IACC Working Group: Improving Health Outcomes for Individuals on the Autism Spectrum

Thursday, September 27, 2018

National Institutes of Health
Neuroscience Center
6001 Executive Blvd
Rockville, MD, 20892

Conference Call Access:
Phone: 800-369-1744
Participant Passcode: 6697418

These slides do not reflect decisions of the IACC and are for discussion purposes only.
Meeting of the IACC

Morning Agenda

8:30 AM  Welcome, Introductions
Susan Daniels, Ph.D.
Director, Office of Autism Research Coordination, National Institute of Mental Health, and Executive Secretary, IACC

Working Group Co-Chairs
David G. Amaral, Ph.D.
Distinguished Professor, Department of Psychiatry and Behavioral Science, University of California, Davis (UC), UC Davis MIND Institute

Julie Lounds Taylor, Ph.D.
Assistant Professor, Pediatrics and Special Education, Vanderbilt University, and Investigator, Vanderbilt Kennedy Center
IACC Working Group: Improving Health Outcomes for Individuals on the Autism Spectrum

September 27, 2018

Susan A. Daniels, Ph.D.
Director, Office of Autism Research Coordination
Executive Secretary, IACC
National Institute of Mental Health
Improving Health Outcomes for Individuals on the Autism Spectrum WG

• The IACC voted to convene a working group on health and wellness issues for individuals with ASD

• The Working Group will explore ways to:
  • Support research to better understand the health conditions that affect individuals on the autism spectrum
  • Increase community/provider awareness of these conditions and their treatment
  • Foster development of practice guidelines, policies, service approaches and other efforts to improve the health and quality of life of people on the autism spectrum
Working Group Scope

- Health and general wellness for people with ASD
- Co-occurring physical and mental health conditions
- Premature mortality
- Patient-provider interactions (including medical practitioner training)
- Parental/family mental health
Expected Working Group Activities and Products

• Workshop: Addressing the Health Needs of People on the Autism Spectrum
  • Health epidemiology
  • Patient-provider interactions
  • Co-occurring health conditions

• A written document providing an update on issues

• Continued discussions in Working Group conference calls, Working Group meetings, and/or IACC full committee meetings

• Working Group activities will run from September 2018 – September 2019
Working Group Members

Co-Chairs
• David Amaral, Ph.D., University of California, Davis
• Julie Lounds Taylor, Ph.D., Vanderbilt University

IACC and Federal Members
• Patricia Dietz, Dr.P.H., M.P.H., Centers for Disease Control and Prevention
• Jennifer Johnson, Ed.D., Administration for Community Living
• Alice Kau, Ph.D., *Eunice Kennedy Shriver* National Institute of Child Health and Human Development
• Kevin Pelphrey, Ph.D., George Washington University and Children's National Medical Center ●
• Denise Juliano-Bult, M.S.W., National Institute of Mental Health
• Scott Michael Robertson, Ph.D., U.S. Department of Labor ●
• Marcella Ronyak, Ph.D., LCSW, CDP, Indian Health Service ●
• Nina Schor, M.D., Ph.D., National Institute of Neurological Disorders and Stroke
• Alison Tepper Singer, M.B.A., Autism Science Foundation ●

● Self-advocate  ● Parent/Family member
External Members

- Gregory Barnes, M.D., Ph.D., University of Louisville School of Medicine
- Timothy Buie, M.D., Harvard Medical School
- Dan Coury, M.D., The Ohio State University College of Medicine
- Lisa Croen, Ph.D., Kaiser Permanente Northern California
- Orrin Devinsky, M.D., New York University
- Sarah Gardner, MIND Institute, University of California, Davis
- Dena Gassner, M.S.W., Adelphi University
- Antonio Hardan, M.D., Stanford University Medical Center
- Joseph Joyce, M.B.A., Autism Society of America
- Connor Kerns, Ph.D., University of British Columbia
- Bryan King, M.D., M.B.A., University of California, San Francisco

- Self-advocate
- Parent/Family member
Working Group Members

External Members
• Clarissa Kripke, M.D., University of California, San Francisco
• Beth Ann Malow, M.D., M.S., Vanderbilt University Medical Center
• Micah Mazurek, Ph.D., University of Virginia
• Donna Murray, Ph.D., University of Cincinnati
• Christina Niclaidis, M.D., M.P.H., Oregon Health and Science University

• Dora Raymaker, Ph.D., Portland State University
• Elliott Sherr, M.D., Ph.D., University of California, San Francisco
• Matthew Siegel, M.D., Tufts University
• Sarah Spence, M.D., Ph.D., Harvard Medical School
• Jeremy Veenstra-VanderWeele, M.D., Columbia University

● Self-advocate ● Parent/Family member
Meeting of the IACC

Morning Agenda

8:45 AM  Health and Healthcare for Adults on the Autism Spectrum: The Newcastle University Adulthood and Ageing Research Programme

Jeremy Parr, M.D.
Professor of Pediatric Neurodisability, Newcastle University Institute of Neuroscience, United Kingdom
Health and healthcare for adults on the autism spectrum: The Newcastle University adulthood and ageing research programme

Jeremy Parr
Professor of Paediatric Neurodisability
@jeremyparr
Funding, and conflicts of interest

I have no financial conflicts of interest

The autism spectrum adulthood and ageing research programme is funded by the UK autism charity Autistica

Received funding from the UK MRC, NIHR and charities for research described

Editorial Committee for the *Autism in Adulthood* journal
Lots of work by lots of people

Autistic people and relatives, parents of children, children

Tom Berney, Carla Black, Sam Brice, Tracy Finch, Mark Freeston, Deborah Garland, The Goth, Vicki Grahame, Jahnese Hamilton, Barry Ingham, Ann Le Couteur, David Mason, Joan Macintosh, Morag Maskey, Helen McConachie, Cos Michael, Chris Mitchell, Alex Petrou, Jacqui Rodgers, Sarah Wigham, Colin Wilson, Marc Woodbury-Smith

Autism specific health checks consortium

Many other colleagues nationally and internationally. The Programme Advisory and Steering committee
Research priorities: Longitudinal cohort study re the lives of autistic people. Their quality of life, mental health, physical health

Engagement strategies

https://research.ncl.ac.uk/adultautismspectrum/newsevents/
International leaders in autism research registers/databases, and cohorts (cross sectional and longitudinal data); web based, paper materials

- Hypothesis driven research
- Improve research infrastructure

**UK research registers/databases (with consent); 80 health providers (NHS Trusts)**

ASD-UK: Over 4500 families of children; 2000 local (55% of local ASD families – largest internationally). Co-existing conditions, age at diagnosis

**Longitudinal cohorts (consent); work with 60 NHS Trusts, plus community**

Adult ASC-UK: Over 1700 adults on the autism spectrum, 700 relatives of adults. Among the largest internationally. Mental health, physical health, how lives change with time; mixed methods

Expertise and materials shared and exported (Ireland, US, Canada)
2018: Newcastle University research programme on autism lifecourse and ageing

**Designing intervention:** Methods and measures used in diagnosis

**Understanding:** Uncertain futures for autistic people and relatives (Rodgers)

**Design intervention:** Personalised phobia treatment

**Survey, design intervention & RCT:** Personalised anxiety treatment

**Survey, design intervention & RCT:** Autism specific health checks in Primary care

**Survey, design intervention & RCT:** Accessing health care

**Measurement:** Quality of life WHO-QoL-BREF and ASQoL

**Designing intervention:** Post diagnostic support
Top ten questions for autism research

1. Which interventions improve mental health or reduce mental health problems in autistic people? How should mental health interventions be adapted for the needs of autistic people?

2. Which interventions are effective in the development of communication/language skills in autism?

3. What are the most effective ways to support/provide social care for autistic adults?

4. Which interventions reduce anxiety in autistic people?

5. Which environments/supports are most appropriate in terms of achieving the best education/life/social skills outcomes in autistic people?

6. How can parents and family members be supported/educated to care for and better understand an autistic relative?

7. How can autism diagnostic criteria be made more relevant for the adult population? And how do we ensure that autistic adults are appropriately diagnosed?

8. How can we encourage employers to apply person-centred interventions and support to help autistic people maximise their potential and performance in the workplace?

9. How can sensory processing in autism be better understood?

10. How should service delivery for autistic people be improved and adapted in order to meet their needs?
How are autistic people and the research team working together?

• Collaborative working started when shaping the project. Autistic people were not integrated into a pre-designed project

• Autistic people were asked what outcomes we wanted

The autistic researchers’ job is ongoing. We meet regularly to:

• suggest ways the research team can engage with autistic adults

• advise on the range of communication methods possible for gathering information

• advise on tailoring autism friendly environments for meeting contributors

• advise on respecting autistic preferences and behavioural traits

• make suggestions, such as providing feedback and updates on progress, to promote inclusion and help keep people engaged over the longer term
Characteristics

The adult cohort includes 54% males, 44% females, and 2% who report another gender

30% need support to complete materials

130 people who are unable to consent for themselves (consultee consent)

Age range 16-80 years

50% age 16-35 years, 20% 36-45 years and 30% over age 46; more than 150 people aged over 56 years

Consent to recontact: update information, give new information, many agreed to meet
Predictors of Quality of Life for Autistic Adults

David Mason, Helen McConachie, Deborah Garland, Alex Petrou, Jacqui Rodgers, and Jeremy R. Parr

N=370; Autistic adults have lower QoL than the general population

<table>
<thead>
<tr>
<th>Physical</th>
<th>Positive Predictors</th>
<th>Negative Predictors</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Employed</td>
<td>Female</td>
</tr>
<tr>
<td></td>
<td>β = .112*</td>
<td>β = -.133*</td>
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<tr>
<td></td>
<td></td>
<td>Mental health condition</td>
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<tr>
<td></td>
<td></td>
<td>β = -.211***</td>
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<td>SRS total</td>
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<td></td>
<td>β = -.413***</td>
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<td>Female</td>
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<td></td>
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<td>Mental health condition</td>
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<td></td>
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<td>β = -.150**</td>
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<td>SRS total</td>
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<td>β = -.274***</td>
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<td>Older age</td>
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<td>β = -.187**</td>
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<td>β = -.194**</td>
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<td>SRS total</td>
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<td>β = -.260***</td>
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<td>Female</td>
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<td></td>
<td></td>
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<td>β = -.160**</td>
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<table>
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<tr>
<th>Psychological</th>
<th>Positive Predictors</th>
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<td>In a relationship</td>
<td>β = .285***</td>
<td>Mental health condition</td>
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<td>Receiving support</td>
<td>β = .129*</td>
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<th>Social</th>
<th>Positive Predictors</th>
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<td></td>
<td>Receiving support</td>
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<td></td>
<td>β = .180**</td>
<td>Mental health condition</td>
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<tr>
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*p < .05, **p < .01, and ***p < .001
424 autistic adults participated

Impact: Reliability and validity of the WHOQoL BREF for the measurement of QoL for autistic adults

9 ASQoL items created that can be used by researchers internationally; freely available online and can be downloaded at:

(Search: ASQoL Newcastle)

https://research.ncl.ac.uk/neurodisability/leafletsandmeasures/autismqualityoflife measure/

Email: Jeremy.Parr@ncl.ac.uk or Jacqui.Rodgers@ncl.ac.uk
## Co-existing conditions of children

Data from 3900 families of children (often or frequent):

<table>
<thead>
<tr>
<th>Condition</th>
<th>Boys</th>
<th>Girls</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sleep problems</td>
<td>74.6  (2356)</td>
<td>78.0  (583)</td>
<td>75.2  (2939)</td>
</tr>
<tr>
<td>Hyperactivity</td>
<td>83.0  (2622)</td>
<td>82.3  (615)</td>
<td>82.9  (3727)</td>
</tr>
<tr>
<td>Injury to self</td>
<td>41.7  (1317)</td>
<td>42.6  (318)</td>
<td>41.9  (1635)</td>
</tr>
<tr>
<td>Anxiety, fears, or phobias</td>
<td>80.3  (2538)</td>
<td>83.3  (622)</td>
<td>80.9  (3160)</td>
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<td>Feeding problems</td>
<td>80.0  (2527)</td>
<td>77.8  (581)</td>
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Equally prevalent in children with and without intellectual disability
### Co-existing conditions of children

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Equally prevalent in children with and without intellectual disability
### Mental health conditions (equal numbers autistic adults: males and females) (n=1198) Petrou et al., in preparation

<table>
<thead>
<tr>
<th>SRS total</th>
<th>16-25 (n=315)</th>
<th>26-40 (n=407)</th>
<th>41-60 (n=408)</th>
<th>61+ (n=68)</th>
<th>Total (n=1198)</th>
<th>Association between age groups</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>107.0 (34.3)</td>
<td>115.7 (25.6)</td>
<td>112.9 (25.5)</td>
<td>103.3 (29.7)</td>
<td>111.7 (28.5)</td>
<td>$X^2(3)=12.5$, p=.006</td>
</tr>
<tr>
<td>ADHD</td>
<td>45 (14.3)</td>
<td>44 (10.8)</td>
<td>25 (6.1)</td>
<td>8 (11.8)</td>
<td>122 (10.2)</td>
<td>$X^2(3)=13.5$, p=.004</td>
</tr>
<tr>
<td>Depression</td>
<td>111 (35.2)</td>
<td>210 (51.6)</td>
<td>221 (54.2)</td>
<td>29 (42.6)</td>
<td>571 (47.7)</td>
<td>$X^2(3)=29.6$, p&lt;.001</td>
</tr>
</tbody>
</table>

#### Access to mental health services

<table>
<thead>
<tr>
<th>Tried to access mental health services</th>
<th>16-25 (n=315)</th>
<th>26-40 (n=407)</th>
<th>41-60 (n=408)</th>
<th>61+ (n=68)</th>
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</tr>
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<tbody>
<tr>
<td></td>
<td>194 (61.6)</td>
<td>308 (75.7)</td>
<td>293 (71.8)</td>
<td>45 (66.2)</td>
<td>843 (70.1)</td>
<td>$X^2(3)=17.87$, p&lt;.001</td>
</tr>
<tr>
<td>Accessed the mental health services</td>
<td>128 (40.6)</td>
<td>187 (45.9)</td>
<td>164 (40.2)</td>
<td>26 (38.2)</td>
<td>505 (42.2)</td>
<td>$X^2(3)=15.20$, p=.002</td>
</tr>
</tbody>
</table>
**Mental health conditions (equal numbers autistic adults: males and females (n=1198) Petrou et al., in preparation**

<table>
<thead>
<tr>
<th>Condition</th>
<th>16-25 (n=315)</th>
<th>26-40 (n=407)</th>
<th>41-60 (n=408)</th>
<th>61+ (n=68)</th>
<th>Total (n=1198)</th>
<th>Association between age groups</th>
</tr>
</thead>
<tbody>
<tr>
<td>Arthritis</td>
<td>5 (1.6)</td>
<td>16 (3.9)</td>
<td>57 (14.0)</td>
<td>19 (27.9)</td>
<td>97 (8.1)</td>
<td>$X^2(3)=82.33$, $p&lt;.001$</td>
</tr>
<tr>
<td>Diabetes</td>
<td>5 (1.6)</td>
<td>14 (3.4)</td>
<td>35 (8.6)</td>
<td>7 (10.3)</td>
<td>61 (5.1)</td>
<td>$X^2(3)=24.38$, $p&lt;.001$</td>
</tr>
<tr>
<td>Gastrointestinal problems</td>
<td>35 (11.1)</td>
<td>83 (20.4)</td>
<td>118 (28.9)</td>
<td>22 (32.4)</td>
<td>258 (21.5)</td>
<td>$X^2(3)=38.45$, $p&lt;.001$</td>
</tr>
<tr>
<td>Irritable bowel syndrome</td>
<td>34 (10.8)</td>
<td>57 (14.0)</td>
<td>73 (17.9)</td>
<td>12 (17.6)</td>
<td>176 (14.7)</td>
<td>$X^2(3)=7.78$, $p=.05$</td>
</tr>
<tr>
<td>Obesity</td>
<td>17 (5.4)</td>
<td>59 (14.5)</td>
<td>53 (13.0)</td>
<td>9 (13.2)</td>
<td>138 (11.5)</td>
<td>$X^2(3)=16.19$, $p&lt;.001$</td>
</tr>
<tr>
<td>Sleep problems</td>
<td>76 (24.1)</td>
<td>96 (23.6)</td>
<td>116 (28.4)</td>
<td>13 (19.1)</td>
<td>301 (25.1)</td>
<td>$X^2(3)=4.35$, $p=.226$</td>
</tr>
</tbody>
</table>
Health care adjustments / Accommodations: Data from >500 autistic adults and relatives, >100 parents of children (Brice, Wigham; in preparation)

For anxiety: some examples, needed most frequently but infrequently provided

Therapists with expertise in autism (not just therapy)
Information pre clinic about what to expect
Waiting rooms small, with appropriate activities
Meeting people’s sensory needs (lighting, noise)
Health summary document (e.g., health passport)
Tailoring the appointment according to information given by the person/relative
Follow up appointments to enable further discussion

‘It was in an unfamiliar place in an unfamiliar town, though this was my fault because I tend to avoid going out. What was particularly hard was that the building had an outside intercom that, had I been alone, I would not have used, would have panicked instead and returned home’
1. Tailoring of existing measures of pain to better suit autistic people.
2. An international collaborative effort to agree a core set of demographic, health behavior and health outcome indicators most relevant to autistic people that can be compared with general population data.
5. A review of evidence on autism-specific health service accommodations and service design to inform what an autism-friendly health service looks like.
6. Adaptation of an online healthcare “toolkit” developed in the United States to facilitate the primary healthcare of autistic adults for use in the UK.
7. Development and evaluation of a personalized annual health check program for autistic people.
8. Evaluation of the types of cardiovascular and gut problems most prominent in older autistic adults, contributory factors, and treatment effectiveness.
9. Engagement with autistic people regarding opportunities to use knowledge about genetics and biology to improve health and well-being.
10. Exploration of the research priorities regarding sexual development and health in autism.
11. Investigation of autistic people’s use and experiences of residential facilities for older people.
Design and initial evaluation of an autism-specific health check for use with autistic adults in UK National Health Service Primary Care

Funded in response to competitive, open call for proposals regarding design and evaluation of an autism specific health check (primary care)

In partnership with autistic people and relatives, and professionals, design web based autism specific health check, and trial use in the UK NHS (2019-22); includes Nicolaidis, Raymaker, Urbanowicz. Commissioners, managers, clinicians

Autistic people and relatives involved throughout: Priority setting, developing outline, co-investigators in the consortium designing and writing the application

Outcomes: Acceptability, feasibility, access, health outcomes. Utilise standard NHS datasets, in addition to research data collected
Some key messages

Value in research programmes that build critical mass in autism adulthood and ageing

An integrated research approach: use basic science, improved understanding to design trials, improve interventions and services, implement change

Longitudinal studies allow investigation of personal change, and accelerated cohort studies; ideally, across the lifecourse

Build datasets through informed consent, enabling sharing of anonymised data

Ensure access to usual healthcare and other data, big datasets; UK NHS is an ideal environment for this

National and international collaborations will lead to early results – using parallel protocols and measures
Thank You

Jeremy.Parr@ncl.ac.uk

@jeremyrparr

https://research.ncl.ac.uk/neurodisability/conditionsandtopics/autism spectrumdisorderasd/
Newcastle University research programme: Jeremy.Parr@ncl.ac.uk; @jeremyrparr

- **Designing intervention:** Methods and measures used in diagnosis
- **Designing intervention:** Post diagnostic support
- **Survey, design intervention & RCT:** Accessing health care
- **Understanding:** Uncertain futures for autistic people and relatives (Rodgers)
- **Survey, design intervention & RCT:** Autism specific health checks in Primary care
- **Design intervention:** Personalised phobia treatment
- **Survey, design intervention & RCT:** Personalised anxiety treatment
- **Measurement:** Quality of life WHO-QoL-BREF and ASQoL
Register with the Adult Autism Spectrum Cohort - UK
Some challenges

What to measure? When to measure it? When to re-measure?


What to measure with? Are our measures fit for purpose? Acceptable, psychometric properties?

Comparison (control) data; comparison between adults; different settings or countries? Or compare with the general population?

(National, and International collaboration)
Discussion
<table>
<thead>
<tr>
<th>Time</th>
<th>Agenda Item</th>
</tr>
</thead>
<tbody>
<tr>
<td>9:30</td>
<td>Physical and Mental Health in Autism – Epidemiology of Co-occurring Conditions</td>
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<td></td>
<td>Lisa Croen, Ph.D.</td>
</tr>
<tr>
<td></td>
<td>Senior Research Scientist, Division of Research, Kaiser Permanente Northern California, and Director, Kaiser Permanente Autism Research Program</td>
</tr>
<tr>
<td>10:15</td>
<td>Break</td>
</tr>
<tr>
<td>10:30</td>
<td>Oral Public Comments</td>
</tr>
<tr>
<td>11:00</td>
<td>Written Public Comments</td>
</tr>
<tr>
<td>11:15</td>
<td>Working Group Discussion of Comments</td>
</tr>
</tbody>
</table>
Physical and Mental Health in Autism – Epidemiology of Co-occurring Conditions

Lisa Croen, Ph.D.
Senior Research Scientist, Division of Research, Kaiser Permanente Northern California, and Director, Kaiser Permanente Autism Research Program
What do we know?

Individuals with ASD have higher burden of medical and psychiatric conditions than individuals without ASD

- Higher utilization of healthcare services and higher associated costs

Common co-occurring conditions with ASD

- Common medical: GI, sleep, seizure, overweight/obesity, allergy/immune
- Common psychiatric: depression, anxiety

Less prevalent conditions also occur more often in individuals with ASD than general popn

- Medical: neurologic, metabolic, endocrine, ophthalmologic, cardiovascular, genetic
- Psychiatric: suicide/suicidal ideation, bipolar disorder, OCD, tic
What do we know?

Co-occurring conditions cluster together in individuals with ASD
  ◦ E.g., sleep and constipation, feeding and speech disorders

Co-occurring conditions – emergence across the lifespan
  ◦ Early childhood – GI, sleep, seizure, overweight, immune conditions
  ◦ Middle childhood/adolescence – obesity, depression, anxiety
  ◦ Adulthood – cardiovascular conditions, diabetes, Parkinsons, dementia
What gaps need to be addressed?

What do co-occurring conditions tell us about biologic pathways? Etiology of ASD?

- Temporality of co-occurring conditions
  - Share cause with ASD?
    - E.g., shared genetics
  - Conditions are consequence of core ASD symptoms?
    - E.g. obesity consequence of poor diet, tx with antipsychotics
  - Conditions share environmental risk factor with ASD
    - E.g., maternal metabolic disorders during pregnancy associated with ASD and obesity

How can co-occurring conditions aid detection of ASD?

- Are there patterns of co-occurring conditions that signal ASD?
- Can pattern of emergence of co-occurring health conditions in first years of life be used as an early warning sign/red flag, early screening tool for ASD?
What gaps need to be addressed?

What is natural history of co-occurring medical and psychiatric disorders among individuals with ASD?

◦ How are genetic and environmental risk factors for ASD associated with the trajectories of co-occurring conditions (type, timing of emergence, clustering of conditions, expression over the life course)?

Health service provision

◦ Healthcare provider education
◦ Health system, clinic, and practice organization to accommodate patients with ASD and complex health needs
◦ Transition from pediatric to adult care
◦ Communication gap between pediatric and adult providers
Discussion
Break
Meeting of the IACC

Morning Agenda

10:30 Oral Public Comments

11:00 Written Public Comments

11:15 Working Group Discussion of Comments

11:30 Epilepsy in Individuals with Autism – State of the Science

Basic Science: Shared Mechanisms

Gregory Barnes, M.D., Ph.D.,
Director, University of Louisville Autism Center, and Associate Professor, Child Neurology, Department of Neurology, University of Louisville School of Medicine
Oral Public Comments

Susan A. Daniels, Ph.D.
Director, Office of Autism Research Coordination
Executive Secretary, IACC
National Institute of Mental Health
Discussion
Meeting of the IACC

Morning Agenda

11:30 Epilepsy in Individuals with Autism – State of the Science

Basic Science: Shared Mechanisms

Gregory Barnes, M.D., Ph.D.,
Director, University of Louisville Autism Center, and Associate Professor, Child Neurology, Department of Neurology, University of Louisville School of Medicine

11:45 Clinical Science: Epidemiology and Management

Sarah Spence, M.D., Ph.D.,
Co-Director, Autism Spectrum Center, Boston Children’s Hospital, and Assistant Professor of Neurology, Harvard Medical School

12:30 PM Lunch
Epilepsy in Autism Spectrum Disorders: Shared Mechanisms

Gregory Neal Barnes MD/PhD
UL Autism Center & BioImaging Laboratory, Departments of Bioengineering and Neurology
University of Louisville
Disclosures

Investigator and Research Grant Funding from GW Pharmaceuticals
Common Mechanism of ASD and Epilepsy

ASD/ID

ASD/ID Epilepsy

Epilepsy/ID
Common Mechanism of ASD and Epilepsy

Threefold increased risk of epilepsy for children with a composite standard score <70 [45/294 (15.3%)] comparing children with a composite standard score ≥70 [5/92 (5.4%)] (OR=3.1; 95% CI: 1.2 to 10.5; \( P=0.015 \))
Shared Neurobiology of ASD and Epilepsy

- Both disorders largely involving the synapse
- Both disorders of activity dependent pathways
- Seizures can dysregulate autism-related protein cascades
- Both occurring in critical periods
- Both disorder have similar neuroanatomical and functional alterations of shared brain circuitry
Possible Mechanisms

Cells Involved

- Forebrain excitatory neurons
- Forebrain inhibitory neurons (PV+, social; SS+, repetitive behaviors)
- Serotoninergic neurons
- Basal forebrain cholinergic neurons
- Cerebellar Purkinje neurons

Hulbert and Jiang, 2017

Early life epilepsy (30%)

- Altered organization of mini-columns are associated with defects in local GABAergic circuits and their GABA$_A$ receptors in the setting of ID
What is the minicolumn?

- The minicolumn is a vertical arrangement of neurons that grows in the cortical surface.

Findings*: Autistic subjects had smaller minicolumns whose dimensions varied according to neocortical area. The greatest difference between autistic and control groups was observed in area 44.

Variation by Age?
Superpathways of ASD Genes: Homeostatic Regulation
Large Effect Size Genes Impact GABA Signaling
Impacted Function of GABA Signaling

Genes:
- GABA transaminase
- GABA transporters
- Gephyrin
- GABA_A Receptors
- Voltage gated calcium channels
Impacted Function of GABA Signaling in ASD
Shared Neurobiology of ASD and Epilepsy

Both disorders largely involving the synapse

Both disorders of activity dependent pathways

Seizures can dysregulate autism-related protein cascades

Evidence for epilepsy in human autism syndromes and animal models

Both occurring in critical periods

Both disorder have similar neuroanatomical and functional alterations of shared brain circuitry
Impact of Premature Activity on Critical Periods in Sensory Perception

Critical Periods occur in many brain circuits relevant to ASD

Humans

Social, intellectual, cognitive skills: age 2 years

Hearing: age 7 years

Vision: age 8 years
Impact of Premature Activity on Critical Periods in ASD

A brain that is too plastic at the wrong times could result in noisy and unstable processing.

A brain that lacks plasticity early in life might remain hyper- or hypoconnected and unresponsive to environmental changes early in life.

Mechanisms: GABAergic or Excitatory
Shared Neurobiology of ASD and Epilepsy

- Both disorders largely involving the synapse
- Both disorders of activity dependent pathways
- Seizures can dysregulate autism-related protein cascades
- Evidence for epilepsy in human autism syndromes and animal models
- Both occurring in critical periods
- Both disorder have similar neuroanatomical and functional alterations of shared brain circuitry
Functional Connectivity MRI Studies

PWE had deficits in Theory of Mind and Facial Emotion Recognition Tasks > TD controls

Deficits in PWE were less than deficits of ASD relatives

Both groups were free of ID

Deficits in PWE groups were independent of epilepsy characteristics

Common histopathology: focal cortical dysplasia, heterotopias, increased dendritic spine density
Shared Neurobiology of ASD and Epilepsy

- Both disorders largely involving the synapse
- Both disorders of activity dependent pathways
- Seizures can dysregulate autism-related protein cascades
- Evidence for epilepsy in human autism syndromes and animal models
- Both occurring in critical periods
- Both disorder have similar neuroanatomical and functional alterations of shared brain circuitry
- All in the setting of shared genetics
Thanks to Our Collaborators

UL Bioengineering
Dr Ayman El-Baz
Dr Robert Keynton
Omar Dekhil
Andy Switala
Ahmed Soliman

UL Computer Engineering
Dr Eric Roucka

Pediatric Research Institute
Dr Lu Cai
Dr Evelyne Gozal
Dr Rekha Jagadapillai

South Carolina
Dr Manual Casanova

Funding:
AES, Autism Speaks, UL 21st Century Initiative
A. Transcriptional Programs Increased for ASD Genetic Risk during Human Neocortical Development

M2, M3: Early fetal development, transcriptional regulators upregulated

M13, M16, M17: Late fetal into early postnatal development, upregulated synaptic genes

B. Cell Birth
De novo SNVs, M2, M3

Migration
Axonal/Dendritic Outgrowth
Programmed Cell Death
Synaptic Production
Myelination

Majority of Cells
Mostly Cortical Cells

ID genes - non-specific involvement throughout development

C. Neocortical Layers Increased for ASD Genetic Risk

Fetal
MZ
CPo/CPi
SP
Iz
SZi/SZi
VZ

M3

asDM12, M16, M17

Adult
L2/
L3
L4
L5
L6

Correlated to markers of
a general glutamatergic neurons
b upper layer glutamatergic neurons
A Gene Lists
Autism genes from SFARI (SFARI ASD)
Differential co-expression in autism from Voineagu et al., 2011 (asDM12)
Intellectual disability genes (ID genes)
Genes with rare de novo variants in autistic probands (RDNV genes)

Map Genes to Developmental and Anatomical Relationships

Developmental Dynamics
Neocortical development gene expression (BrainSpan)
Gene co-expression networks
Module-level characterization
- Reproducibility
- List over-representation
- Co-regulation

Laminar Specificity
Cortical laminar gene expression
- Human fetal, adult primate
Laminar differential expression
Laminar-level analyses
- List enrichment
- Module enrichment
- Cell-type marker enrichment

B Autism Spectrum Disorder (ASD) | Intellectual Disability (ID)

Genes
Rare de novo exome variants
Siblings
ASD | No ASD
Differential coexpression
Candidate genes

Molecular Networks
Gene modules sharing:
- Function
- Expression pattern
- Protein interactions
- Regulation
Age (prenatal to infancy)
Transcriptional regulation
Synaptic development

Anatomical Circuits
Cortical layers
L2-3
L4
L5
L6
ASD genes converge to disrupt neural development and cortical-cortical connectivity
ID genes show less specificity
Epilepsy in Autism Spectrum Disorder: The Clinical Picture
Sarah J Spence MD PhD
Boston Children’s Autism Spectrum Center
Disclosures

- No relevant financial relationships
- Past and present grant funding from NIH, Simons Foundation, Nancy Lurie Marks Foundation, Autism Speaks, Cure Autism Now, MIND Institute
- Member of DSM 5 Neurodevelopmental Disabilities workgroup.
- Current Co-Investigator in Roche trial for ASD (not epilepsy)
- Consultant to Yamo pharmaceuticals for new compound (not epilepsy)

*Apologies in advance for using “person first” language*
Association is frequent
Major impact on patient quality of life
Could represent common neural mechanisms
Overlapping phenotypes

EPILEPSY

ASD

Behavior

Communication

Cognition

Is there any causal relationship or is this epiphenomenon?
Epilepsy is increased in ASD

- But - rates very variable (5-45%)
- Probably dependent on sample characteristics:
  - SAMPLE ASCERTAINMENT
    - Population based samples have lower rates than clinic based
  - AGE
    - Bimodal age of onset (early childhood & adolescence).
    - Bolton (2011) found >50% had seizure onset after age 10
  - NON-IDIOPATHIC or SYNDROMIC AUTISM
    - Neurogenetic syndromes or brain injury have more epilepsy.
  - IQ and LANGUAGE skills
    - Most studies show that lower IQ associated with epilepsy.
    - Some studies show language regression and poorer language skills predict epilepsy.
### Variability in published reports

<table>
<thead>
<tr>
<th>Citation</th>
<th>Sample size</th>
<th>Age</th>
<th>Ascertainment</th>
<th>Diagnosis</th>
<th>Syndrome</th>
<th>Epilepsy rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amiet 2008</td>
<td>2112</td>
<td></td>
<td>Mixed</td>
<td>Autism, PDD</td>
<td>yes</td>
<td>With intellectual disability: 21.4 %</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Without intellectual disability: 8%</td>
</tr>
<tr>
<td>Miles et al. 2005</td>
<td>233</td>
<td>Mean 7.8 yrs</td>
<td>Clinic based</td>
<td>Autism, Asperger’s</td>
<td>no</td>
<td>17% “essential”</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>39% “complex”</td>
</tr>
<tr>
<td>Canitano 2005</td>
<td>46</td>
<td></td>
<td>Clinic based</td>
<td>Autism or “Autistic Like”</td>
<td>yes</td>
<td>13%</td>
</tr>
<tr>
<td>Danielson 2005</td>
<td>108</td>
<td>Mean 7.8 yrs</td>
<td>Population Based</td>
<td>Autism or ASD</td>
<td>yes</td>
<td>46%</td>
</tr>
<tr>
<td>Hughes 2005</td>
<td>59</td>
<td>0.5-21 yrs</td>
<td>Clinic based</td>
<td>Autism</td>
<td>yes</td>
<td>13%</td>
</tr>
<tr>
<td>Gianotti 2008</td>
<td>104</td>
<td>30mo. -8 yrs</td>
<td>Clinic based</td>
<td>Autism or ASD</td>
<td>yes</td>
<td>19.4%</td>
</tr>
<tr>
<td>Hara 2007</td>
<td>130</td>
<td>18-35 yrs</td>
<td>Clinic based</td>
<td>Autism, PDD</td>
<td>no</td>
<td>17% (25% when 1 seizure included)</td>
</tr>
<tr>
<td>Bolton 2011</td>
<td>150</td>
<td>All adult</td>
<td>Prospective research cohort</td>
<td>ASD</td>
<td>yes</td>
<td>22%</td>
</tr>
<tr>
<td>Mouridsen 2011</td>
<td>118</td>
<td>All adult</td>
<td>Clinic/ population</td>
<td>ASD</td>
<td>no</td>
<td>25%</td>
</tr>
<tr>
<td>Kohane 2012</td>
<td>14,381 (2,393,778)</td>
<td>0-35 yrs</td>
<td>Hospital EMR</td>
<td>ASD</td>
<td>yes</td>
<td>19.4%</td>
</tr>
<tr>
<td>Suren 2012</td>
<td>1726 (731,318)</td>
<td>0-11 yrs</td>
<td>Population based</td>
<td>ASD</td>
<td>yes</td>
<td>11.2%</td>
</tr>
</tbody>
</table>

**Effect of age**

- Canitano 2005: Mean 7.8 yrs
- Danielson 2005: Mean 25.5 yrs
- Hara 2007: 18-35 yrs
- Kohane 2012: 0-35 yrs
- Suren 2012: 0-11 yrs

**Effect of ascertainment**

- Canitano 2005: Clinic based
- Danielson 2005: Clinic based
- Hara 2007: Clinic based
- Kohane 2012: Hospital EMR
- Suren 2012: Population based

**Effect of comorbidity (syndrome, ID)**

- Amiet 2008: Mixed Autism, PDD
- Miles et al. 2005: Clinic based Autism, PDD
- Gianotti 2008: Clinic based Autism or ASD
- Hara 2007: Clinic based Autism, PDD
- Kohane 2012: Hospital EMR ASD
- Suren 2012: Population based ASD
# Overlap between epilepsy syndromes and autism

<table>
<thead>
<tr>
<th>Infantile Spasms</th>
<th>Tuberous Sclerosis Complex</th>
<th>Landau Kleffner Syndrome</th>
</tr>
</thead>
<tbody>
<tr>
<td>- High rates of intellectual disability with social communication deficits &gt;&gt; expected for IQ</td>
<td>- Very high rates of epilepsy and high rates of ASD (~40%)</td>
<td>- Language and behavioral regression</td>
</tr>
<tr>
<td>- 10-15% of kids develop autism</td>
<td>- ASD higher in those with intellectual disability</td>
<td>- EEG abnormalities</td>
</tr>
<tr>
<td>- IS history in 6% of all ASD and up to 30% of ASD patients with epilepsy</td>
<td></td>
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</tbody>
</table>
No single epilepsy syndrome

Seizure types
- Generalized convulsive seizure
- Partial/focal seizure
- Absence

Sometimes hard for even expert epileptologists to tell the difference between seizure and behavior

Seizure Behavior
- Unresponsiveness
- Eye deviation
- Repetitive behavior (automatisms)

Autism Behavior
- Not responding to name
- Peering from the corner of eyes
- Stereotypies
Epilepsy in ASD

- Treatment refractory epilepsy may be common
  (Sansa et al., 2011)
  - 34% treatment refractory
    - significantly earlier age of seizure onset
  - 39% with infrequent or difficult to categorize
  - 27% seizure free

- Epilepsy may increase mortality in ASD
  (Pickett et al., 2011)
  - data from California DDS
  - 5-6x higher mortality in those with ASD plus epilepsy than ASD alone

- Epilepsy may impact outcome of early intervention
  (Eriksson et al, 2013)
  - Epilepsy (among other medical problems) associated with lower adaptive function scores
Risk factors

**Intellectual disability**
- Most (but not all) show epilepsy associated with intellectual disability
- Meta-analysis of 10 studies epilepsy in 21% with ID vs 8% without (Amiet et al., 2008)

**Co-morbid conditions: syndromic or non-idiopathic autism**
- 2-5 x increased risk (Pavone et al., 2004; Miles et al., 2005; Parmegianni et al., 2010)

**Female gender**
- Most studies (but not all) show higher epilepsy in females
- Meta-analysis epilepsy in 34% of females vs 18% of males (Amiet et al., 2008)

**Developmental regression**
- Several studies suggest an association (Kobayashi & Murita, 1998; Hrdlicka et al., 2004; Giannotti et al., 2004; Parmegianni et al., 2010)
- Other studies show no association (Tuchman & Rapin, 1997; Canitano et al., 2005; Hara, 2007)

**Pre and perinatal factors**
- Finish birth cohort study n=4705
- Prematurity, birth weight, low APGARS (Jokiranta et al., 2014)
Relationship between epilepsy and ASD clinical profile

Less is known

- Hara 2007 retrospective clinical review
  - lower social scores and more medication use

- Turk et al 2009 age and IQ matched sample
  - Increased motor & adaptive behavior deficits
  - One item in nonverbal communication: “stares too long and too hard”
  - Several items on social interaction scale: difficulties with peers, psychological barriers, and socially shocking behaviors.

- Smith & Matson 2011
  - Epilepsy makes everything worse – in ASD and non-ASD developmental delay.
But are these associations independent?

Viscidi et al., 2013 PLOS-ONE

□ Large study designed to examine the clinical characteristics of epilepsy and ASD

□ Sample of convenience

■ Large data sets available from genetic studies
  □ AGRE, Boston Autism Consortium, Simons Simplex Collection

■ Strengths
  □ Good ASD diagnostic data
  □ Detailed ASD and related behavioral phenotyping data

■ Weaknesses
  □ Turns out mediocre epilepsy data

□ Initial analysis showed significant effects of:

■ Regression, Language, IQ, Adaptive function, ASD severity
<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Model 1: Unadjusted</th>
<th></th>
<th>Model 2: Adjusted for FSIQ</th>
<th></th>
<th>Model 3: Fully Adjusted</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>OR (95% CI)</td>
<td>p-value</td>
<td>OR (95% CI)</td>
<td>p-value</td>
<td>OR (95% CI)</td>
<td>p-value</td>
</tr>
<tr>
<td>Age</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>9 years and younger</td>
<td>1.00 [Reference]</td>
<td></td>
<td>1.00 [Reference]</td>
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<td>1.00 [Reference]</td>
<td></td>
</tr>
<tr>
<td>10 years and older</td>
<td>3.05 (2.29–4.06)</td>
<td>&lt;.001</td>
<td>2.40 (1.51–3.82)</td>
<td>&lt;.001</td>
<td>2.35 (1.42–3.88)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Gender</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>1.00 [Reference]</td>
<td></td>
<td>1.00 [Reference]</td>
<td></td>
<td>1.00 [Reference]</td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>1.86 (1.35–2.56)</td>
<td>&lt;.001</td>
<td>1.43 (0.82–2.49)</td>
<td>0.21</td>
<td>1.36 (0.77–2.43)</td>
<td>0.29</td>
</tr>
<tr>
<td>Cognitive Ability</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Full Scale IQ Score</td>
<td>0.51 (0.41–0.63)</td>
<td>&lt;.001</td>
<td>0.51 (0.41–0.63)</td>
<td>&lt;.001</td>
<td>0.53 (0.39–0.73)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Adaptive Functioning</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Adaptive Behavior Composite Score</td>
<td>0.52 (0.45–0.61)</td>
<td>&lt;.001</td>
<td>0.80 (0.58–1.10)</td>
<td>0.17</td>
<td>0.98 (0.70–1.37)</td>
<td>0.89</td>
</tr>
<tr>
<td>Language</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Meaningful Use of Single Words, Two-Word Phrases, or Three-Word Phrases</td>
<td>1.00 [Reference]</td>
<td></td>
<td>1.00 [Reference]</td>
<td></td>
<td>1.00 [Reference]</td>
<td></td>
</tr>
<tr>
<td>Fewer than 5 Words</td>
<td>2.00 (1.39–2.87)</td>
<td>&lt;.001</td>
<td>0.75 (0.27–2.05)</td>
<td>0.57</td>
<td>0.75 (0.27–2.13)</td>
<td>0.59</td>
</tr>
<tr>
<td>Developmental Regression</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No Loss of Language or Skills</td>
<td>1.00 [Reference]</td>
<td></td>
<td>1.00 [Reference]</td>
<td></td>
<td>1.00 [Reference]</td>
<td></td>
</tr>
<tr>
<td>Loss of any Language or Skills</td>
<td>1.93 (1.45–2.57)</td>
<td>&lt;.001</td>
<td>1.05 (0.64–1.72)</td>
<td>0.86</td>
<td>1.14 (0.69–1.89)</td>
<td>0.60</td>
</tr>
</tbody>
</table>

Abbreviations: OR, odds ratio; CI, confidence interval; FSIQ, full scale IQ score.

*Genetic Collaborative Samples (AGRE, SSC, and AC) combined.

Model 1: Individual models for each variable.
Model 2: Individual models for each variable, adjusted for full scale IQ score only.
Model 3: Single model adjusted for all variables.

Odds ratios for full scale IQ score and adaptive behavior composite score represent the odds of epilepsy for a one standard deviation increase.

doi:10.1371/journal.pone.0067797.t006
Treatment

- Anti-Seizure drugs dependent on:
  - seizure type
  - side effect profile
  - practicalities
    - formulation, dosing schedule, need for blood draws in monitoring, etc

- All seizure medications can have behavioral and cognitive effects ... so practitioners need to be careful in children who already show impairment.

- New cannabis data is sparking a lot of interest
  - GWPharma Epidiolex trial in severe epilepsy (Devinsky et al. 2017)
    - Lots of interest in using CBD in autism for behavior
    - Safety and Tolerability of GWT42006 (cannabidivarin) in subjects with drug resistant epilepsy and autism (U of Louisville, G Barnes PI)
      - Measuring both behavioral and seizure outcomes
In reality: Probably multiple kinds of epilepsy in autism

When early onset seizures actually contribute to autism

• infantile spasms

When other disorders co-exist

• neurogenetic syndromes (eg Tuberous Sclerosis, Fragile X, 15q duplication)
• neurologic injury (eg CNS malformation or stroke)
• severe intellectual disability

True idiopathic autism

• whatever that means…
THANK YOU
SOME WAYS TO INTRODUCE DISCUSSION
Challenges to research

DISORDER HETEROGENEITY

“The autisms”

“The epilepsies”

Disparate Fields of Investigation

Behavioral Science

Neurology

Basic Science
Bedside to Bench and Back: Translational Research

- Clinical research questions:
  - Effects of
    - Severity (of both autism and epilepsy)
    - Development (which comes first – the autism or the epilepsy?)
  - Relationship specifically to ASD symptoms?
    - Is there a causal relationship or is this epiphenomenon?
    - What is the role for intervention?
Translational Research: Are there common mechanisms?

- **pathways**
  - A disconnection syndrome with overconnectivity in local regions and underconnectivity in long range.
  - Are focal discharges a result of increased local connectivity gone awry?

- **cells**
  - A disorder of the synapse.
  - Excitatory inhibitory imbalance during critical period of brain development

- **genes**
  - Many overlapping genes and regions
  - Monogenic examples: CNTNAP2, PTEN, TSC 1 and 2, FMRP, SCN1A, MECP2, CDKL5, PCDH19
  - CNV: 15q11 duplications, 16p11 deletions and duplications, 22q11-13 (PMS)
Translational Research: Data from animal models

TSC Alert

PREVeNT Trial Enrolling Participants

The Preventing Epilepsy Using Vigabatrin in Infants with Tuberous Sclerosis Complex (PREVeNT) trial, led by Martina Bebin at the University of Alabama Birmingham, is continuing to enroll participants at seven sites across the country.

The central hypothesis of this Phase IIb trial, supported by a $7 million grant from NINDS, is that early identification of electroencephalography (EEG) biomarkers and early treatment versus delayed treatment with vigabatrin in infants with tuberous sclerosis complex (TSC) will have a positive impact on developmental outcomes at 24 months of age. It would also prevent or lower the risk of developing infantile spasms and refractory seizures. This preventative approach would be expected to result in more favorable long-term cognitive, behavioral, developmental and psychiatric outcomes and significantly improve overall quality of life.
Autism & Epilepsy: Moving forward

- Genetics
- Basic molecular mechanisms
- Prevalence
- Phenotypic descriptions
- Development of targeted treatments

We have a lot more work to do
Global Summit

Autism & Epilepsy

A collaborative workshop to act as a catalyst for further research into autism and epilepsy to enable autistic people to live longer, happier, healthier lives.

AUTISTICA

Building brighter futures through autism research

Research themes generated at the AUTISTICA global summit:

1. Distribution and determinants of autism and co-occurring epilepsy
2. Understanding epilepsy onset in autism
3. Medication and onset of epilepsy
4. Epilepsy medication side effects
5. Autism characteristics versus epilepsy seizures
6. Seizure frequency in autism
7. Understanding the role of seizures in autism
8. Epilepsy onset in individuals with autism
9. Genetics and autism
10. Understanding autism
11. Genetics – understanding seizures
12. Risk factors for premature death
13. Premature death education
Discussion
Lunch
Meeting of the IACC

Afternoon Agenda

1:30 Autism and Gastrointestinal Disorders

Timothy Buie, M.D.,
Attending Physician, Division of Gastroenterology, Hepatology and Nutrition, Boston Children’s Hospital, and Assistant Professor of Pediatrics, Harvard Medical School

2:15 Autism Spectrum Disorder and Sleep – Identifying Challenges and Finding Solutions

Beth Ann Malow, M.D., M.S.,
Burry Chair in Cognitive Childhood Development, Professor of Neurology and Pediatrics, Vanderbilt Kennedy Center, and Director, Vanderbilt Sleep Disorders Division

3:00 Break
Meeting of the IACC

Afternoon Agenda

3:10 Patient – Provider Interactions

Healthcare Experiences of Children with Autism: Opportunities for Improvement

Micah Mazurek, Ph.D.
Associate Professor of Education, Curry School of Education, University of Virginia
Meeting of the IACC

Afternoon Agenda
3:25 Healthcare Experiences of Adults on the Autism Spectrum: Challenges and Solutions

Christina Nicolaidis, M.D., M.P.H.
Professor and Senior Scholar in Social Determinants of Health, School of Social Work, Portland State University, and Adjunct Associate Professor, Division of General Internal Medicine, Oregon Health and Science University

Dora Raymaker, Ph.D.
Research Assistant Professor, Portland State University; Co-Director, Academic Autism Spectrum Partnership in Research and Education (AASPIRE)
Meeting of the IACC

Afternoon Agenda
4:20 Working Group Discussion
5:00 Adjournment
Gastrointestinal Problems in Autism

NIH/IACC 09/27/2018
Prior to 20 years ago there was sparse research into GI or dietary problems in autism. In 1998, papers discussing possible GI links were published including discussion about colitis, possible dietary factors, intestinal permeability issues and even possible treatments. GI clinics were filled with individuals with autism but few GI providers had training or experience with autism and there wasn’t guidance available for them to help.
We accept GI problems are common and may be more common than the general pediatric population. Our findings didn’t find significant differences in the kind of problems seen but we were looking...

Although Pediatricians and GI doctors are aware of these issues it is not clear if providers are confident in evaluating these individuals or confident who to work up if lacking obvious symptoms
Studies quote an 8-90% prevalence of GI issues in autism. That is useless data. Why?

- Early studies had enrollment bias identifying far too few or too frequent cases. Good writers need to stop quoting bad studies.
Cross-sectional study; 3 groups-50 per group

GI issues identified in each group:
- 70% children with ASD
- 42% children with developmental disorder
- 28% children with typical development

In May 2008, a consensus meeting of experts was brought to Boston in an attempt to review and vet the quality of the literature and research regarding Autism and GI issues. Sponsored by Easter Seals of Oregon, The Autism Society (of America), The Autism Research Institute.

The resulting consensus papers have been published in Pediatrics, 23 consensus statements issued by 27 experts.

http://pediatrics.aappublications.org/cgi/content/full/125/Supplement_1/S1

http://pediatrics.aappublications.org/cgi/content/full/125/Supplement_1/S19
Prevalence of GI issues in autism

- Meta-analysis (1980-2012) of 15 qualified studies
- Number of pooled patients = 961

So, newer data support a more consistent prevalence of **45-70%** of children with autism have GI issues.

McElhanon BO et al. Pediatrics. 2014 May;133(5):872-83
Early dietary or GI discussions in autism were hypotheses of causation:

**Opioid Peptide Theory**: Peptides from milk (casein) and wheat (gluten) caused childhood schizophrenia (autism).


**Autistic Enterocolitis**: Intestinal inflammation caused intestinal permeability problems and immune disruption.

Others have built on the suggestion that many children with autism suffering GI symptoms have a variety of GI findings including:

<table>
<thead>
<tr>
<th>GI Findings</th>
<th>References</th>
</tr>
</thead>
</table>
# Food Allergy/Sensitivity

<table>
<thead>
<tr>
<th>Findings</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>Food allergy was reported in 36% of 36 children with ASD</td>
<td>Lucarelli S et al. Panminerva Med. 1995 Sep; 37(3): 137-41.</td>
</tr>
</tbody>
</table>
Food Allergy in Autism

- Large, population-based case-control study (CHARGE); maternal reporting of asthma and allergies

Multi-factorial issues well described:

1) Rigid, perseverative behavior could be a core autism component

2) Textural sensitivity could be related but often occurs associated with GE Reflux and can be seen with oral allergy response.

3) Avoidant restrictive food intake disorder (ARFID) is a DSM V diagnosis seen commonly in children with autism
Reviews are inconsistent but include concern for inadequate intake of key nutrients:

Comparative GI Findings

- No difference in GI findings of 61 children with autism compared to 50 unaffected children undergoing endoscopy.
- This included evaluation of inflammation, intestinal permeability and disaccharide activity
Could GI issues CAUSE autism?

- Environmental/nutritional/microbiome associated factors modulating genetically predisposed individuals

- An inflammation model where an inflammatory process (colitis, allergy, infection) releases chemical or immune mediators that affect brain function (Vargas 2005, Welch 2005)
Intestinal microbiome disruptions may alter behavior, immune responses, intestinal permeability, metabolic by products which may affect nervous system communication.

Intestinal microbiome disruptions exist in the autism population.

Diet change and early exposure to antibiotics may alter microflora and metabolome.
A growing number of studies point to altered microbiome in populations of children with autism.

Potential Etiologic Factors of Microbiome Disruption in Autism, Clinical Therapeutics, Buie, T Volume 37 Number 5, 2015

Consumption of fermented milk product with probiotic modulates brain activity. (Bifidobacterium Lactis, Streptococcus thermophiles, Lactobacillus bulgaricus, and Lactococcus lactis)

Microbiota Modulate Behavioral and Physiological Abnormalities Associated with Neurodevelopmental Disorders


Cell 2013
Microbiota Transfer Therapy alters gut ecosystem and improves gastrointestinal and autism symptoms: an open-label study

Dae-Wook Kang†, James B. Adams‡, Ann C. Gregory3,15†, Thomas Borody4, Lauren Chittick5,15, Alessio Fasano6,
Alexander Khoruts7,8,9, Elizabeth Geis2, Juan Maldonado1, Sharon McDonough-Means10, Elena L. Pollard2,
Simon Roux5,15, Michael J. Sadowsky8,11, Karen Schwarzberg Lipson12, Matthew B. Sullivan3,5,15,16*,
J. Gregory Caporaso12,13* and Rosa Krajmalnik-Brown1,14*
Key Statement (Statement 1): Individuals with ASDs who present with GI symptoms warrant a thorough evaluation, as would be undertaken in individuals without ASDs who have the same symptoms or signs.

Statement 6: Individuals with ASDs and GI symptoms are at risk for problem behaviors. When patients with GI disorders present with behavioral manifestations, the diagnostic evaluation can be complex.

Evaluation, Diagnosis, and Treatment of Gastrointestinal Disorders in Individuals With ASDs: A Consensus Report
T. Buie et al, Pediatrics 2010; 125: S1-S18
Discussion of presentation of several common GI problems in children with autism including abdominal pain, constipation, diarrhea and gastroesophageal reflux.

Some basic suggestions for evaluation and treatment are offered holding mostly to established guidelines for pediatric patients in general, until better data is available to guide evaluation and treatment.


http://pediatrics.aappublications.org/cgi/content/full/125/Supplement_1/S19
GI issues are common in autism although a unique entity has not been identified

Diet therapy may have a place in a subgroup of individuals but data are still debated and being gathered

Problem behaviors can be medically based, behavior is communication in non-verbal individuals

Profound or self-injurious behaviors may require pharmacological management, but a response to this should not replace proper medical evaluation.
- Office Hours recently launched video series on AutismSpeaks website discussing medical issues and autism. Topics discussed included reflux, sleep, probiotics
  
www.autismspeaks.org/site-wide/office-hours

- Food for Thought: recurring blog, Autism Speaks

- A series of Cleveland Clinic CME sessions discussing medical co-morbidity in autism
  
www.clevelandclinicmeded.com/online/webcasts/autism-spectrum-disorders/medical-comorbidities/
Thanks to:

**MGH Team:** Harland Winter, Margaret Bauman, Katherine Murray, Rafail Kushak, Aeri Moon, Sarah Kadzielski, Alessio Fasano

**Boston Children’s Hospital Team:** Sonia Ballal, Athos Bousvaros, Elana Bern, Fiona Paul

**My Support:** Newman Foundation, Autism Research Institute, AutismSpeaks, The Buie Family
Discussion
Meeting of the IACC

Afternoon Agenda
2:15  Autism Spectrum Disorder and Sleep – Identifying Challenges and Finding Solutions
      Beth Ann Malow, M.D., M.S.,
      Burry Chair in Cognitive Childhood Development, Professor of Neurology and Pediatrics, Vanderbilt Kennedy Center, and Director, Vanderbilt Sleep Disorders Division

2:30  Discussion

3:00  Break
Autism Spectrum Disorder and Sleep--Identifying Challenges and Finding Solutions

Beth A. Malow, M.D., M.S.
Burry Chair in Cognitive Childhood Development
Professor of Neurology and Pediatrics
Director, Sleep Disorders Division
Vanderbilt University Medical Center
Disclosures

- Grant support from Neurim Pharmaceuticals and Autism Treatment Network
- Consultant for Janssen and Vanda Pharmaceuticals
- Royalties from Woodbine House for “Solving Sleep Problems in Children with Autism Spectrum Disorders: A Guide for Frazzled Families” (with Dr. Terry Katz)
- I will discuss off-label uses of medications for sleep in autism (there are no approved FDA medications indicated for sleep in this population!)
Questions to Consider

- What kinds of sleep problems do individuals on the autism spectrum experience?
- What are the causes and contributors to these problems?
- What are the consequences on the individual and family?
- What are the latest treatments and guidelines?
- What areas are most in need of future research to move the field forward?
Alex is a 10-year-old boy with autism spectrum disorder. Bedtime is 8 pm. He takes hours to fall asleep. His parents state that “he can’t shut his brain down.” He takes methylphenidate (Ritalin) in the afternoon for ADHD symptoms, drinks sweet ice tea with dinner, and plays video games after dinner. He can’t settle down to go to sleep and leaves his room repeatedly to find his parents. They rub his back to help him fall asleep.

Once asleep, he awakens multiple times during the night. Sometimes he sleepwalks and sometimes he comes to his parents’ bedroom and falls asleep there (they are too exhausted to move). He snores in his sleep, and is very restless with frequent leg kicks.

It is “nearly impossible” to awaken Alex in the morning for school. Alex’s teacher describes him as being sleepy as well as hyperactive and “disruptive” in class. His parents are exhausted and very overwhelmed.
Unpacking Alex’s sleep problems

- Insomnia
- Hypersomnia
- Parasomnia

- Snoring
- Leg movements
- Tea
- Methylphenidate
- Video Games (light/content)
- Parent interactions
- Bedtime of 8 pm (“forbidden zone”)

Sleep study
Eliminate tea at dinner
Methylphenidate earlier
Turn off screens
Teach Alex to fall asleep on his own
Later bedtime

Factors:
- Biological
- Medical
- Environmental
- Behavioral
**Table 5**

Clock genes and autism spectrum disorder (ASD).

<table>
<thead>
<tr>
<th>Studies</th>
<th>Measure</th>
<th>Individuals with Psychiatric Disorder (n)</th>
<th>Controls (n)</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nicholas et al.</td>
<td>Screening of eleven clock/clock-related genes</td>
<td>High-functioning ASD individuals (n = 110)</td>
<td>Healthy parents (n = 220)</td>
<td>Significant association for two single-nucleotide polymorphisms in <em>Per1</em> and in <em>Npas2</em>.</td>
</tr>
<tr>
<td>Yang et al. [188]</td>
<td>Direct sequencing analysis of the coding regions of 18 canonical clock genes and clock-controlled genes</td>
<td>ASD individuals with sleep disorders (n = 14); ASD individuals without sleep disorders (n = 14)</td>
<td>Healthy individuals (n = 23)</td>
<td>Mutations in circadian-relevant genes (specifically <em>Per1, Per2, Per3, Clock, Npas2, Bmal1, Tim, Cry1, Cry2, Dph</em> and <em>Cktc</em>) affecting gene function are more frequent in individuals with ASD than in controls.</td>
</tr>
</tbody>
</table>
Melatonin is abnormally processed in ASD

Kulman, Neuro Endocrine Letters 2000

Nir, JADD, 1995

Tordjman, Bio Psych, 2005

Melke, Mol Psych, 2008

Tryptophan → serotonin → AA-NAT

N-acetylserotonin → ASMT

Melatonin → CYP1A2

6-sulfoxymelatonin (major metabolite)
Melatonin levels may be normal in ASD

Overnight blood sampling in 3-10 year olds with ASD and sleep-onset insomnia whose insomnia responded to melatonin supplements had documented normal endogenous melatonin profiles prior to treatment. (representative child’s profile shown above)

Goldman & Malow, JADD, 2014
NICHD–funded R01

Evening saliva sampling in adolescents with ASD, including those with sleep-onset insomnia, documented normal endogenous melatonin profiles (representative teen’s profile shown above)

Goldman & Malow, JADD, 2017
Autism Speaks Grant
fMRI studies have shown increased amygdala activation and decreased connectivity between prefrontal cortex and amygdala after sleep deprivation (Yoo, Curr Biol, 2007; Reidy, Neuropsychologia, 2016).

In > 2,714 children with ASD in the Simons Simplex Collection, severity scores for social/communication impairment and restricted and repetitive behaviors were increased for children reported to sleep ≤ 7 hours per night (lower 5th percentile) compared to children sleeping ≥ 11 hours per night (upper 95th percentile). (Veatch, Autism Research, 2017)

- 81 children with autism, ages 3-19 years
- Sleep problems were significantly associated with physical aggression, irritability, inattention, and hyperactivity.
- Night wakings was most strongly related to behavioral problems, even after controlling for the effects of age and sex.
### Support Needs and Coping Strategies as Predictors of Stress Level among Mothers of Children with Autism Spectrum Disorder

Sheri R. Kiami\(^1\) and Shelley Goodgold\(^2\)

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**Table 3**

Family needs questionnaire percentages ranked by important unmet needs.

<table>
<thead>
<tr>
<th>“I need” statement</th>
<th>% important unmet needs</th>
<th>% important needs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Financial support in order to provide my child with therapies, treatments, and care. (n/a)</td>
<td>87%</td>
<td>89%</td>
</tr>
<tr>
<td>To get a break from my responsibilities. (P)</td>
<td>86%</td>
<td>94%</td>
</tr>
<tr>
<td>To have the other children in my child's after-school program understand my child's special needs. (n/a)</td>
<td>79%</td>
<td>100%</td>
</tr>
<tr>
<td><strong>To get enough rest or sleep. (P)</strong></td>
<td><strong>79%</strong></td>
<td><strong>96%</strong></td>
</tr>
<tr>
<td>Help remaining hopeful about my child's future. (P)</td>
<td>79%</td>
<td>85%</td>
</tr>
<tr>
<td>To have counseling for myself and my spouse/partner/child's father. (P)</td>
<td>78%</td>
<td>69%</td>
</tr>
<tr>
<td>To have other family members understand my child's problems. (n/a)</td>
<td>77%</td>
<td>94%</td>
</tr>
<tr>
<td>To have time to care for my own health needs (Note: additional question added to Modified FNQ. (P)</td>
<td>76%</td>
<td>90%</td>
</tr>
</tbody>
</table>
Back to Alex (and the future teenage and adult Alex)

• #1 Hunt hard for medical co-occurring conditions that affect sleep
• #2 Behavioral approaches work if you can implement them (Malow, JADD, 2014)
• #3 Consider medications for overwhelmed individuals and families but also do #1 and #2

Sleep study
Eliminate tea at dinner*
Methylphenidate earlier
Turn off screens*
Teach Alex to fall asleep on his own*
Later bedtime*

Biological
Medical
Environmental
Behavioral
ATN/AIR-P Toolkits

Autism Speaks, on line materials

http://www.autismspeaks.org/science/resources-programs/autism-treatment-network/tools-you-can-use/sleep-tool-kit
Children with Limited Verbal Skills

- Rocking and Swinging
- Snuggling
- Massaging
- Music
- White noise
- Night lights
- Calming scents
- Weighted blankets

Schedule Boards:

Some children are not able to use a visual schedule that uses words, photos, or icons. It may help to use objects instead.

Here’s an example: If your child’s bedtime routine consists of using the toilet, taking a bath, washing hair, brushing hair, having a massage, and listening to music, you might have a place near the bathroom or bedroom with the following items: a roll of toilet paper, a bar of soap, a bottle of shampoo, a hairbrush, a bottle of lotion, and a CD. Your child would get each object before the start of an activity and use this to guide his or her actions. Save a special object just for bedtime. This might be a special blanket, pillow, or stuffed animal. Once your child has this object, he or she should go into his or her bed. Even if you do not use objects, write down your child’s schedule so that you are going through the same steps each night. Use single words or two-word phrases to label what you are doing.
Melatonin and melatonin agonists (most studied, safe/well tolerated)
- Several meta-analyses and reviews (Rossignol, Dev Med Child Neuro, 2011)
- Prolonged release preparations improve sleep duration (Gringras, Am Acad Child Adol Psych 2017)
- Melatonin + behavioral therapy most effective (Cortesi, J Sleep Res, 2012)

Gabapentin (Robinson and Malow, J Child Neuro, 2013)

Alpha-adrenergic agonists (Ming, Brain Dev, 2008; Ingrassia, Eur Child Adol Psych, 2005)

Trazadone

Mitazapine (Posey, J Child Adol Psychopharm, 2001)

Benzodiazepines– works in NREM arousal disorders like sleepwalking

Non-benzodiazepine receptor agonists (zolpidem, eszopiclone)

Tricyclic antidepressants

Other OTCs besides melatonin
- Valerian, Tryptophan/5-Hydroxytryptophan
Are any of the old or new medications for insomnia effective in autism and what are the side effects (across the lifespan)?

How do these medications compare in terms of effectiveness and side effects? (as to melatonin)

Can medications and behavioral treatment work synergistically?

How do we get overwhelmed parents of children with autism to use behavioral strategies?

What about teens and adults with autism? How do we motivate them?

Can genetic or biomarker studies guide our treatment plans?
Discussion
Break
Meeting of the IACC

Afternoon Agenda

3:10 Patient – Provider Interactions

Healthcare Experiences of Children with Autism: Opportunities for Improvement

Micah Mazurek, Ph.D.
Associate Professor of Education, Curry School of Education, University of Virginia
Healthcare Experiences of Children with Autism: Opportunities for Improvement

Micah Mazurek, PhD
Associate Professor
ASD: Complex Healthcare Needs

• “Core” Diagnostic Features:

  - Social Communication & Interaction
  - Restricted/Repetitive Behaviors
Co-Occurring Conditions

• Cognitive Problems
  • Intellectual disability
  • Executive functioning problems

• Medical Conditions
  • Seizures
  • Gastrointestinal problems
  • Sleep disturbance
  • Feeding problems

• Emotional/Behavioral Problems
  • Anxiety
  • Depression
  • ADHD symptoms
  • Aggression
  • Self-Injurious behaviors

• Others...
  • Language disorders
  • Sensory processing difficulties
  • Many others...
Co-Occurring Conditions

• Co-occurring conditions are common
  • More than 95% of 8- and 4-year old children with ASD in the 2010 ADDM Network study had at least one co-occurring condition/symptom
  • Many children with ASD have *multiple* co-occurring conditions
  • Many conditions appear to be inter-related
  • Some symptoms overlap and/or mask core symptoms of ASD

(Aldinger et al., 2015; Doshi-Velez, Ge, & Kohane, 2014; Kohane, et al., 2012; Mazurek et al., 2013; Mazurek et al., 2014; Mazurek & Petroski, 2015; Soke et al., 2018)
Impact of Co-Occurring Conditions

• The impact of co-occurring conditions in children with ASD may include:
  • Interference with daily life
  • Greater family stress and burden
  • Worse health care experiences
  • Greater financial strain
  • Higher healthcare costs

(Benson & Karlof, 2008; Estes et al., 2009; Lecavalier et al., 2006; Zablotsky et al., 2014)
Healthcare Needs

• *Despite their need for care,* compared to children with other special healthcare conditions, children with ASD have:
  
  • **Greater unmet** healthcare needs
  • **Worse access** to medical home
  • Less coordinated, family-centered care

• Children with ASD and comorbid conditions have **even worse** health care experiences and greater financial strain

(Brachlow, Ness, McPheeters & Gurney, 2007; Kogan et al., 2008; Krauss et al, 2003; Zablotsky et al., 2014)
Barriers: Access to Care

- Few providers with autism expertise
  - Shortages of autism specialists in most communities
  - Long wait-lists at specialty centers
- Geographic/transportation barriers
  - Remote and rural areas
- Financial barriers
- Cultural or linguistic barriers

(Chiri et al., 2012; Doshi et al., 2017; Krauss et al, 2003; Magaña et al., 2015, Zablotsky et al., 2014; Zhang et al. 2017)
Barriers: Clinic Environment

- Challenges for Children with ASD
  - Noisy and unpredictable clinic environment
  - Discomfort with unfamiliar providers
  - Difficulty with communication
    - Trouble understanding verbal cues and prompts
    - Trouble expressing thoughts, feelings, or experiences
  - Painful or uncomfortable procedures
    - Discomfort being touched by providers
    - Sensory differences
Barriers: Accurate Assessment

• Challenges to accurate assessment of co-occurring symptoms
  • Atypical symptom presentation
    • Overlapping symptoms
    • Atypical displays of discomfort
  • Lack of validated tools for children with ASD
  • Self-report is not always possible
    • Difficulties recognizing or reporting pain or emotional experiences
  • Parent-report may miss internally experienced symptoms
Barriers: Provider Knowledge

• Healthcare providers:
  • Report feeling unprepared to manage complex needs of children with ASD
  • Report a lack of knowledge and confidence in identifying ASD symptoms and in treating comorbid conditions

• Parents of children with ASD
  • Are dissatisfied with healthcare experiences
  • Lack confidence in provider knowledge of ASD

(Boreman et al., 2007; Carbone et al., 2013; Self, Parham, & Rajagopalan, 2015; Bruder, et al., 2012; Golnik, Ireland, & Borowsky, 2009; Liptak et al., 2006; Shah, 2001; Wilkinson et al., 2012)
Perceived Barriers: Primary Care Providers

- Lack of access to autism
- Lack of self-efficacy
- Inadequate...
- Lack of support from...
- Lack of time

Other Barriers Identified:
- Wait time at autism centers
- Limited knowledge of community resources
- The office “flow” is difficult to adjust/make accommodations
- Lack of assessment tools

(Mazurek et al., 2017; Mazurek et al., 2018)
Opportunities for Improvement

• Healthcare Environment & Family Empowerment
  • Toolkits for children & families
  • Resources to improve patient-provider communication/partnership
  • Autism-friendly clinic spaces
  • Family-centered practices
Opportunities for Improvement

- Evidence-based tools & guidelines
- Psychometrically sound screening/assessment tools
- Provider Training
  - Pre-professional training on ASD
  - Training for practicing clinicians
  - Leveraging technology to increase local capacity
Model Program: Project ECHO

• **Extension for Community Healthcare Outcomes**

• Developed at the University of New Mexico to improve outcomes for adults with hepatitis C

• **Purpose:**
  - Expand *local capacity* for treatment of common and complex conditions
  - Improve *access* for rural and underserved populations
  - Train *community-based* providers in best-practice care

(Arora et al., 2010; Arora et al., 2011)
Project ECHO Framework

• Using Multipoint Videoconferencing
• Expert “Hub” Connecting to PCP “Spokes”
• Case-Based Learning
• Didactics
• Learning Network
ECHO Autism Pilot

• Interdisciplinary Expert Hub:
  • Pediatrician specializing in ASD
  • Clinical Psychologist
  • Child & Adolescent Psychiatrist
  • Parent of Child with ASD
  • Dietician
  • Social Worker

• Spokes:
  • Primary Care Providers
  • Underserved areas

(Mazurek, Brown, Curran & Sohl, 2017)
Learning Loop

ECHO Autism Clinic Format

• Introductions 10 minutes
• Case #1 35 minutes
• Didactic 20 minutes
• Case #2 35 minutes
• Wrap Up 20 minutes

(Mazurek, Brown, Curran & Sohl, 2017)
ECHO Autism Pilot

• 6-month pilot
  • Twelve 2-hour ECHO Autism clinics
  • 2 clinics per month
  • 14 PCP participants (79% practicing in underserved area)

Specific focus on:

• **Screening & identification** of ASD symptoms
• Managing common **medical & psychiatric comorbidities**

(Mazurek, Brown, Curran & Sohl, 2017)
Improvements in Self-Efficacy

(Mazurek, Brown, Curran & Sohl, 2017)
Adherence to Autism Screening Guidelines

Percentage Administering ASD Screenings at all 18- and 24-month Well-Child Visits
Pilot Study Conclusions

• Implementation of ECHO Autism was **feasible**

• PCP participants reported **high satisfaction** with the program

• PCPs demonstrated improvements in:
  • **Self-efficacy** in ASD screening and management
  • Adherence to AAP **autism screening** guidelines
  • Use of ASD-specific **resources**

(Mazurek, Brown, Curran & Sohl, 2017)
ECHO Autism Replication Study

Multi-Site Replication Study

• 10 Collaborating Sites
  • n = 150 PCP participants
    • University of Arkansas for Medical Sciences
    • Children’s Hospital of Philadelphia
    • Cincinnati Children’s Hospital Medical Center
    • Lurie Center for Autism
    • Nationwide Children’s Hospital
    • University of Pittsburgh
    • University of Rochester
    • University of Toronto/Holland Bloorview Kids Rehab Hospital
    • University of California Irvine
    • Vanderbilt University Medical Center
Procedures Overview

Each replication site:

• Recruit 15 primary care providers
  • Patient population >50% underserved

• Conduct 12 ECHO Autism clinics over a 6 month period

• Complete assessments at 4 time points
  • Knowledge Test
  • Chart Review
  • Self-Efficacy
### Study Design

- **Cluster-randomized design**
- **Sequential, staggered roll-out**
- **5 Cohorts**
  - 2 Sites & 30 PCPs per cohort
  - Sites are randomized

<table>
<thead>
<tr>
<th>Cohort 1: Arkansas CHOP</th>
<th>Cohort 2: Rochester Toronto</th>
<th>Cohort 3: Lurie Ctr Vanderbilt</th>
<th>Cohort 4: Pittsburgh UC Irvine</th>
<th>Cohort 5: Cincinnati Nationwide</th>
</tr>
</thead>
<tbody>
<tr>
<td>12/1/16</td>
<td>12/1/17</td>
<td>12/1/17</td>
<td>T1: ECHO Launch</td>
<td>T1: ECHO Launch</td>
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<tr>
<td>T1: ECHO Launch</td>
<td>T2: 3 mo Assessment</td>
<td>T2: 3 mo Assessment</td>
<td>T1: ECHO Launch</td>
<td>T2: 3 mo Assessment</td>
</tr>
<tr>
<td>T3: 6 mo Assessment</td>
<td>T4: Final Assessment</td>
<td>T3: 6 mo Assessment</td>
<td>T4: Final Assessment</td>
<td>T3: 6 mo Assessment</td>
</tr>
<tr>
<td>T4: Final Assessment</td>
<td></td>
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<td>T4: Final Assessment</td>
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- Cohort 1: Arkansas Children's Hospital and Oxidative Phosphate Production
- Cohort 2: Rochester University and Toronto Western Research Institute
- Cohort 3: University of Chicago and Vanderbilt University
- Cohort 4: Pittsburgh University and University of Cincinnati
- Cohort 5: Cincinnati Children's Hospital and Nationwide Children's Hospital
Future Directions

• Application of ECHO and other technology-based models for increasing access to best-practice care
  • Early Diagnosis (e.g., ECHO Autism STAT; Mazurek, Curran, Burnette, & Sohl 2018)
  • Adult Healthcare/Transition
  • Crisis Care
  • Education
  • Mental Health
  • Family Support
Thank you!
Discussion
Meeting of the IACC

Afternoon Agenda
3:25 Healthcare Experiences of Adults on the Autism Spectrum: Challenges and Solutions

Christina Nicolaidis, M.D., M.P.H.
Professor and Senior Scholar in Social Determinants of Health, School of Social Work, Portland State University, and Adjunct Associate Professor, Division of General Internal Medicine, Oregon Health and Science University

Dora Raymaker, Ph.D.
Research Assistant Professor, Portland State University; Co-Director, Academic Autism Spectrum Partnership in Research and Education (AASPIRE)
Healthcare for Autistic Adults: Challenges and Solutions

Christina Nicolaidis, MD, MPH
Professor, Portland State University
Co-Director, Academic Autism Spectrum Partnership in Research and Education

Dora Raymaker, PhD
Research Assistant Professor, Portland State University
Co-Director, Academic Autism Spectrum Partnership in Research and Education
Academic Autism Spectrum Partnership in Research and Education (www.aaspire.org)

Co-Founded in 2006 by Christina Nicolaidis and Dora Raymaker

Autistic adults, academics, family members, disability services and healthcare providers

Community Based Participatory Research

- Autistic adults serve as equal partners throughout all phases of our research projects.

Nicolaidis et al, *PCHP*, 2011
A Brief Note About Language

- Ongoing language debate
  - Preference among self-advocates for identity-first (e.g. autistic adult) vs. person-first (e.g. adult with autism)
  - Similar to Deaf community

Healthcare Disparities

- AASPIRE online survey comparing autistic adults (N=209) to non-autistic adults (N=228)
- Greater unmet healthcare needs
  - Physical health needs (aOR 1.9)
  - Mental health needs (aOR 2.2)
  - Prescription medication needs (aOR 2.8)
- Greater Emergency Department use (aOR 2.1)
- Lower use of Pap Smears (aOR 0.5)
- Lower satisfaction with patient-provider communication and healthcare self-efficacy

Nicolaidis et al, JGIM 2013
Healthcare Disparities

- Large Kaiser Permanente case-control study
- Compared to adults with ADHD, autistic adults had:
  - $\uparrow$ primary care visits (74% VS 67%)
  - $\uparrow$ outpt mental health visits (43% vs 33%)
  - $\uparrow$ hospitalizations for ambulatory care sensitive diagnoses (5.4% vs. 2.3%)
  - $\downarrow$ gynecology visits and cervical cancer screening (35% vs 50%)
- Differences even greater when compared with general population

Zerbo et al, *Autism in Adulthood*, 2018
AASPIRE Survey of 129 PCPs

• Brief online survey of internal Medicine and Family Practice Providers who care for adults
• 73% felt uncomfortable in their ability to provide quality care for adults on the spectrum
• 84% no plans to seek additional training on ASD
• 88% would accept autistic adult in their practice
  • If new autistic pt, <50% would attend CME
  • 82% would search information on the Internet
  • 98% would read customized report about pt needs

Nicolaidis et al, JGIM 2016
Kaiser Survey of 922 Healthcare Providers

Zerbo et al, *JADD*, 2015
Provider Self-Efficacy in Caring for Autistic Adults

- Baseline survey data from current AASPIRE intervention
- 143 PCPs in 3 health systems in Northern California and Oregon

Proportion of providers who felt confident in:

- Communicating with patients: 24%
- Performing exams and procedures: 43%
- Treating co-occurring conditions: 40%
- Helping patients stay calm: 37%
- Identifying accommodations: 14%
- Making accommodations: 16%
Patient Experiences with Healthcare
Barriers to Healthcare

- Data from AASPIRE online healthcare survey
- People without disabilities experienced far fewer barriers to healthcare than autistic or other disability groups.
- Autistic group reported more barriers to healthcare than people with other disabilities, plus different pattern.
- Top barriers:
  - Fear or anxiety (35%)
  - Can’t process information fast enough in real-time (32%)
  - Concern about cost (30%)
  - Facilities cause sensory issues (30%)
  - Difficulty communicating with providers (29)

Raymaker et al, Autism, 2017
Healthcare Experiences

39 Autistic Adults
16 Supporters

Nicolaidis et al, JGIM 2015
Sensory Sensitivities

“The lights in the office are very bright and that is exacerbated by the white walls. Sometimes the waiting rooms are crowded and I cannot filter out the background of people talking or shuffling magazines. I feel disoriented by being led down long hallways to different rooms ... I am not able to bring up my concerns because it is all I can manage to figure out what the doctor is saying so I can respond to his questions. But he refills my usual meds and I go on my way.”
Challenges with Body Awareness

• “Like when they ask if pain is shooting or stabbing or burning, it’s like, I don’t know, it just feels funny.”

• “The problem is it is difficult for me to isolate specific sources of pain and identify duration and intensity. It’s sort of like the equivalent to white noise.”
Providers’ Incorrect Assumptions

“I have used my Alphasmart [portable communication device] when my speech is too slow or difficult to understand for medical appointments. Some of the doctors have been really great, but others have acted really condescending when I used it, also immediately assuming I couldn’t be alone, had to have had parents there too ... So I try to go without, even when my speech is in a poorer shape.”

“Usually when I demonstrate a large vocabulary or some fundamentals, my needs especially around communication are then ignored. My choice is then to pretend to be less intelligent and accept their infantilism, or to be confused, frustrated, and stressed out.”
Communication and Openness to Accommodations

“I prefer and find it easier to communicate in text … But with every doctor I speak to, they wave away the note-card and look at me to ask the same question I have just answered and interpret my confusion as my being non-compliant with the medicine. I wish health care providers would read the notes I make for them.”

“But they talk to him in the same words that they’d use if they were talking to me... If they’re gonna talk to him ... they need to say it how he can understand it.”
Decreased patient autonomy

“Just because I might need more information to understand things, it doesn’t mean they can or should just talk to me like a child or leave me without knowledge of my own health. My body is my body, and my experiences and wishes about my body are MINE TO MAKE!”
Very Heterogeneous Condition

“When you have met one autistic person, you have met one autistic person”

Need for individualized tools!
Potential Solutions I: The AASPIRE Healthcare Toolkit
AASPIRE Healthcare Toolkit – www.autismandhealth.org

AASPIRE Healthcare Toolkit
Primary Care Resources for Adults on the Autism Spectrum and their Primary Care Providers

This website has information and worksheets for adults on the autism spectrum, supporters, and healthcare providers. It focuses on primary healthcare, or healthcare with a regular doctor.

The resources on this site are meant to improve the healthcare of autistic adults. They were made by the Academic-Autistic Spectrum Partnership in Research and Education (AASPIRE) through a series of research studies funded by the National Institute of Mental Health. AASPIRE hopes that you will find these resources helpful.

PATIENTS & SUPPORTERS

- Healthcare
- Staying Healthy
- Your Rights in Healthcare
- Autism Information
- Medical Information
- Checklists and Worksheets

HEALTHCARE PROVIDERS

- How Autism Can Affect Healthcare
- Tips for Successful Office Visits
- Legal and Ethical Considerations
- Autism Information, Diagnosis, and Referrals
- Associated Conditions

Healthcare providers also might want to share our Autism Healthcare Accommodations Tool, and other checklists and worksheets with their patients on the autism spectrum.
Provider Information

Tips for Successful Office Visits

- Communication and Interaction
- Sensory Issues
- Body Awareness, Pain, and Sensory Processing
- Planning and Organizing
- Exams and Procedures

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Download Resources

- PDF File Downloads
- For alternate formats, contact info@aaspire.org
- How Autism Can Affect Healthcare
- Tips for Successful Office Visits
- Legal and Ethical Considerations
- Autism Information, Diagnosis, and Referrals
- Resources and Links
- Patient Forms & Worksheets
- All Topics
Patient Information

Finding Providers

Content Outline
- What is this topic about?
- How do I find names of healthcare providers?
- How do I know if I can go to a healthcare provider or clinic?
- How do I know if a healthcare provider is a good choice?
- What if a provider turns out to be a bad fit for me?
- Should I disclose my ASD diagnosis to my healthcare provider?
- Summary
- Links and Resources

What is this topic about?
This section is about how to find a healthcare provider, like a doctor, nurse practitioner, or physician's assistant.

If you don't already have a healthcare provider, or if you want to change healthcare providers, this section gives some ideas about how to find a new one.

It may not be possible to follow these suggestions in a step-by-step fashion. You may need to go through the steps more than once, or in a different order, before you find a healthcare provider you like. Not all steps or suggestions in this section may apply to you.

Back to Top

How do I find names of healthcare providers?

Option 1: Get referrals from people or organizations you know and trust.

For example, you could ask:

- **Friends, family, or co-workers** - Ask people you trust if they have a doctor they like. Someone you know might be able to give you first-hand information about what a healthcare provider and his or her office and staff are like.

- **Other professionals** - If you go to other healthcare professionals, or if you use a disability service or social service agency, ask them for recommendations.

- **Autism Groups or Communities** - If you are involved with a local autism group or community either online or offline, you can ask there. These communities might be able suggest providers with experience...
Forms and Worksheets

NOTE: These forms and worksheets are in PDF format. If you need a different format, please contact us at info@aaspire.org.

1. **Making an Appointment Worksheet** - This worksheet walks through the steps of making a healthcare appointment. It has lines to write in information that you might want handy while making the appointment. It also has lines to write in information the office staff might tell you, like the day and time of the appointment.

2. **What to Bring to a Healthcare Visit Checklist** - This is a checklist you can use when putting together the things you need to bring to a healthcare visit. It has second page with extra things to bring to a first visit, or if you haven’t seen your healthcare provider in a long time.

3. **Symptoms Worksheet** - This worksheet covers the information healthcare providers usually want to know about symptoms. Not all questions apply to all symptoms. But thinking through some of these questions may help you better describe your symptoms or answer your provider’s questions.

4. **After the Visit Worksheet** - Your provider may ask you to do something after the appointment. This worksheet has a page for each of the main things your provider may ask you to do:
   - Make a follow-up appointment with your healthcare provider
   - See a specialist or make an appointment with a different healthcare provider
   - Get a lab, x-ray, or other test
   - Take a medication
   - Do something to manage your health condition at home

5. **Autism Healthcare Accommodations Tool** - This form will guide you through the steps to create a personalized accommodations letter you can print or save and give to your healthcare provider.
Autism Healthcare Accommodations Tool (AHAT)

- Fill out a survey
- Computer uses answers to create a personalized and healthcare provider-friendly report of accommodations
Sample AHAT Item

What can help you make good decisions about your health or healthcare?

Pick up to three suggestions.

- Ask me to tell you in my own words what the choices are and what the consequences would be for each one.
- Give me extra time to make a decision, even if it means I need to come back or communicate the decision at a later time.
- Give me very blunt and concrete examples of what would happen if I did or did not follow a recommendation.
- Direct me to detailed information or resources about my health conditions.
- Give a person I trust detailed information about my health conditions and choices.
- Let me discuss my choices with a person I trust, and then come back to you.
- I don’t need accommodations to make good decisions about my healthcare.
- I need accommodations to make good decisions about my healthcare, but they are not listed here.
- I do not wish to say.
Patient: Dora Raymaker

IV. Recommendations to Assist with Shared Decision Making

- Allow her extra time for making decisions (might involve communicating decision at a later time).
- Be very blunt and give concrete examples of what would happen if a recommendation was or wasn’t followed.
- Give a trusted person detailed information about health conditions and choices.
- Allow time for her to discuss choices with a trusted person.

V. Recommendations to Help Ms. Raymaker Comply with Recommendations

- Write out your impressions and the plan for next steps or treatments.
- Write out detailed step-by-step instructions.
- Show pictures as much as possible.
- Show her what to do while she is still in the office.
- Have staff help with scheduling follow-up visits, referrals, or tests.

(just part of the full report)
Initial Toolkit Evaluation

- Mixed-methods, single arm, 1-month pre-post intervention study design in real-life setting.
- 170 autistic participants; 41 PCPs
- 95-97% found it easy to understand, important, & useful.
- Significant changes between pre- and post-test in:
  - Number of barriers to healthcare
  - Healthcare self-efficacy
  - Patient Provider communication
- Strong qualitative themes around toolkit utility
  - Means to clarify and communicate needs
  - Validation of experience and empowerment re self-advocacy
  - Improved self-efficacy; better able to prepare for visits
  - Examples of changes in provider behaviors

Integrating the Toolkit into Healthcare Systems

- Current NIH grant to integrate AASPIRE Healthcare Toolkit into 3 diverse health systems
  - Kaiser Permanente Northern California, Oregon Health & Science University, and Legacy Health System
- Worked with 7 intervention clinics to find processes that work for their workflows and settings
- Comparing 6-month patient and provider outcomes with those from control clinics
Next Steps

- Need help with dissemination of Toolkit – Available for free at [www.autismandhealth.org](http://www.autismandhealth.org)
- Working with Dr. Parr and collaborators to adapt toolkit for use in the National Health System in the UK.
- Fulbright Scholar, Dr. Urbanowicz, will be adapting toolkit for use in inpatient settings.
- Looking for collaborators for multi-site randomized controlled trial.
- With appropriate resources, would like to:
  - Expand to mental health care, dental care, emergency care
  - Add multi-media training segments
  - Connect directly to EMRs
Healthcare Provider Training

- Medical / nursing school / residency curricula
  - No current training requirements
  - Crowded curricula
  - Potential for collaborations with accreditation councils?
  - A few model programs – need to be expanded
- CME / CEU trainings for practicing providers
  - Many competing priorities
  - Low number of patients for any one provider
  - Need for creative recruitment strategies and novel formats
  - Possible collaborations with professional societies
- Decision Support Tools / Referral Resources
  - Must include perspective of autistic patients and supporters
Healthcare Workforce / Systems

- Consult services / specialized clinics
  - Challenges with access for large parts of the population
- Developmental Medicine as a new field?
  - Equivalent of Developmental Pediatrics for adults
  - Some interest in med/peds community and family practice
- Annual Health Check model in UK
- Peer navigators
- Other ??
Patient Activation and Self-Advocacy / Self-Management

- mHealth Tools
  - Most currently not very accessible
  - If done correctly, could capitalize on autistic characteristics and strengths
- Patient Advocacy Trainings for Supporters
- Other ??
Take Home Points

- Autistic adults currently experience significant healthcare disparities
- Adult healthcare system is currently not equipped to manage autistic adults’ needs
  - Gaps in provider knowledge and skills
  - Many barriers to care
  - Successful interactions depend on addressing patient, provider, and health system factors
- AASPIRE Healthcare Toolkit is a first step to improving care
- Many more solutions are needed at patient, provider, and system levels!
A New Home for Research on Autism in Adulthood

- Focuses on the most pressing issues affecting autistic adults, from emerging adulthood to late life.
- Includes autistic adults as editorial board members, reviewers, and authors

www.liebertpub.com/aut
Funding

AASPIRE

- National Institute Of Mental Health
  - R34MH092503, R34MH092503, R21MH112038
- NIH BUILD EXITO Pilot Projects
- The Oregon Clinical and Translational Research Institute (OCTRI), grant number UL1 RR024140 from the National Center for Research Resources (NCRR), a component of the National Institutes of Health (NIH), and NIH Roadmap for Medical Research
- Portland State University
- The Burton Blatt Institute and Michael Morris

AASPIRE Collaborations (violence, pregnancy)

- Centers for Disease Control
- National Institute of Child Health and Development R21HD078830
Discussion and Questions

Thank you to all our AASPIRE partners

Feel free to contact us:
- nicol22@pdx.edu
- draymake@pdx.edu

Our Websites:
- www.aaspire.org
- www.autismandhealth.org
- www.libertpub.com/aut
Discussion
Working Group Discussion
Adjournment
Thank You OARC Staff

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  Public Health Analyst
• Angelice Mitrakas, B.A.
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• Jeffrey Wiegand, B.S.
  Web Development Manager
Next IACC Meeting

Wednesday, October 17th 2018