The State of Autism - 2020

Sara Jane Webb, PhD
Frederick Shic, PhD
Gary Stobbe, MD
Karen Bearss, PhD
Jim Mancini MS, CCC-SLP
2019 Updates

Risk for ASD

Biomarkers

Sara Jane Webb
Professor
Psychiatry & Behavioral Sciences, Psychology & Neuroscience
University of Washington
Seattle Children’s Research Institute
Autism 200
Infant behaviors | Social Attention Markers of Risk

• 6 & 12 months
  • Decreased attention to the face,
  • Altered time to learn about a face,
  • Decreased brain activity to social information

• 12 – 24 months Early Red Flags for autism
  • Poor eye contact
  • Lack of attention to others
  • Difficulties with joint attention
  • Failure to differentiate and respond to emotions
  • Poor imitation
Risk for ASD

2018 Updates
- Prematurity: Agrawal et al.
- Sensory: Wolf / IBIS
- RRB: McKinnon / IBIS
- Motor: LeBarton & Landa

Low Birth Weight: Talmi et al.

Prenatal & Perinatal

2019 Updates
- Rare CNV: D'Abate / BSRC
- Family Risk: McDonald / BSRC
- Environmental
- Picture Based Screeners: Janvier et al.

Measurement of Risk

RRB: McKinnon / IBIS
Summary: Familial-risk infants informs understanding of developmental trajectories preceding ASD diagnosis, potentially improving early detection.
Risk for ASD based on Familial-Risk Status

Does the number of older siblings with ASD influence the likelihood a younger sibling will also have ASD?

<table>
<thead>
<tr>
<th># older sibs with ASD</th>
<th>N</th>
<th>Autism</th>
<th>Other</th>
<th>Typ</th>
</tr>
</thead>
<tbody>
<tr>
<td>Multiplex (2+)</td>
<td>80</td>
<td>36.3%</td>
<td>31.3%</td>
<td>32.5%</td>
</tr>
<tr>
<td>Single incidence (1)</td>
<td>355</td>
<td>16.1%</td>
<td>27.3%</td>
<td>56.5%</td>
</tr>
</tbody>
</table>

Figure: Developmental Trajectories of Autism Spectrum Disorder (ASD) Symptoms, Cognitive Abilities, and Adaptive Skills

Depiction of results from generalized linear mixed models. Autism Diagnostic Observation Schedule (ADOS) measured ASD symptoms (A), Mullen Scales of Early Learning (MSEL) measured cognitive abilities (B), and the Vineland-II measured adaptive skills (C). CSS indicates Calibrated Severity Score; ELC, Early Learning Composite.
Risk for ASD--> Genetic Risk

Summary: Recurrence risk estimates can be tailored to individual families, with potential for intensified surveillance for infants at increased likelihood due to positive CNV findings (in parents or older ASD sibs).
De novo & inherited rare genetic variants ~ 5–40% ASD.

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<th>Other</th>
<th>Typ</th>
</tr>
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<tbody>
<tr>
<td>Infant sibling</td>
<td>288</td>
<td>35.8%</td>
<td>18.8%</td>
<td>45.5%</td>
</tr>
<tr>
<td>Older sibling with ASD</td>
<td>253</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Infant sibling</td>
<td>288</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Risk for ASD --> Low Birth Weight

Summary: Increased risk of ASD diagnosis in infants born <3000g (not <2500g) and or SGA.
Low Birth Weight & Small for Gestational Age

- 12,635 ASD cases (born 2000-2012) compared to a random sample of 20% of the children born in Israel ($N = 369,548$ controls).
Risk for ASD

- Infant Behaviors
  - Sensory: Wolf / IBIS
  - RRB: McKinnon / IBIS
  - Motor: LeBarton & Landa

- Prenatal & Perinatal
  - Prematurity: Agrawal et al.
  - Low Birth Weight: Talmi et al.

- Genetic
  - Rare CNV: D'Abate / BSRC
  - Family Risk: McDonald / BSRC

- Environmental
  - Picture Based Screeners: Janvier et al.

Measurement of Risk
DO YOU HAVE AN INFANT UNDER 6 MONTHS?

Researchers at Seattle Children’s are studying brain development during the first 3 years of life and giving parents information about their baby’s development as part of the WONDER study.

Currently recruiting:

**Infants with an older sibling with Autism**

**Participation includes:**
- 5 In-Person Study Visits over 3 Years
- Phone Interviews and Online Surveys

**Families will receive:**
- Developmental Feedback Reports
- Compensation for Completing Activities

To learn more or submit an interest form: Hover over our QR code with any smartphone camera. No app required!

Or contact us directly:
- Phone: 206-884-WNDR (9637)
- Email: wonder@seattlechildrens.org

http://depts.washington.edu/pbslab/wordpress/wonder/
2019 Updates

Risk for ASD

Biomarkers

Sara Jane Webb
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bi·o·mark·er  noun

“a characteristic that is objectively measured and evaluated as an indicator of normal biological processes, pathogenic processes, or pharmacologic responses to a therapeutic intervention.”

NIH Biomarkers Definitions Working Group
How does brain functioning relate to treatment responses?

- Not all individuals with ASD
  - respond to an intervention
  - responses differ in strength and timing
  - there is no reliable way to predict who will be responders versus non-responders.

- E.g., Medication
  - There is no FDA approved medication for the core symptoms of ASD.
  - Fail to demonstrate efficacy above to show above placebo.

  - YET...65% of children with ASD were taking a psychotropic medication, with rates higher when considering ASD+ other co-morbid conditions
Biomarkers to Enable Therapeutics Development in Neurodevelopmental Disorders

Conceptual, Regulatory and Strategic Imperatives in the Early Days of EEG-Based Biomarker Validation for Neurodevelopmental Disabilities

Joshua B. Ewen1,2,3*, John A. Sweeney4 and William Z. Potter5
<table>
<thead>
<tr>
<th>COU</th>
<th>Description</th>
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<td>Diagnostic</td>
<td>Concurrent biomarker that specifies whether or not an individual has a disorder/pathologic process</td>
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<tr>
<td>Monitoring</td>
<td>Concurrent biomarker that concurrently reflects a change in a disease or in a side effect</td>
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<tr>
<td>Safety</td>
<td>Concurrent biomarker that reflects presence/degree of toxicity from an exposure</td>
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<tr>
<td>Response</td>
<td>Prospective biomarker that reflects a response to an intervention; when highly well validated, may serve as a surrogate endpoint in a clinical trial</td>
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<tr>
<td>Prognostic</td>
<td>Prospective biomarker that predicts clinical course</td>
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<tr>
<td>Predictive</td>
<td>Prospective biomarker that predicts response to an intervention</td>
</tr>
<tr>
<td>Susceptibility/Risk</td>
<td>Prospective biomarker that reflects potential for developing or disease sensitivity to a negative outcome following an exposure</td>
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</table>
Development of the Social Brain

- Interactive Specialization (Johnson 2007, 2010)
  - Changes in the properties of cortical regions occur as they interact and compete with each other to acquire their role in computational abilities.
  - The spatial extent of activity in *networks* of brain regions TUNES in response to social stimuli.

Large scale network changes in social brain
(Insel & Frenald, 2004)
Autism Biomarkers Consortium for Clinical Trials

Evaluate candidate biomarkers for clinical trials

• Feasible to acquire?
• Are we testing what we think we are?
• Reliability over time and across sites?
• Does it differ between children with ASD or TD?
• Can it tell us something about subgroups?

Develop infrastructure to support future clinical trials
New Findings in Children with ASD
Seattle Children’s Innovative Technologies Lab

Frederick Shic, Ph.D. SCRI / UWSOM pediatrics
Looking at Faces in Toddlers with ASD

The role of limited salience of speech in selective attention to faces in toddlers with autism spectrum disorders

Frederick Shic, Quan Wang, Suzanne L. Macari, and Katarzyna Chawarska

1 Child Study Center, Yale School of Medicine, New Haven, CT; 2 Center for Child Health, Behavior and Development, Seattle Children’s Research Institute, Seattle, WA; 3 Department of Pediatrics, University of Washington School of Medicine, Seattle, WA, USA

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<td>50</td>
<td>47</td>
<td>-</td>
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<tr>
<td>N Male [%]</td>
<td>44 [88%]</td>
<td>24 [51%]</td>
<td>&lt;.001</td>
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<td>Age months (SD)</td>
<td>22.6 (3.1)</td>
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<td>.439</td>
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<tr>
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SSA 2.0 – Mouth (between group)
Δ%Face discrimination

- AUC: .888
- Sensitivity = 88.6%
- Specificity = 80.0%
Summary

• In Toddlers with ASD
  • No Face Avoidance
  • Decreased attention to faces associated with limited salience of speech
  • Strongly disassociates groups
RESEARCH ARTICLE

Promoting Social Attention in 3-Year-Olds with ASD through Gaze-Contingent Eye Tracking

Quan Wang, Carla A. Wall, Erin C. Barney, Jessica L. Bradshaw †, Suzanne L. Macari, Katarzyna Chawarska, and Frederick Shic ©
Creating and promoting prototypical attention

a. b.
Randomized Control Trial (R21 MH102572 01)

ClinicalTrials.gov
NCT02488226

- 44 videos
- 15 minutes
Results

The graph shows the percentage of face (%Face) across different conditions: TD, ASD No-Cue, and ASD Cue, at three stages: Pre-Training, Training, and Post-Training. The results indicate significant differences between the conditions at the Post-Training stage, with the ASD Cue condition showing the highest %Face, followed by the TD condition, and then the ASD No-Cue condition. The significance levels are indicated by asterisks: ** for p < 0.01 and *** for p < 0.001.
Results

\[ NVDQ \approx \Delta \%

\begin{align*}
    r &= -0.64, \\
    p &= 0.013
\end{align*}
Conclusions

• GC ET training mitigates decreases of attention to faces in very young children with ASD
• Larger effects in children with ASD with lower nonverbal ability

Limitations
• Novelty? Contigency
• Looking ≠ Learning

Future Work:
• More controls
• Different content
  • More complex scenes
  • More analytics
• Expanded intensity
## Functional Near Infrared Spectroscopy

<table>
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<tr>
<th></th>
<th>ASD</th>
<th>TD</th>
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<td>30 (23:7)</td>
<td>30 (13:17)</td>
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<td>Age in Years (SD)</td>
<td>6.8 (2.0)</td>
<td>6.9 (1.8)</td>
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<td>ADOS RRB Severity (SD)</td>
<td>8.0 (1.6)</td>
<td>-</td>
<td>-</td>
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<tr>
<td>ADOS CSS (SD)</td>
<td>7.9 (1.5)</td>
<td>-</td>
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<td>SB Nonverbal Score (SD)</td>
<td>8.7 (3.8)</td>
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<td>SB Standard Score (SD)</td>
<td>83.4 (17.2)</td>
<td>102.9 (10.9)</td>
<td>&lt;0.001</td>
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<td>ABAS GAC (SD)</td>
<td>76.2 (10.9)</td>
<td>94.0 (16.5)</td>
<td>0.025</td>
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Recognizing biological motion (BM) from point light displays (PLD)
Underlying Mechanism

TD-ASD (red: TD>ASD, blue: ASD>TD)
# Functional Near Infrared Spectroscopy

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<tr>
<th>S</th>
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<th>Channel Location</th>
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<th>ASD Bio-Rot</th>
<th>TD-ASD Bio-Rot</th>
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<td>3</td>
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<td>.077</td>
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<td>.166</td>
<td>.029*</td>
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**Notes:**
- Δ represents the difference.
- p values are indicated as follows:
  - <.001***: p < .001
  - <.01**: p < .01
  - <.05*: p < .05
## Functional Near Infrared Spectroscopy

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Summary

- Homogeneous modulation of brain regions in response to biological motion in TD, not seen in ASD
- Degree of response in rSTS strongly associated with severity of autism symptoms
- More work needed to link brain->attention->behavior
Why research autism?

If you’ve met one person with Autism, you’ve met one person with Autism. So how can we find effective treatments to treat such a diverse group of people with different needs? Through research.

- Research can help us identify **better treatment options**
- Research can help us identify some of genetic factors associated with autism, which in turn can help us find **precision medicine** to treat rare genetic conditions
- We use research data to make advance in diagnosing, treating and **improving the lives of people with autism**
What is a clinical trial?

- Clinical studies (also known as ‘clinical trials’) are carefully controlled scientific investigations.
- Most **Clinical Trials** are designed to find out about the **safety and efficacy** of an investigational drug, device or treatment, or to define a biomarker.
• A **research subject** is recruited using **inclusion criteria** specific to the study.

• Each study is different, some test an investigational drug or device, while others might include testing DNA through saliva or blood samples.

• **Study partners**, such as a family member or close friend, are necessary to enroll a subject in a clinical trial. This person might need to attend clinic visits, completing questionnaires, and ensure compliance by research subject.
Why participate: risks and benefits

Risks

- There may be risks involved in research.
- By law, participants must be told about all the risks and benefits prior to consenting to participation. This process is called ‘informed consent’.

Benefits

- There may or may not be direct benefit to the research subject.
- Research participants will get study-related medical care, monitoring, and frequent visits with a study doctor or investigator.
- Research findings may also help us learn to better care for others with autism spectrum disorders in the future.
Clinical Trials

Preclinical

Phase 1
20-80 Participants
Drug Approved for Testing in Humans

Phase 2
100-300 Participants
Drug Submitted for FDA Approval

Phase 3
1,000-3,000 Participants
FDA Review
To Confirm Safety and Effectiveness

Phase 4
1,000+ Participants
Drug Approved
Current studies

The V1ADUCT trial

The oRBiting study
Observational study

Ages 13-17 with ASD diagnosis
Better understand different scales used to measure certain behaviors associated with autism.
Wearable technologies-smartphone app and wrist worn gadget. No drugs involved.
Study partner required.

What’s involved

During clinic visits, we’ll ask you to complete a range of questionnaires and we’ll collect data from wearable devices (a study smartphone and wrist gadget) that we’ll provide you with at screening.
There is no cost for the study procedures. Some compensation is provided for attending the clinic visits.

How long does it go on

approximately 15 weeks, including screening (where we make sure the study is right for you).
This includes
4 clinic visits
2 phone interviews
If you join the trial and then change your mind, you can leave at any time without any impact on your usual healthcare.

Contact Study Coordinator: Daniel Cho - (206) 987-7503 or daniel.cho@seattlchildrens.org
Principal Investigator: Gary Stobbe, MD
Drug study

Testing a new investigational drug to see if it can help adults with ASD manage certain communication and social challenges a little easier.

Participants must:
Be at least 18 years old
Be diagnosed with autism spectrum disorder (ASD)
Have someone they see and speak to regularly, who is willing and able to be their ‘study partner’ for the duration of the trial

What’s involved

Screening: information about trial and assessments to see if suitable for you
Dosing: participants randomly assigned to drug or placebo. Neither you nor study doctor will know which one.
Extension: all participants get the study drug
Follow up: final visit after last dose
There is no cost for the study procedures. Some compensation is provided for attending the clinic visits.

How long does it go on

1. Screening up to 4 weeks
2. Dosing period 24 weeks
3. Extension period up to 2 years (optional participation)
4. Follow-up period 12 weeks
8 clinic visits and 1 phone call for the screening and dosing, regular health checks during extension period
If you join the trial and then change your mind, you can leave at any time without any impact on your usual healthcare.
How does it work? The investigational drug (balovaptan) is thought to block a hormone receptor in the brain that is linked to the control of socialization, stress, anxiety and aggression.

More information http://adultasdclinicaltrial.com/

- Contact Study Coordinator: Stacy Riffle - (206) 987-7502 or stacy.riffle@seattlechildrens.org
- Principal Investigator: Gary Stobbe, MD
Drug study

Studying the effectiveness of an investigational drug to improve the symptoms of ASD
Study may be a good fit if:
You are an individual between 13-35 years old
You have been diagnosed with ASD
You have an IQ of at least 50
You have a BMI of between 18-35 or between the 5th-95th%

What’s involved

You would come to Seattle Children’s every other week for a total of 8 study visits.
Take either the investigational drug or placebo (a “sugar pill”) during the study and get your blood taken at 5 of the visits.
You will be evaluated with a computer-based system that involves the use of electronic assessments and biosensors, such as EEG, Eye Tracker and Actigraph, which measures your activity and movement.

How long does it go on

17 weeks including screening and follow up
If you join the trial and then change your mind, you can leave at any time without any impact on your usual healthcare.
There is no cost for the study procedures. Some compensation is provided for attending the clinic visits.

stacy.riffle@seattlechildrens.org
Spark study

- The largest genetic study of autism ever
- 50,000 families needed nationwide
- DNA from saliva samples
- **Contact Study Coordinators:**
  - Daniel Cho (206) 987-7503 daniel.cho@seattlechildrens.org
  - Theo Ho (206) 987-7917 theodore.ho@seattlechildrens.org

https://sparkforautism.org/portal/homepage/
How to stay connected with research opportunities

- Seattle Children’s research registry keeps families up to date on new research opportunities
- Our website include information about research at our center and research opportunities with our collaborators in our network
- For more information, contact any of our study coordinators:
Advances in Autism Clinical Research

Karen Bearss, PhD
Assistant Professor
Seattle Children’s Autism Center
Department of Psychiatry and Behavioral Sciences
University of Washington
A Multisite Randomized Controlled Two-Phase Trial of the Early Start Denver Model Compared to Treatment as Usual

Sally J. Rogers, PhD, Annette Estes, PhD, Catherine Lord, PhD, Jeff Munson, PhD, Marie Rocha, PhD, Jamie Winter, PhD, Jessica Greenson, PhD, Costanza Colombi, PhD, Geraldine Dawson, PhD, Laurie A. Vismara, PhD, Catherine A. Sugar, PhD, Gerhard Hellemann, PhD, Fiona Whelan, MS, Meagan Talbott, PhD
Research on Parent-Mediated Interventions for Core Symptoms of ASD

- 2013 Cochrane Review of 19 RCTs
  - only one study (Green, 2010) adequately powered

- Within the last 5 years:
  - Naturalistic Developmental Behavioral Intervention (NDBI)
  - JASPER, ESI, ESDM, PRT

- 2016 meta-analysis of 19 RCTs (Nevill et al)
  - ES=0.18-0.23
What are we targeting when we treat autism spectrum disorder? A systematic review of 406 clinical trials

Umberto Provenzani, Laura Fusar-Poli, Natascia Brondino, Stefano Damiani, Marco Vercesi, Nicholas Meyer, Matteo Rocchetti and Pierluigi Politi
Measuring treatment response in children with autism spectrum disorder: Applications of the Brief Observation of Social Communication Change to the Autism Diagnostic Observation Schedule

So Hyun Kim¹, Rebecca Grzadzinski²,³, Kassandra Martinez¹ and Catherine Lord¹

RESEARCH ARTICLE

Development of the Behavioral Inflexibility Scale for Children with Autism Spectrum Disorder and Other Developmental Disabilities

Luc Lecavalier, James Bodfish, Clare Harrop, Allison Whitten, Desiree Jones, Jill Pritchett, Richard Faldowski, and Brian Boyd

NEW RESEARCH

Development of the Parent-Rated Anxiety Scale for Youth With Autism Spectrum Disorder

Lawrence Scahill, MSN, PhD, Luc Lecavalier, PhD, Robert T. Schultz, PhD, Andrea Nichole Evans, BA, Brenna Maddox, PhD, Jill Pritchett, MA, John Herrington, PhD, Scott Gillespie, MS, Judith Miller, PhD, R. Toby Amoss, PhD, Michael G. Aman, PhD, Karen Bearss, PhD, Kenneth Gadow, PhD, Michael C. Edwards, PhD
Implementing EBPs in Community Settings: RUBI in Schools

Original Investigation

Effect of Parent Training vs Parent Education on Behavioral Problems in Children With Autism Spectrum Disorder
A Randomized Clinical Trial

Karen Bearss, PhD; Cynthia Johnson, PhD; Tristram Smith, PhD; Luc Lecavalier, PhD; Naomi Swiezy, PhD; Michael Aman, PhD; David B. McAdam, PhD; Eric Butter, PhD; Charmaine Stillitano, MSW; Noha Minshawi, PhD; Denis G. Sukhodolsky, PhD; Daniel W. Mruzek, PhD; Kylan Turner, PhD; Tiffany Neal, PhD; Victoria Hallett, PhD; James A. Mulick, PhD; Bryson Green, MS; Benjamin Handen, PhD; Yanhong Deng, MPH; James Dziura, PhD; Lawrence Scahill, MSN, PhD

Figure 1. Proposed RUBIES study design
Thank you!

- Thank you to the Seattle Children’s Autism Center community, to our sponsors who fund research, to our participants and families who dedicate time to advancing research, and to you for interest in research!