79.5%)	95 (63.3%)
Native Hawaiian or Pacific Islander	0 (0.0%)	2 (0.9%)	0 (0.0%)	1 (0.7%)
Other	18 (7.1%)	26 (11.8%)	17 (9.2%)	23 (15.3%)
Unknown	1 (0.4%)	1 (0.5%)	0 (0.0%)	1 (0.7%)
Ethnicity – no. (%) [c]				
Hispanic	24 (9.4%)	44 (19.9%)	16 (8.7%)	26 (17.3%)
Non-Hispanic	225 (88.6%)	177 (80.1%)	166 (89.7%)	124 (82.7%)
no response	5 (2.0%)	0 (0.0%)	3 (1.6%)	0 (0.0%)
Maternal Education – no. (%) [d]				
Less than 8th Grade	1 (0.4%)	0 (0.0%)	1 (0.5%)	0 (0.0%)
Some High School	3 (1.2%)	4 (1.8%)	3 (1.6%)	3 (2.0%)
High School or GED	12 (4.7%)	33 (14.9%)	6 (3.2%)	23 (15.3%)
Some College, No Degree	22 (8.6%)	39 (17.7%)	12 (6.5%)	31 (20.7%)
Vocational School	2 (0.8%)	12 (5.4%)	0 (0.0%)	7 (4.7%)
Associate's Degree	13 (5.1%)	13 (5.9%)	12 (6.5%)	8 (5.4%)

Jones et al. (2023) *JAMA*.

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Associate's Degree	13 (5.1%)	13 (5.9%)	12 (6.5%)	8 (5.4%)
Bachelor's Degree	79 (31.1%)	71 (32.1%)	59 (31.9%)	50 (33.3%)
Master's Degree	82 (32.3%)	41 (18.6%)	59 (31.9%)	23 (15.3%)
Professional or Doctoral Degree	35 (13.8%)	2 (0.9%)	29 (15.7%)	0 (0.0%)
no response	5 (2.0%)	6 (2.7%)	4 (2.2%)	5 (3.3%)
Autism Diagnostic Observation Schedule, 2nd Ed. (ADOS-2) [e,f]				
Social Affect Score, mean (SD)	2.9 (3.0)	14.7 (4.3)	2.1 (2.1)	16.1 (3.5)
median (q1, q3)	2 (1, 4)	16 (11, 18)	1 (0, 3)	17 (14, 19)
RRB Score, mean (SD)	1.2 (1.3)	4.9 (2.0)	0.9 (1.0)	5.4 (1.9)
median (q1, q3)	1 (0, 2)	5 (4, 6)	1 (0, 1)	6 (4, 7)
Total Score, mean (SD)	4.1 (3.5)	19.6 (5.1)	2.9 (2.4)	21.4 (4.1)
median (q1, q3)	3 (2, 6)	20 (16, 24)	3 (1, 4)	22 (18, 24)
Mullen Scales of Early Learning [g]				
Verbal Age Equiv., mean (SD)	24.5 (8.3)	12.5 (7.1)	26.0 (8.2)	10.5 (5.3)
median (q1, q3)	24 (19, 31)	11 (8, 16)	25 (20, 32)	9 (7, 13)
Nonverbal Age Equiv., mean (SD)	26.5 (8.7)	18.5 (5.9)	27.4 (9.0)	17.3 (5.0)
median (q1, q3)	25 (20, 30)	18 (15, 21)	26 (21, 31)	17 (14, 21)
Other Non-Autism Diagnoses [h]				
Developmental Disability	210 (82.7%)	124 (56.1%)	162 (87.6%)	86 (57.3%)
no other diagnoses (unaffected)	44 (17.3%)	0 (0.0%)	23 (12.4%)	0 (0.0%)

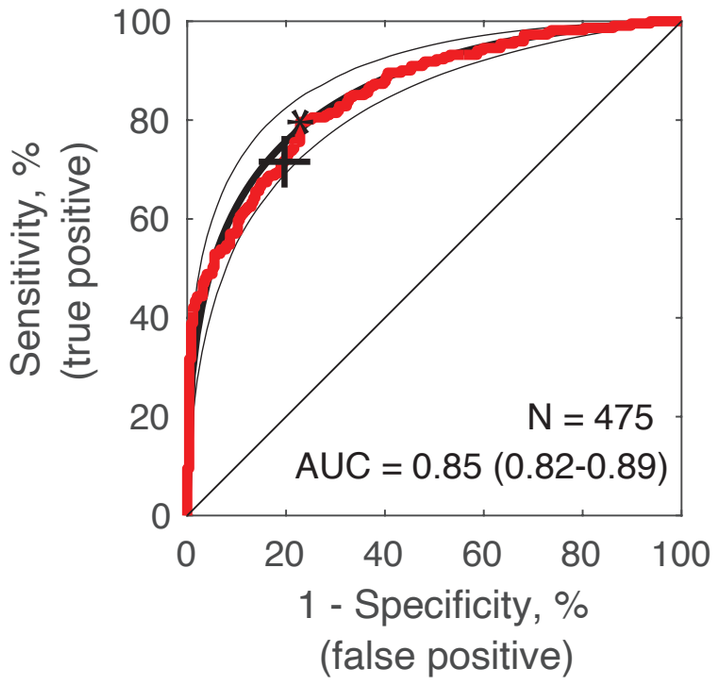
Jones et al. (2023) *JAMA*.

[a] - For a table summarizing participant characterization and demographics data for all participants eligible and enrolled (N=499), irrespective of diagnostic outcomes, please see Supplementary Table 1.

Diagnostic Performance

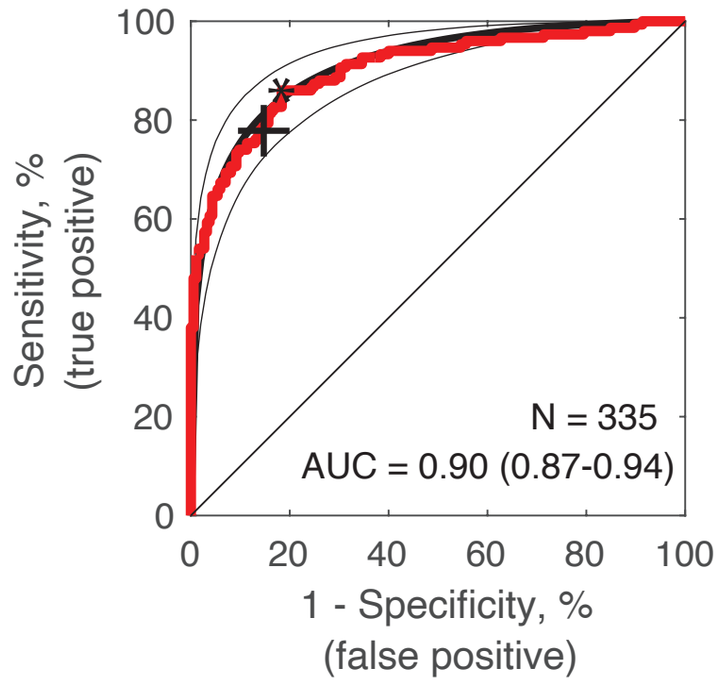
Eye-Tracking in Comparison with Reference Standard Expert Clinicians

All Participants



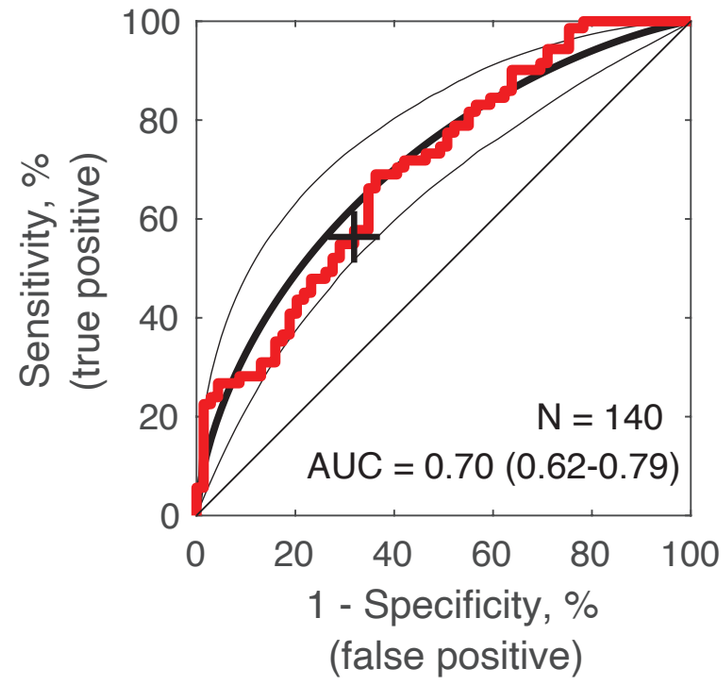
	%	95% CI
Sensitivity	71.0	(64.7-76.6)
Specificity	80.7	(75.4-85.1)
PPV	76.2	(69.9-81.5)
NPV	76.2	(70.8-80.9)
Accuracy	76.2	(72.2-79.8)

Certain Diagnosis



	%	95% CI
Sensitivity	78.0	(70.7-83.9)
Specificity	85.4	(79.5-89.8)
PPV	81.2	(74.0-86.8)
NPV	82.7	(76.7-87.5)
Accuracy	82.1	(77.6-85.8)

Uncertain Diagnosis



	%	95% CI
Sensitivity	56.3	(44.8-67.3)
Specificity	68.1	(56.4-77.9)
PPV	64.5	(52.1-75.3)
NPV	60.3	(49.2-70.4)
Accuracy	62.1	(53.9-69.8)

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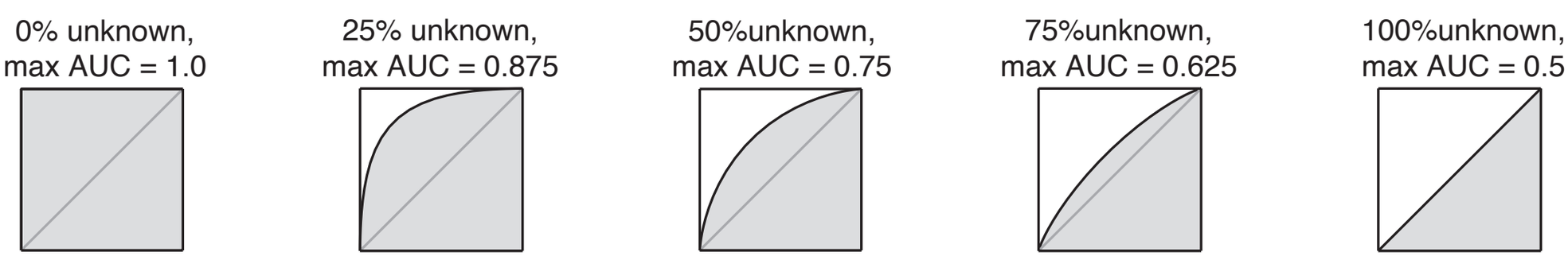
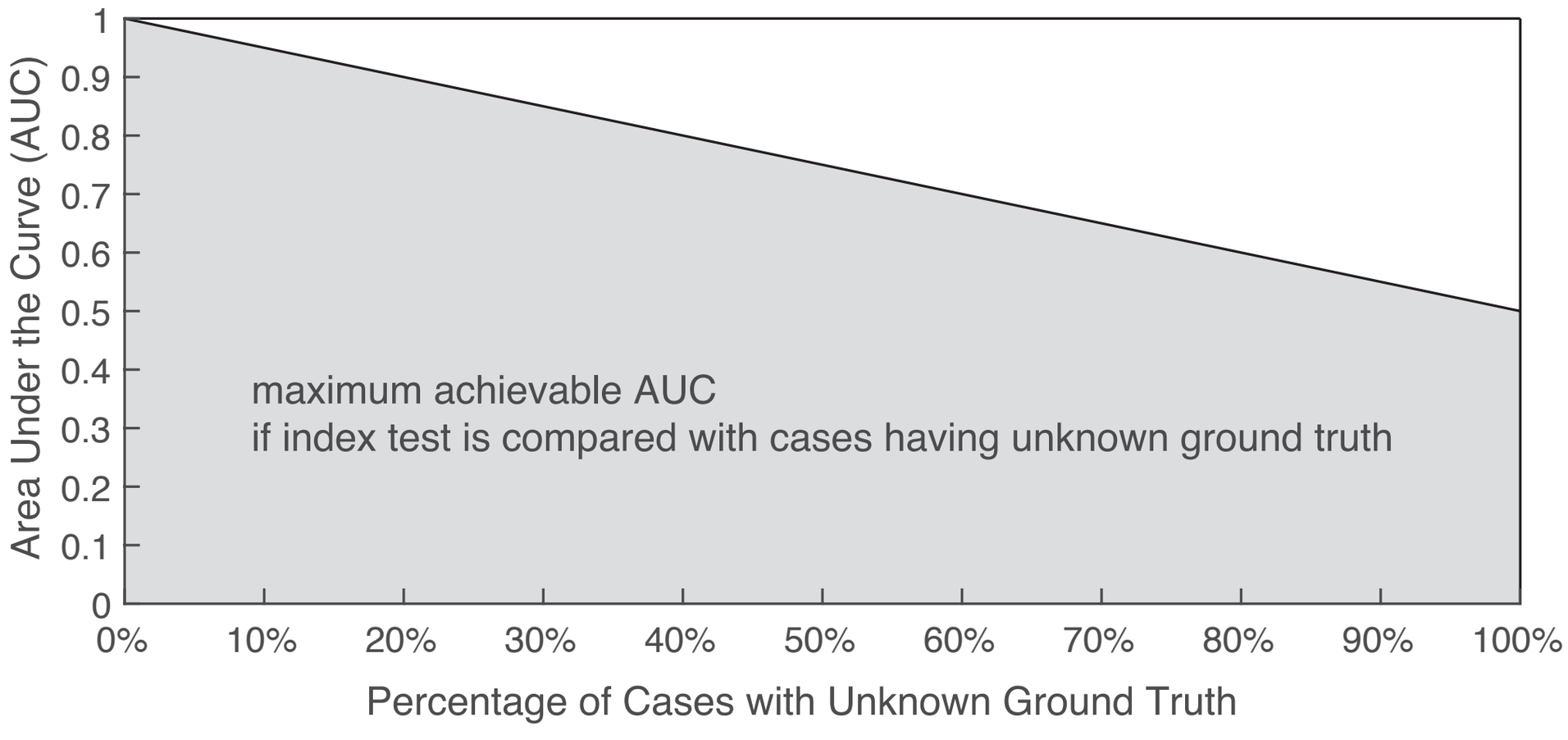
(2023) *JAMA*.

Effects of Unknown Reference Standard on Index Test Performance Metrics





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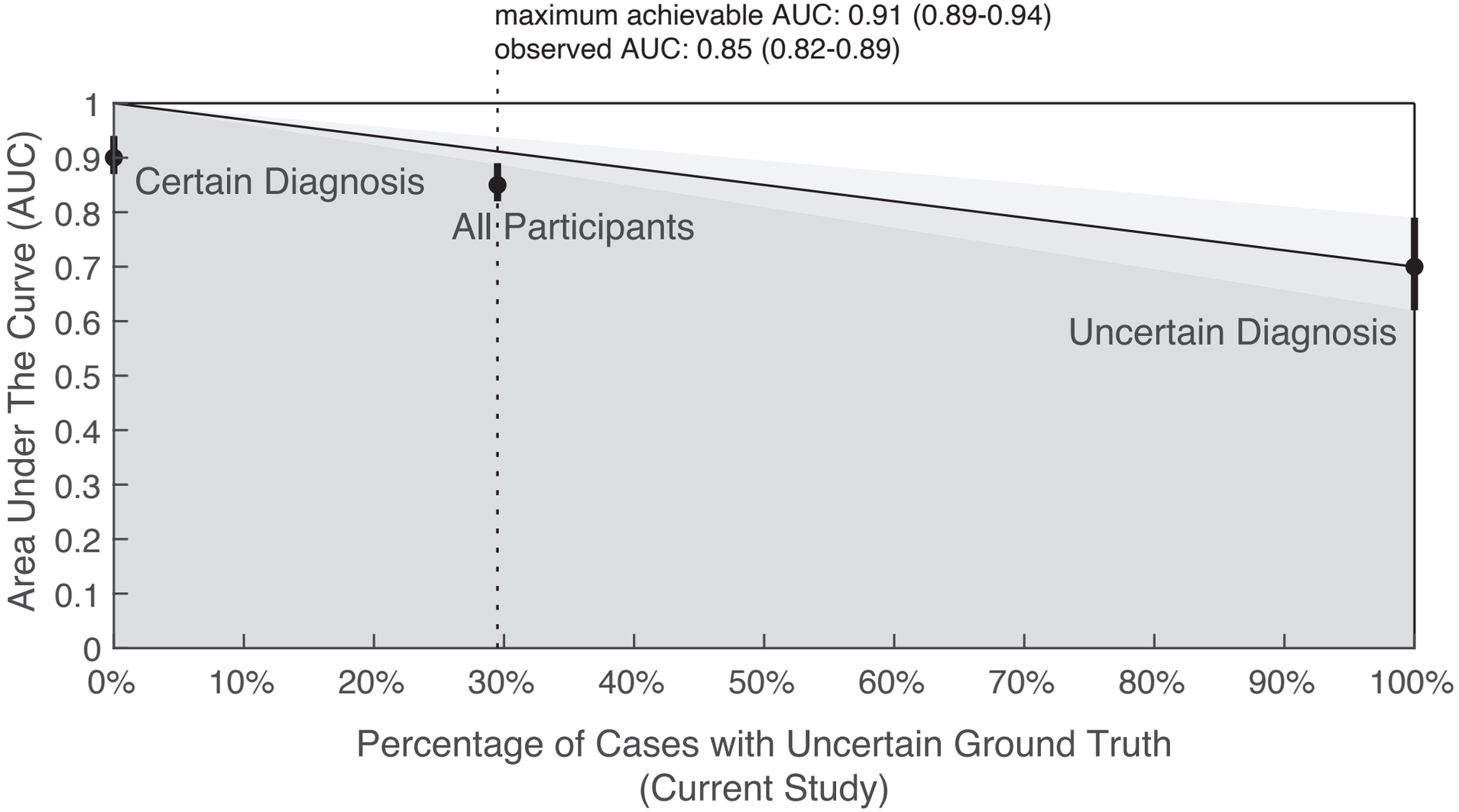
Effects of Uncertain Reference Standard on Index Test Performance Metrics



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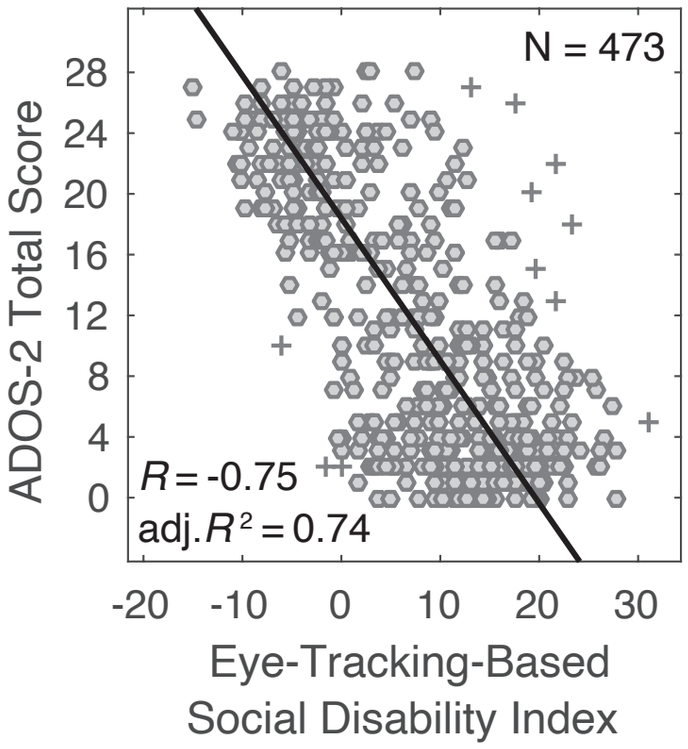
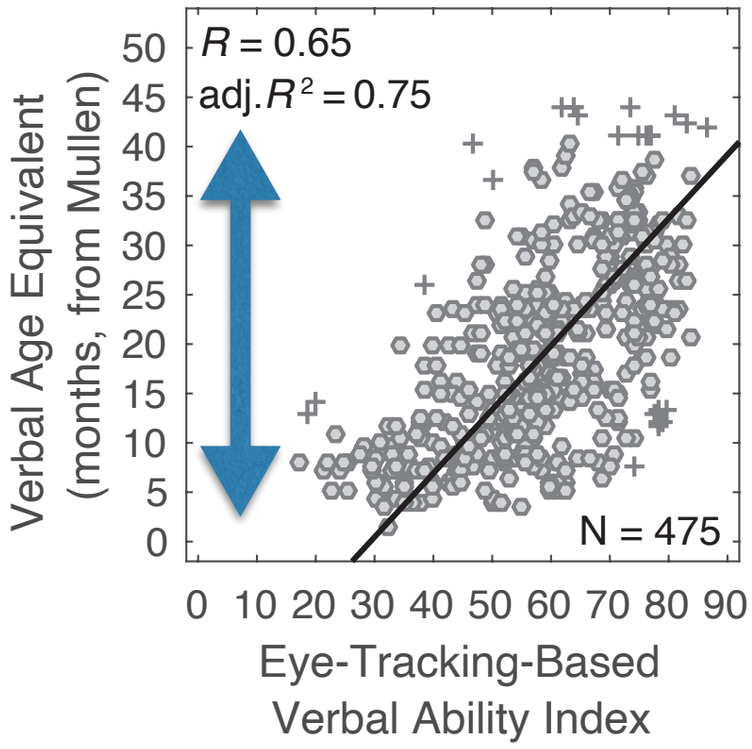
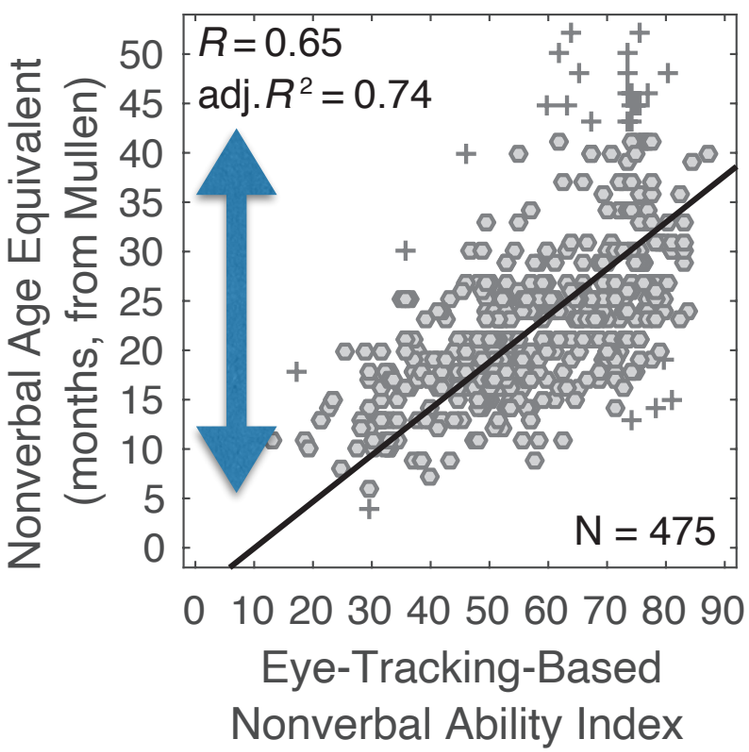
Assessment Performance

Assessment of Individual Symptom Severity in 3 Behavioral Domains







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(2023) *JAMA*.

Assessment Performance

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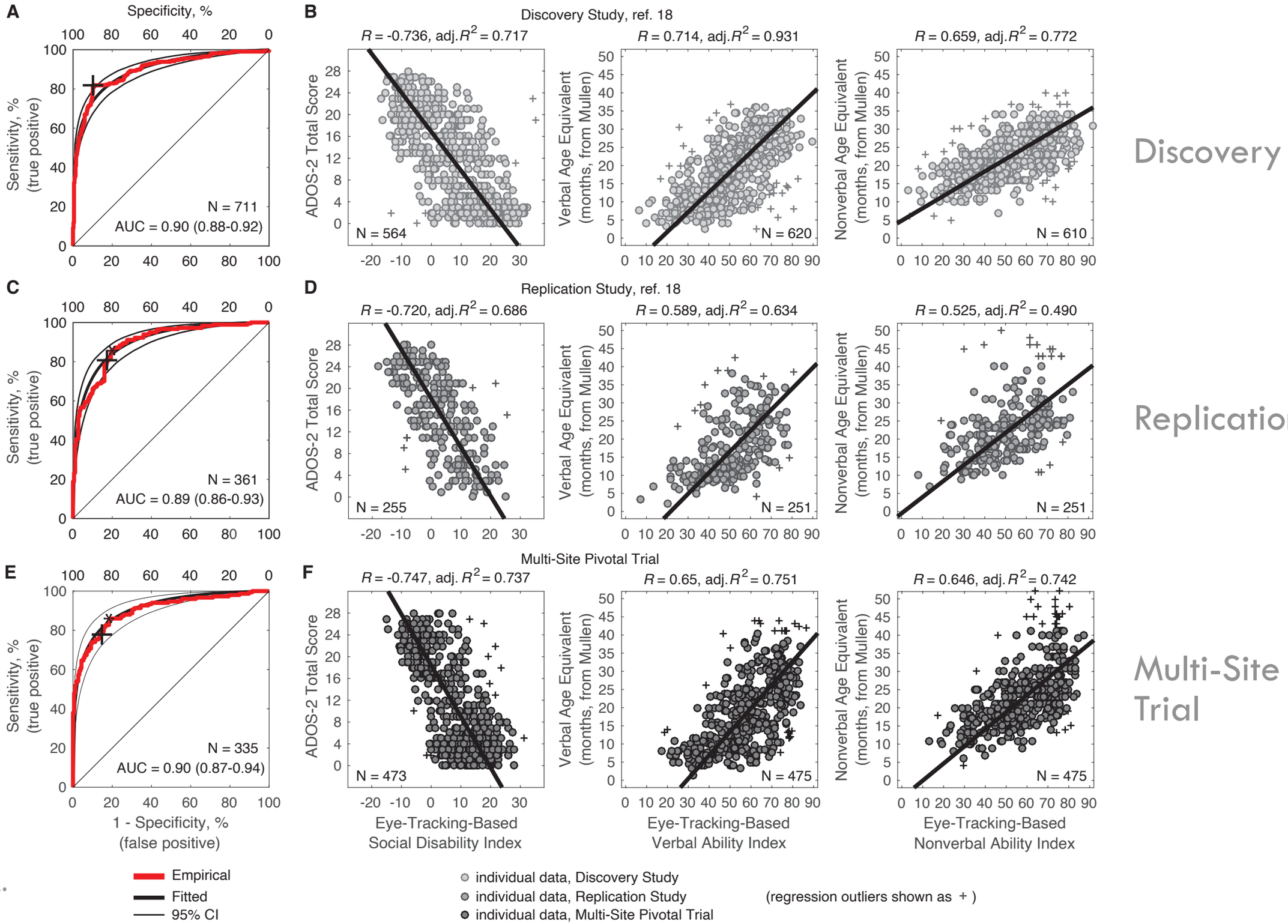

Discovery

Replication

Multi-Site Trial

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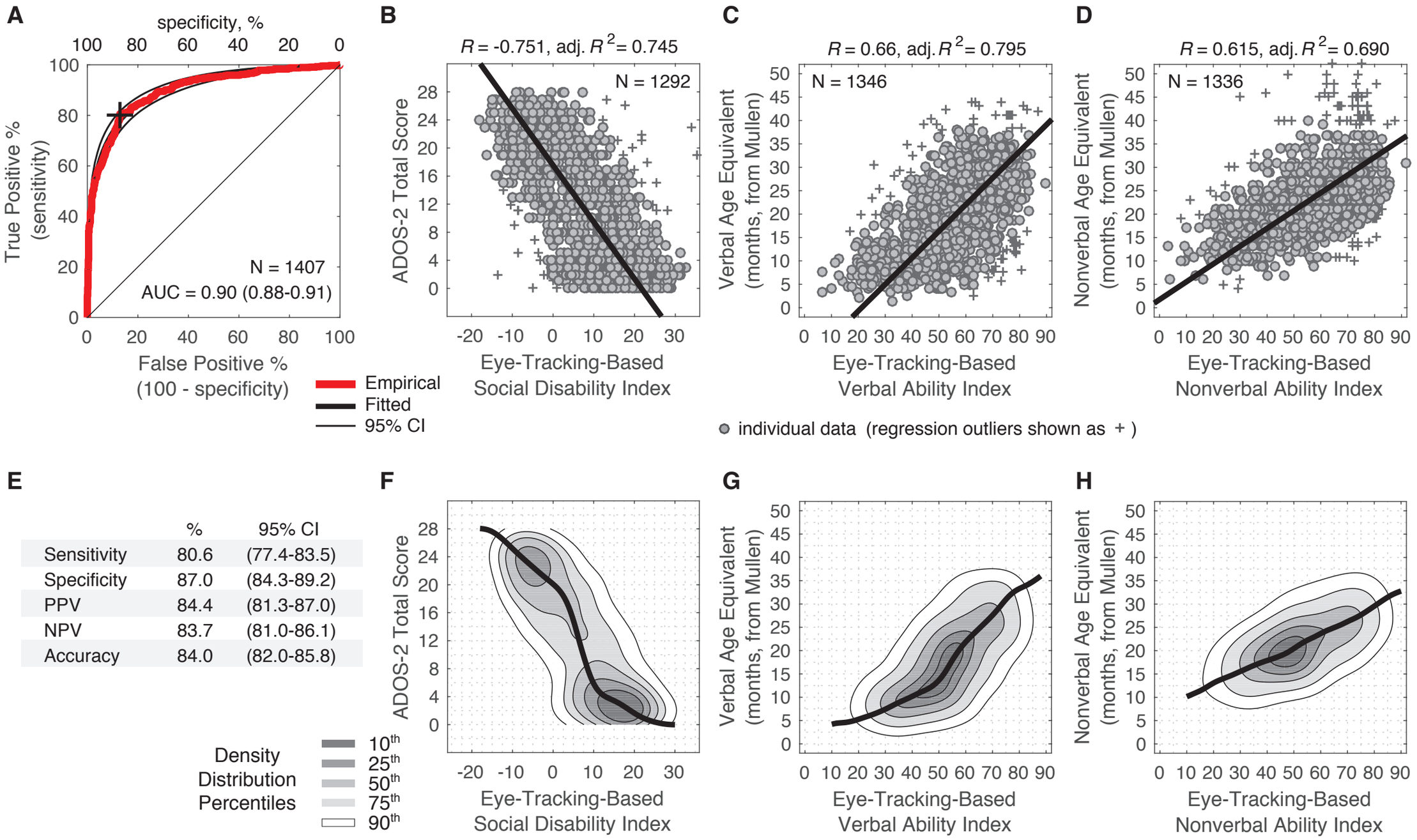
Pooled Results
Across Discovery, Replication, and Pivotal Trial



Summary

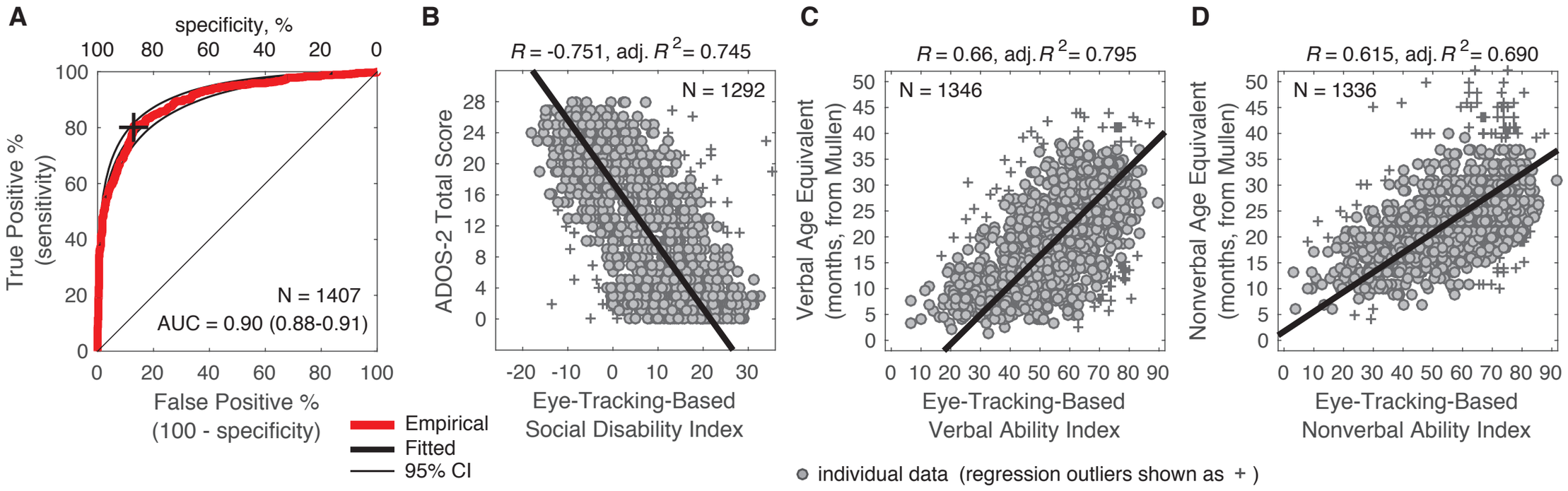
- Results show high sensitivity and specificity when comparing eye-tracking-based measures of social visual engagement with expert clinician diagnosis in children as young as 16-30 months old (*se* ~80%, *sp* ~87%).
- Results show strong correlation with standardized assessments given by experienced expert clinicians. ~12 min. of social visual engagement measures can effectively explain
  - ~74% of variance in ADOS total scores.
  - ~79% of variance in Mullen verbal age equivalents.
  - ~69% of variance in Mullen nonverbal age equivalents.

Tool to Aid in the Diagnosis & Assessment of Autism in 16-30-Month-Old Children

Objective eye-tracking-based measures of social visual engagement can effectively proxy expert clinician diagnosis and comprehensive evaluation of symptom severity in children under 3 years.

Results submitted to FDA for review in 510(k) submission (4,856 pages of data and documentation).

FDA cleared for clinical use on June 29, 2023.



Implementation

Tablet-based data collection device, easily used in real-world clinical settings.
Cloud-based data-processing & analysis. Returns results in <15 minutes.

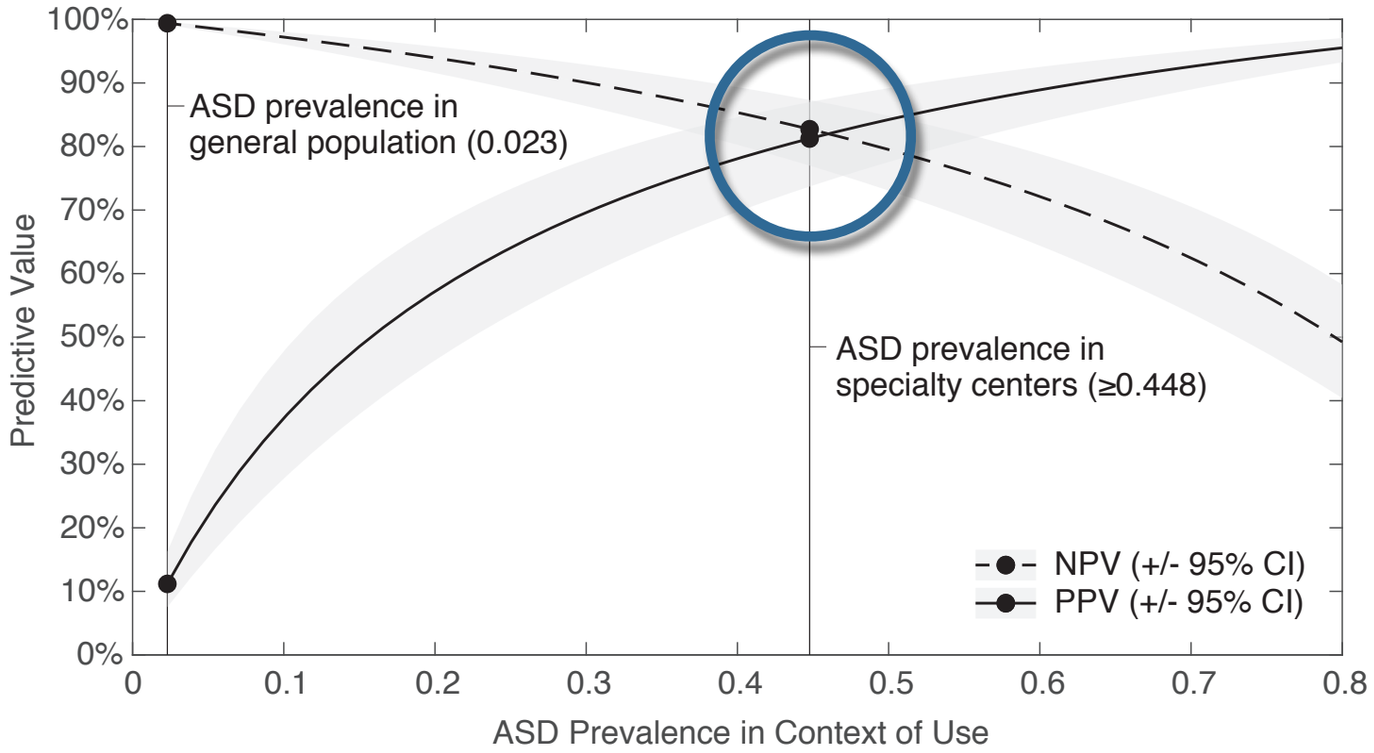
Images courtesy of EarliTec Diagnostics, Inc.

Clinical Opportunities

- Supporting a public health system that does not have enough expert clinicians (support, not replace)
- Deployment of objective diagnostic tools in the community
- Early identification, early intervention, improved long-term outcome

Implementation

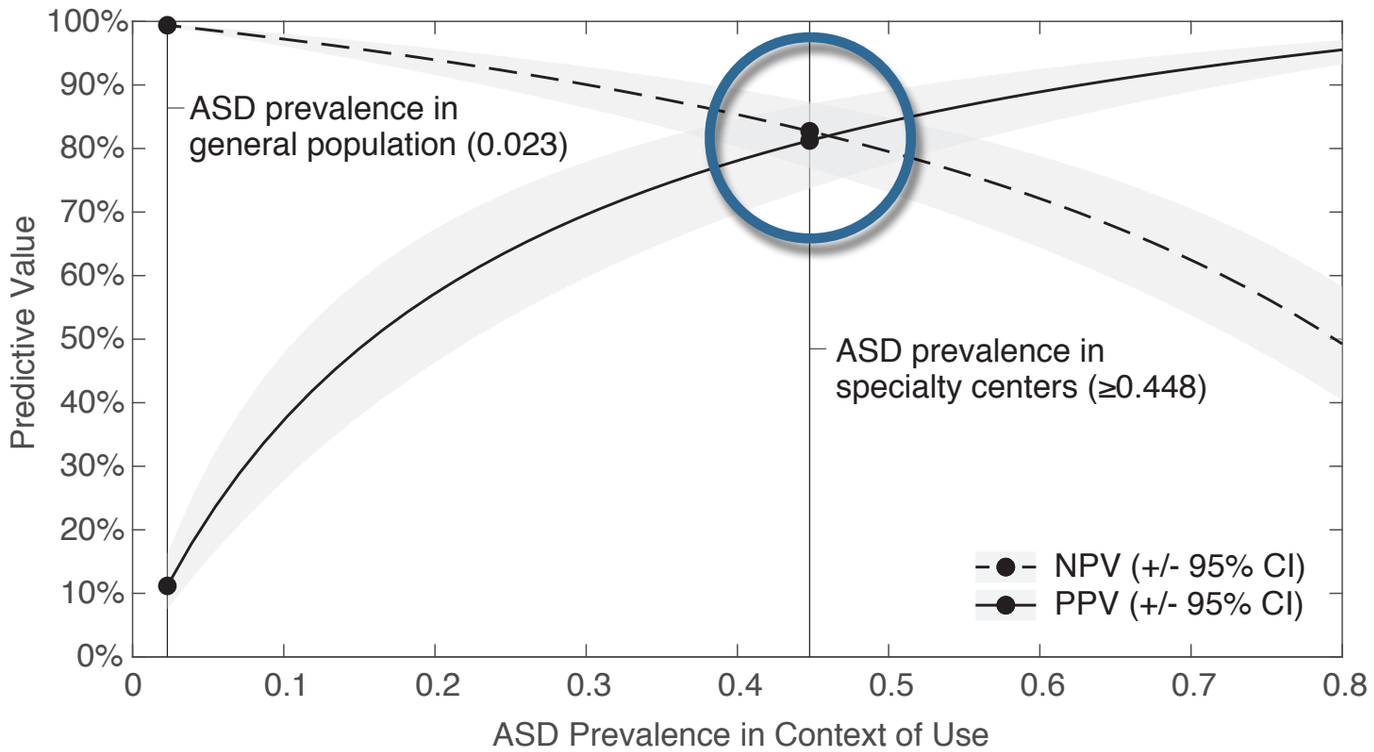
Goal of diagnosis is to facilitate path to targeted beneficial intervention

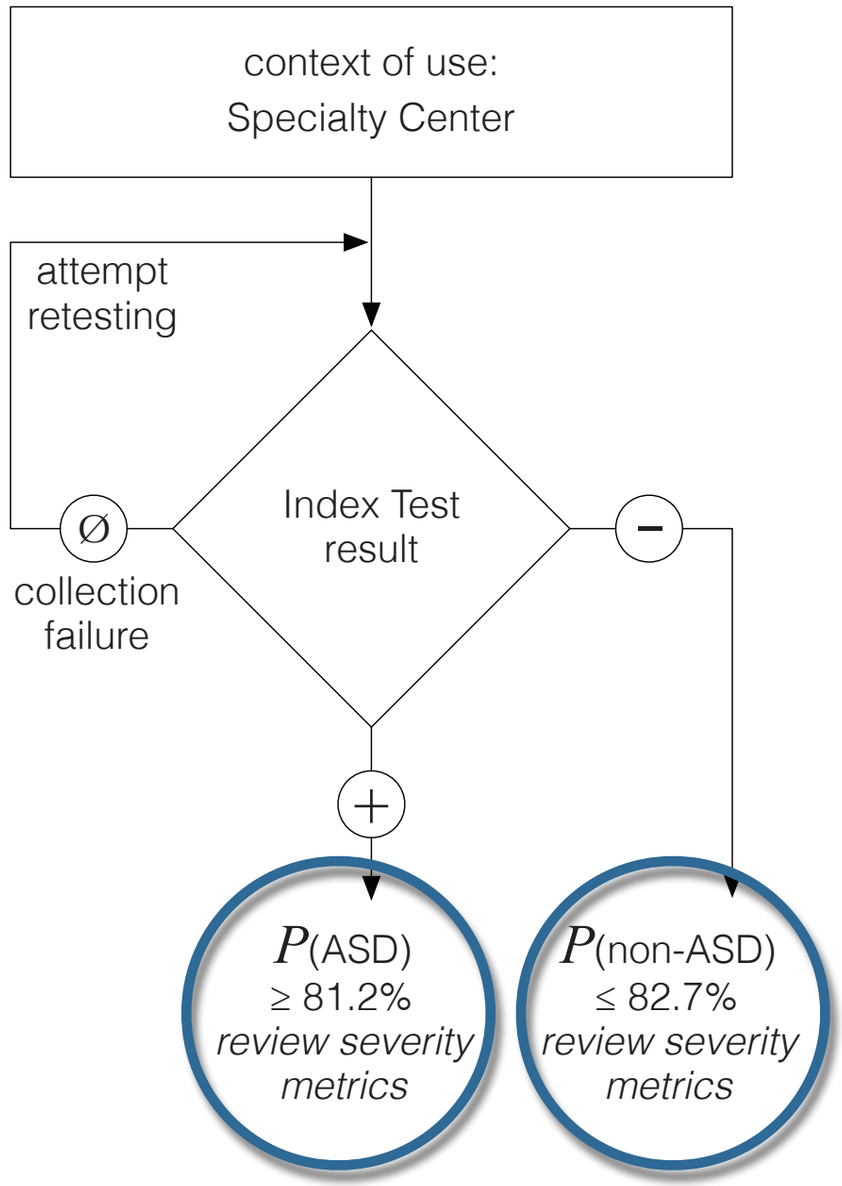


Tool for evidence-informed practice

Implementation

Goal of diagnosis is to facilitate path to targeted beneficial intervention

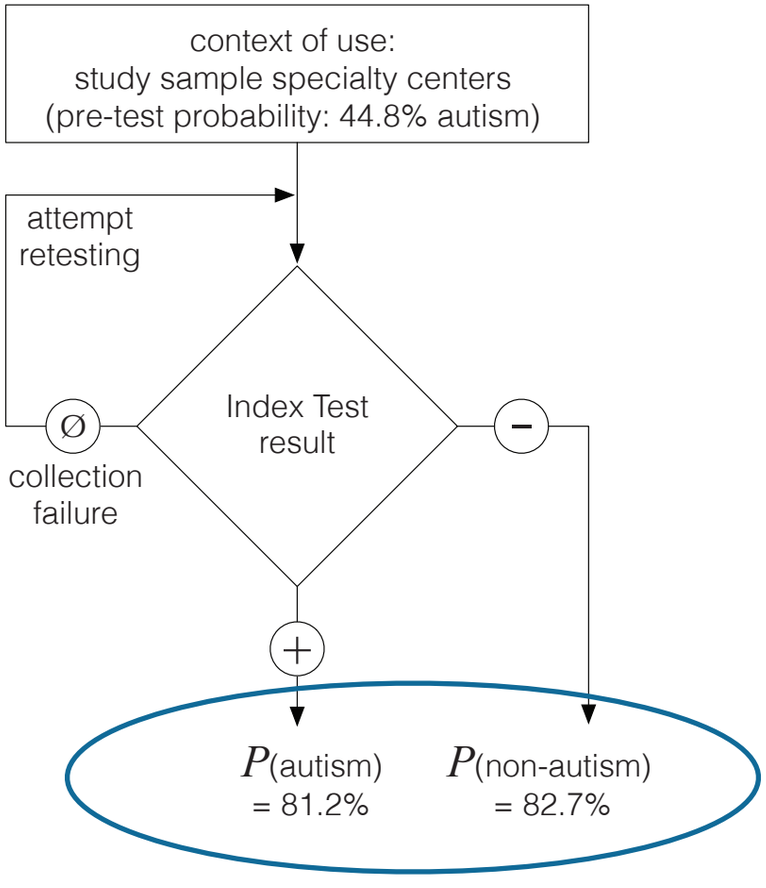


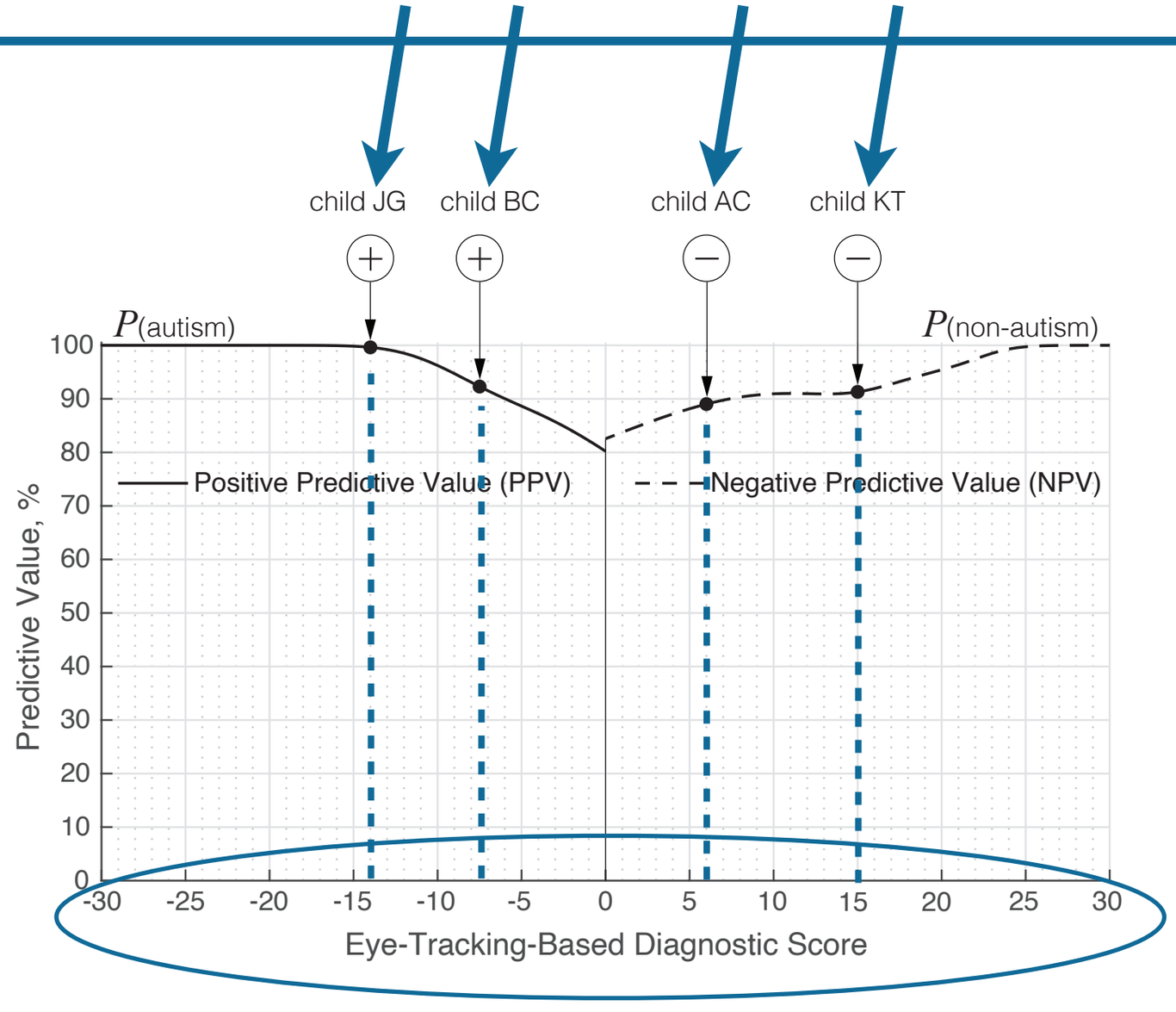


Tool for evidence-informed practice

Implementation

Evidence-Informed Clinical Decision Support





	test result	individual post-test probability
child JG	+	99.6% autism
child BC	+	92.3% autism
child AC	−	89.0% non-autism
child KT	−	91.3% non-autism

>90% Probability Autism

>90% Probability Non-Autism

Performance-Based, Objective

Participant demographics, grouped by either reference standard or eye-tracking-based diagnostic labels

	N = 335 Grouped by Reference Standard Diagnosis		N = 335 Grouped by Eye-Tracking-Based Diagnosis	
Diagnostic Label	non-ASD	ASD	non-ASD	ASD
N	185	150	191	144
Race* – no. (%)				
Native Hawaiian or Pacific Islander	0 (0.0%)	1 (0.7%)	0 (0.0%)	1 (0.7%)
Asian	10 (5.4%)	14 (9.3%)	15 (7.8%)	9 (6.3%)
Black / African / African-American	11 (5.9%)	16 (10.7%)	18 (9.4%)	9 (6.3%)
Caucasian	147 (79.5%)	95 (63.3%)	138 (72.3%)	104 (72.2%)
Other	17 (9.2%)	23 (15.3%)	20 (10.5%)	20 (13.8%)
Prefer not to answer / unknown	0 (0.0%)	1 (0.7%)	0 (0.0%)	1 (0.7%)
	$\chi^2 = 12.14$, $p = 0.0329$		$\chi^2 = 4.78$, $p = 0.4437$	
Ethnicity – no. (%)**				
Hispanic	16 (8.7%)	26 (17.3%)	19 (9.9%)	23 (16.0%)
Non-Hispanic	166 (89.7%)	124 (82.7%)	169 (88.5%)	121 (84.0%)
Prefer not to answer / unknown	3 (1.6%)	0 (0.0%)	3 (1.6%)	0 (0.0%)
	$\chi^2 = 7.89$, $p = 0.0193$		$\chi^2 = 2.09$, $p = 0.1487$	

Performance-based eye-tracking results were independent of race and ethnicity, but reference standard diagnosis was not.

Clinical Opportunities

- Supporting a public health system that does not have enough expert clinicians (support, not replace)
- Deployment of objective diagnostic tools in the community
- Early identification, early intervention, improved long-term outcome

Thank You

- The children and families for their participation.

- The Marcus Foundation
- The Simons Foundation
- The National Institute of Mental Health
- The National Institute of Child Health and Human Development
- The JB Whitehead Foundation
- Autism Science Foundation

Thank You

- Cheryl Klaiman, Shana Richardson, Meena Lambha, Morganne Reid, Taralee Hamner, Chloe Beacham, Peter Lewis, Jose Paredes, Laura Edwards, Natasha Marrus, John N. Constantino, Sarah Shultz.
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- Jason Davis, Travis Dennison, Robert Frazier, Mike Glatzer, Theodore Nicholson, Shyamal Shah, Steven Shifke, Jenny Taylor, and Antonio Terrell for help in investigational device development and device deployment to all study sites.

EMORY UNIVERSITY SCHOOL OF MEDICINE

Children's Healthcare of Atlanta

Marcus AUTISM CENTER