

# Overview of Connections between the Gut, Autism, and Mental health

Calliope Holingue, MPH, PhD  
Assistant Professor

Center for Autism Services, Science, and Innovation (CASSI™),  
Kennedy Krieger Institute  
Dept Mental Health,  
Johns Hopkins Bloomberg School of Public Health

Autism Research Institute  
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Center for Autism and Related Disorders  
at Kennedy Krieger Institute

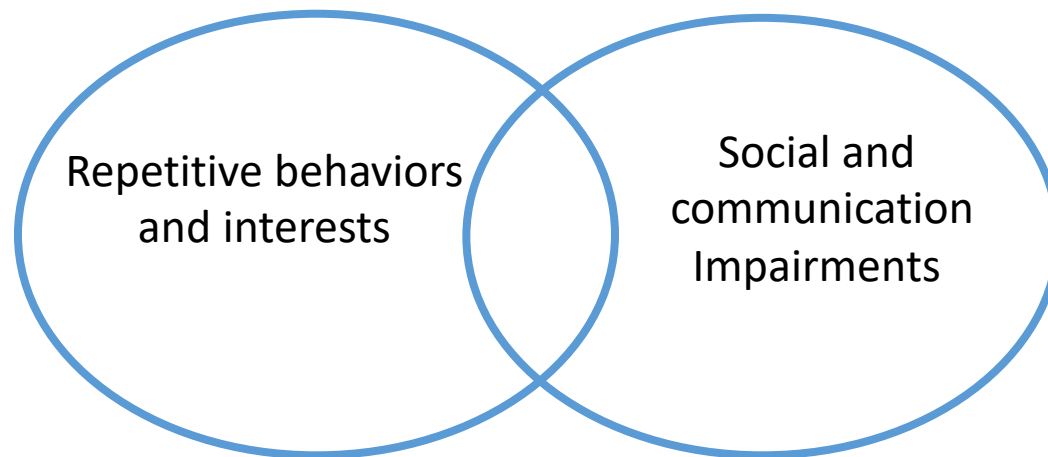
# Outline

1. What is Autism Spectrum Disorder?
2. Why care about ASD and GI symptoms?
3. Pathways linking GI symptoms/gut dysregulation and ASD
4. Overview of ASD gut-microbiome research
5. Identifying GI symptoms in autistic individuals

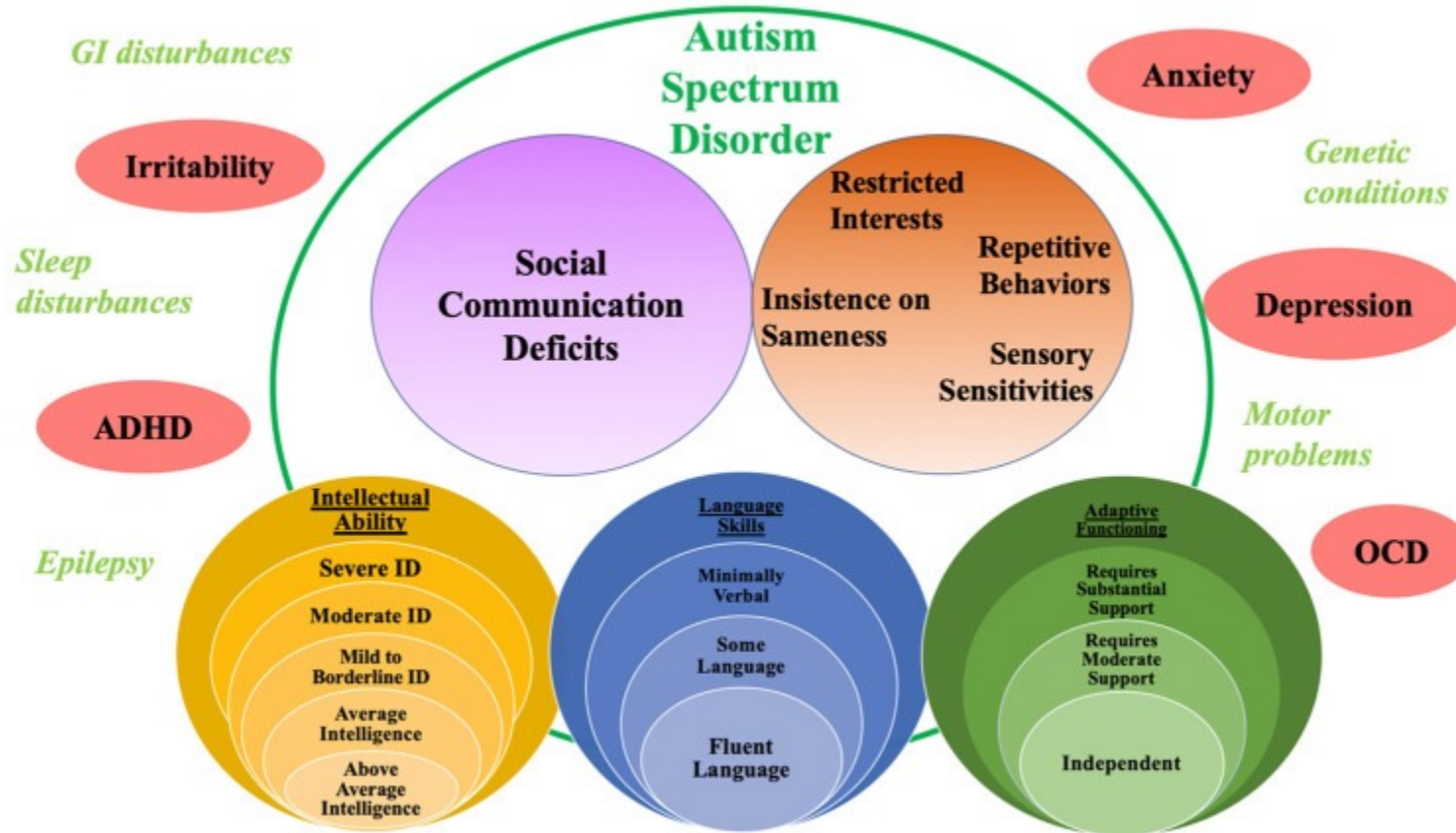


# What is Autism Spectrum Disorder?

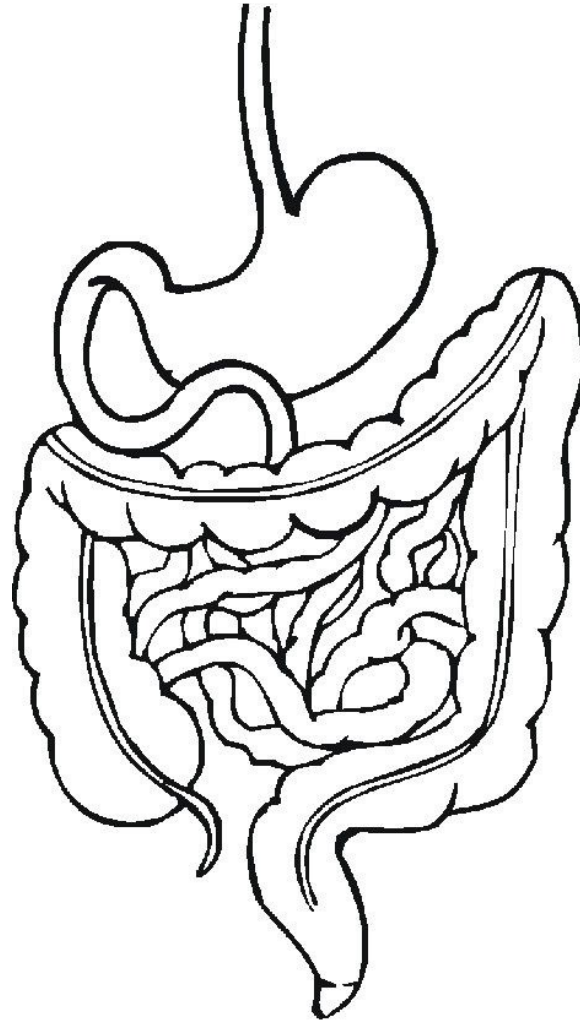
- Clinical Characteristics of Autism Spectrum Disorder (ASD), DSM-V 2015
  - Impairments in social communication and social interaction
  - Restricted and repetitive behaviors and interests
  - Present in early developmental period
  - Cause significant impairment in social, occupational, or other areas of functioning
  - Not better explained by intellectual disability or global developmental delay



# Heterogeneity and Co-occurring Conditions

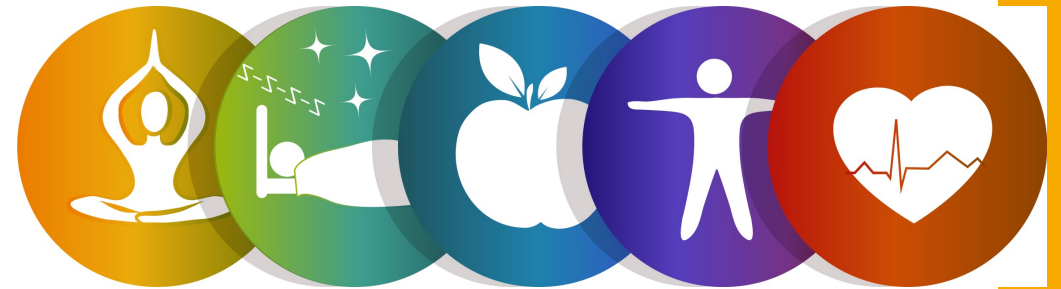
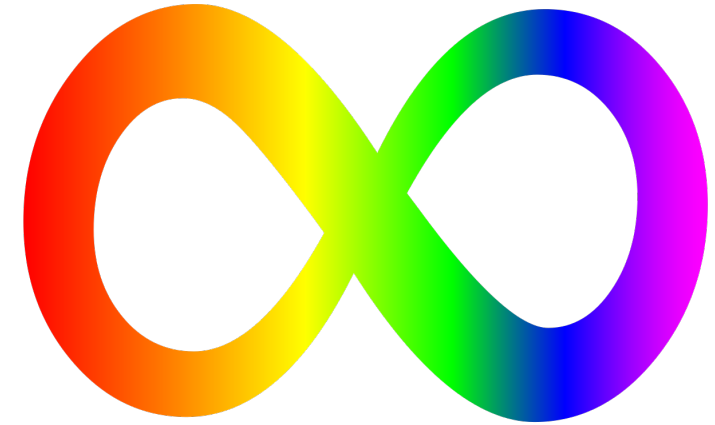


# Why care about ASD and GI symptoms?



# Health of Individuals with ASD

- Individuals with ASD often have complex health needs
- Greater use of health care services, higher costs, more ED visits and inpatient hospitalizations
- Yet, more unmet health needs, lower quality of care
- Health affects *everything*
- Equity Issue



# GI symptoms are common

- Constipation (22%)
- Diarrhea (23%)
- Abdominal pain and discomfort (14%)
- **Any symptom (47%)**
  
- Food sensitivities/preferences, mealtime difficulties, toileting problems often co-occur
  
- No evidence that ASD-specific gut pathology



# GI symptoms are associated with co-occurring conditions

- Strong links between GI symptoms and ASD comorbidities
- GI dysfunction associated with seizures and sleep disorders
- Functional constipation linked with worse behavioral symptoms, stress, anxiety, increased cortisol





# Qualitative Study of Families with Autistic Children w/ GI

- What are the experiences that children with ASD & GI symptoms (& families) face?
- Advertised qualitative study to local ASD groups
- Recruited parents of child with ASD with history of GI Symptoms
- 12 interviews (in-person, video, phone)
- Inductive analysis, derived themes



# Theme 1 (Preview)

- Children with ASD often had difficulty verbally communicating the presence of GI symptoms...
- We will come back to this!



## Theme 2

- GI issues impacted the child's wellbeing and ability to participate in and fully engage in activities.
  - child's ability to attend school, focusing during class, accommodations
  - child's ability to engage in social or extracurricular activities
  - child's emotional and overall wellbeing

*“When he is not right in his gut...the whole world isn't right...a lot of his behavior and his issues really crop up when he is constipated...he will get in trouble more. He will lose privileges. He will get low point chart numbers from school...it impacts his daily life.”* (Parent of autistic child)



## Theme 3

- The child's GI issues impacted the family's wellbeing
  - overall temperament and wellbeing of the household
  - parental distress and frustration
  - family's ability to go out
  - family's financial health and stress

*"It's painful as a parent to have to try and do something that's uncomfortable or out of the norm to your child, just because you know, they don't really care for it."*  
(Parent of autistic child)



## Theme 4

- Parents often experienced challenges with seeking accessible and quality healthcare for their child's GI problems.
  - Lengthy, complicated processes to make healthcare appointment
  - Medical office settings not conducive to the child's ASD
  - Parents reported that healthcare providers lacked experience/training in treating children with ASD with complex medical needs.
  - Not taken seriously by healthcare providers due to ASD
  - Consequences of these challenges



## Theme 4 Example

*“I think that some of the issues that happen are more complex and they are expecting a child to come in with a fever and you know figure out the cause of that fever and whether or not they require medication. And that’s the end of it. We have a lot of ongoing issues and things that may affect other things and it’s just more complex.”*  
(Parent of autistic child)



....How about in autistic adults?



# “GI Wanna Talk About Autism”

Mixed-methods (qual + quant) research project partnering with community

## Study Goals

- 1) Gain an understanding of the experiences, needs, and priorities of autistic adults as they pertain to GI health and related issues.
- 2) Develop recommendations for potential services, interventions, tools, or policies to improve the GI health of autistic adults.







# Study Team

## Key findings (1)

- In many instances, GI symptoms have profound and extensive negative impacts on many or all areas of life (“...I don't know if I'll be able to hold down a full-time job or not...Will I ever be able to date or do anything?”).
- Common triggers of GI issues include stress, sensory overwhelm, and changes in routine and food, though triggers were not always apparent.



## Key findings (2)

- Most autistic adults and their parents described primarily frustrating and unhelpful healthcare interactions. They found the system difficult, unpleasant, and expensive to navigate and felt healthcare providers were often dismissive and did not offer useful diagnoses or advice (“They weren’t concerned at all.”).
- Autistic adults relied on medications, extensive planning and preparation, avoidance of triggers, and positive supports such as family or friends to help prevent and manage their symptoms.



## Potential Areas of Recommendation

1. Healthcare provider trainings
2. Healthcare advocacy training for autistic adults
3. Interoception intervention for autistic adults
4. Anxiety interventions for autistic adults
5. Electronic GI toolkit
6. GI symptom questionnaires
7. Behavioral interventions for diet
8. Healthcare professional database
9. Care coordination model



Scan this QR code to view our March 2023 AIR-P webinar, which goes into more information about this study



# Pathways linking GI symptoms/gut dysregulation and ASD

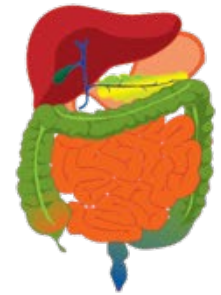


# Having ASD may increase GI symptoms

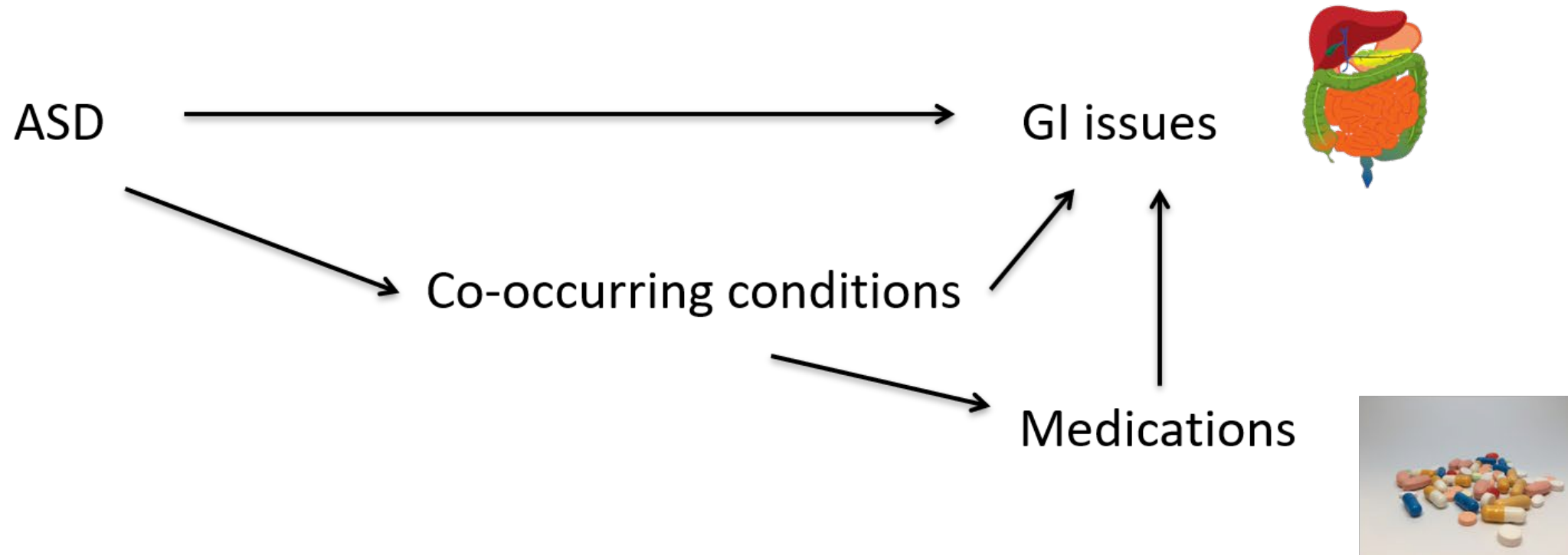
ASD



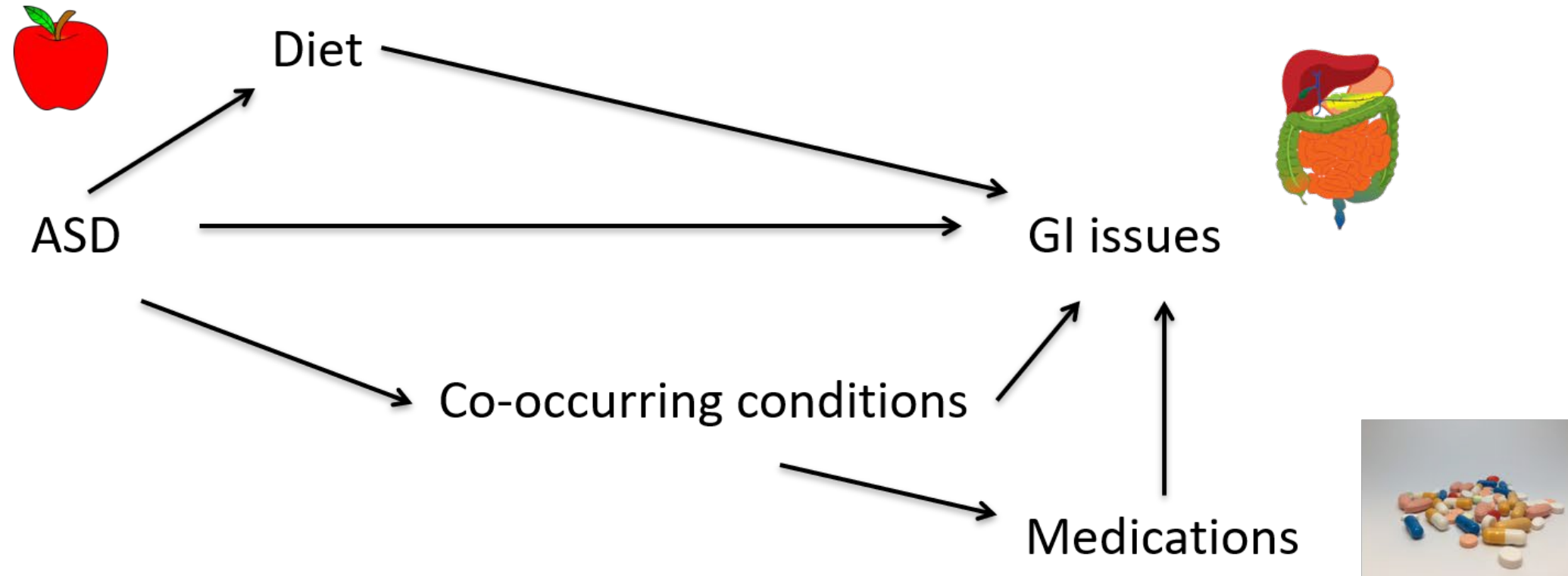
GI issues



# Co-occurring conditions and meds may increase GI symptoms

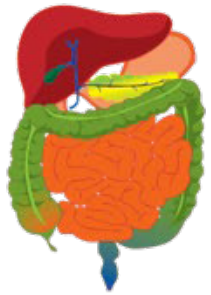


# Dietary restrictions or preferences may increase GI symptoms





# Having GI symptoms may influence ASD/related behaviors



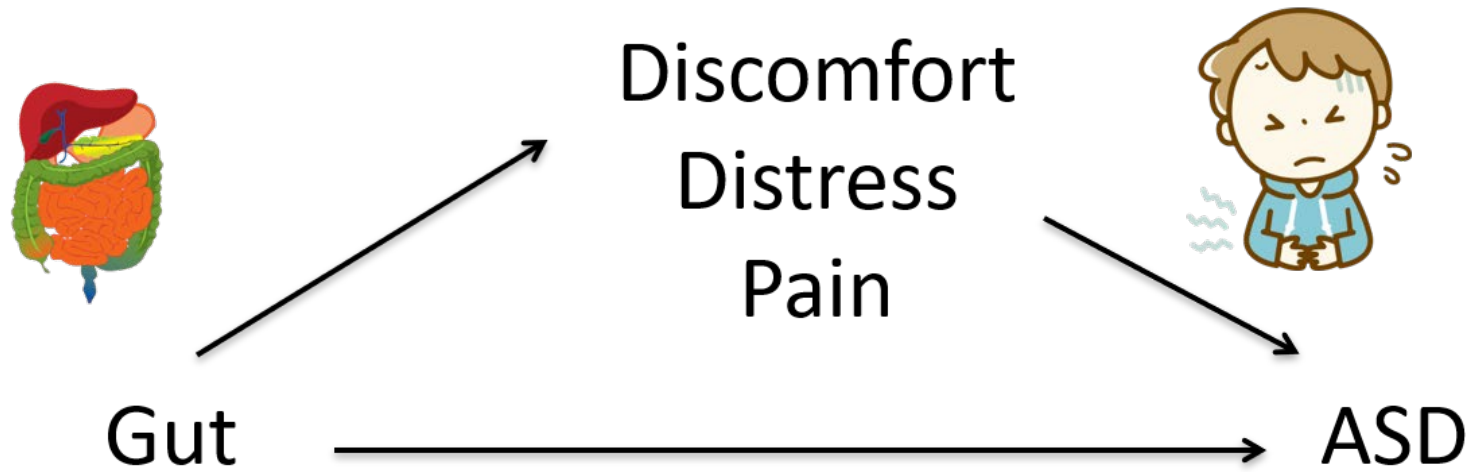
Gut



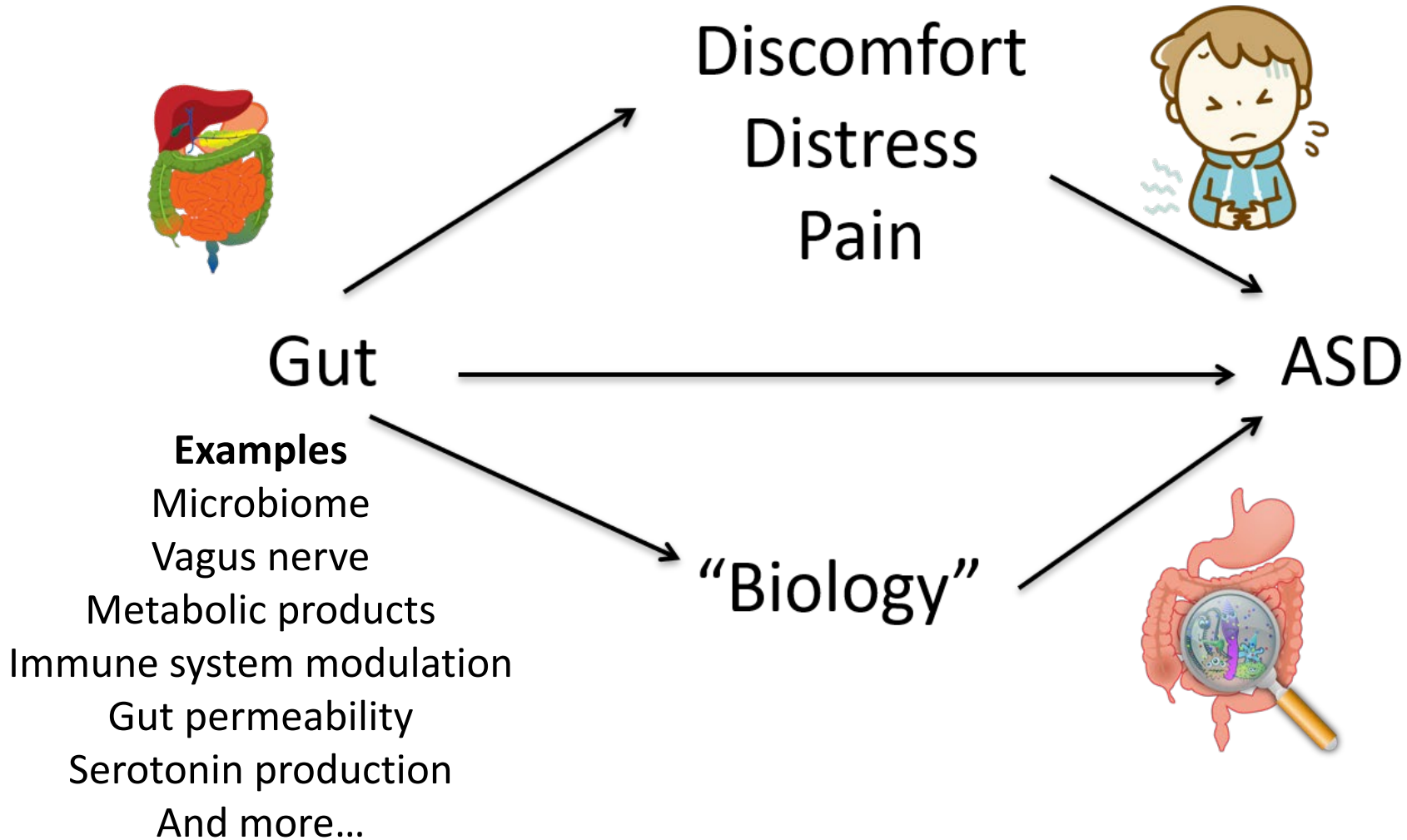
ASD



# GI discomfort and pain may influence ASD and related conditions



# Gut 'biology' may influence risk of ASD and related conditions?



# Historical overview of ASD gut-microbiome research



## Early 2000s: Initial Observations

- Research spurred by anecdotal and case study reports of changes in autism related behaviors that coincided with illness, antibiotic exposure
- Researchers began to observe differences in the gut microbiota of individuals with ASD compared to neurotypical controls, sparking interest in gut-brain axis.
- Studies were preliminary and often had small sample sizes but laid groundwork for future research.
- Example: Finegold, S. M. et al. (2002). "Gastrointestinal microflora studies in late-onset autism." *Clinical Infectious Diseases*.



## Mid to Late 2000s: Establishing the Gut-Brain Axis

- Studies began to more firmly establish the concept of the gut-brain axis
- Suggest that gut microbiota could influence brain function and behavior, potentially affecting ASD symptoms.
- Example: Mayer, E. A., Padua, D., & Tillisch, K. (2014). "Altered brain-gut axis in autism: Comorbidity or causative mechanisms?" *BioEssays*.



## 2010s: Microbiome Diversity and Specific Strains

- Research expanded to explore diversity of microbiome in autistic individuals, finding (on average) reduced microbial diversity and alterations in specific bacterial strains.
- Studies identified certain gut microbial profiles associated with ASD and began to investigate how these profiles could influence neurodevelopment and behavior.
- Example: Kang, D.-W. et al. (2013). "Reduced incidence of Prevotella and other fermenters in intestinal microflora of autistic children." PLoS ONE.



## 2015 Onwards: Intervention Studies

- Intervention studies started to emerge, exploring the effects of probiotics, prebiotics, and fecal microbiota transplantation (FMT) on ASD symptoms.
- These studies have shown promising but varied results
- Highlights complexity of the gut-brain relationship and the need for personalized approaches.
  
- Example: Kang, D.-W. et al. (2017). "Microbiota Transfer Therapy alters gut ecosystem and improves gastrointestinal and autism symptoms: an open-label study." *Microbiome*.





## Recent Trends and Ongoing Research

- Focus has shifted towards understanding the *mechanisms* by which the gut microbiome influences the brain and behavior (e.g., immune system modulation, neurotransmitter and hormone production, direct neural pathways)
- Increasing interest in how environmental factors, diet, and early life antibiotic use may influence the gut microbiome and development of ASD.
- Ongoing research is exploring potential for gut microbiome modulation as a therapeutic strategy for ASD, with a focus on long-term outcomes and safety.
- Example: Hsiao, E. Y. et al. (2013). "Microbiota modulate behavioral and physiological abnormalities associated with neurodevelopmental disorders." *Cell*.



# Gut Microbiome Alterations in ASD

- Multiple distinct microbiota populations have been associated with ASD, mostly pediatric population
- Findings highly divergent across studies



# Reasons for discrepancies

- Small cohorts
- Different comparison groups (unrelated controls, unaffected siblings)
- Failure to control for potential confounders (diet, antibiotics, mediations, etc.)
- ASD heterogeneity
- Variations in laboratory, analytic techniques, geographic location
- Microbiome of stool versus intestinal mucosa



# Role of Gut in Development of ASD

- Maternal gut microbiome interacts with immune system during pregnancy
- Animal models show that this interaction influences brain development and behavior
- These studies are much harder to do in humans; research ongoing
- Early-life exposures (delivery mode, diet/breastfeeding, medications) shape development of microbiome
  - Work underway to understand how this affects child health, neurodevelopment and behavior



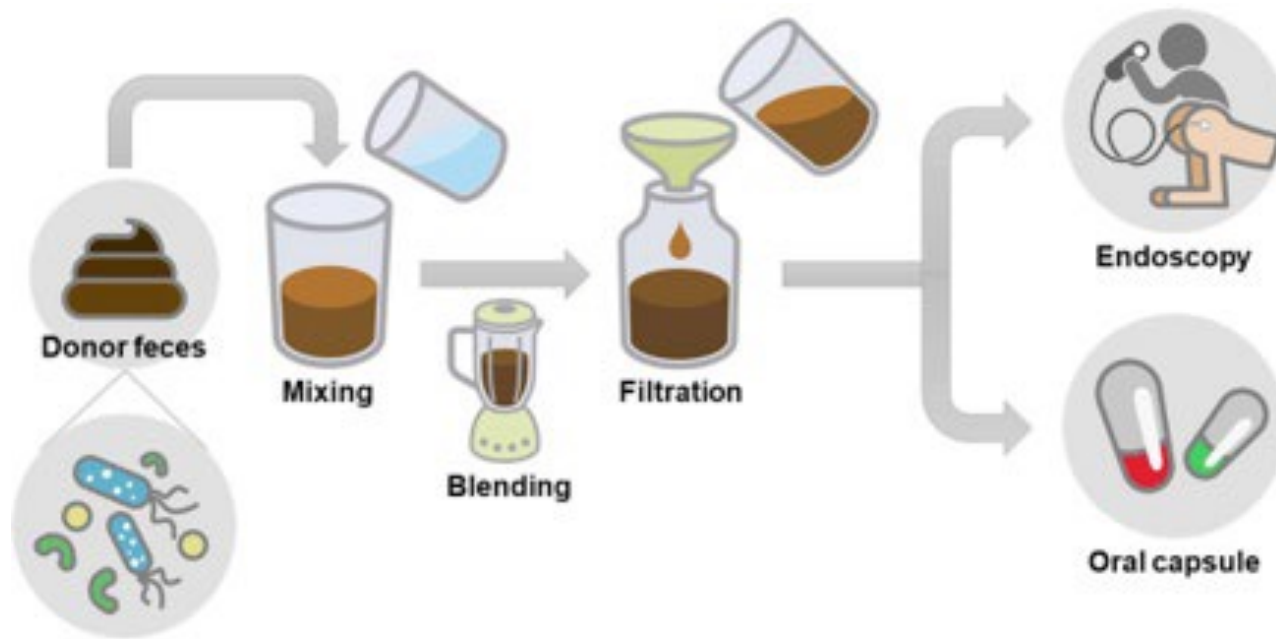
# Types of Microbial Interventions

- Diet is one of the biggest influences of the gut microbiome
- Diet/microbial interventions hold promise; effects vary across people
- Common microbial therapies
  - Antibiotics
  - Probiotics – live, beneficial bacteria (e.g., yogurt, miso, fermented vegetables)
  - Prebiotics – food for the probiotics (e.g., garlic, bananas, oats)
  - Fecal transplants / fecal microbiota transplants



# Fecal Transplants


1. Health donor feces
2. Processing
3. Delivery: endoscopy (via mouth or rectum), pills






# ASD and Microbiota Transfer Therapy

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



Dae-Wook Kang<sup>1†</sup>, James B. Adams<sup>2†</sup>, Ann C. Gregory<sup>3,15†</sup>, Thomas Borody<sup>4</sup>, Lauren Chittick<sup>5,15</sup>, Alessio Fasano<sup>6</sup>, Alexander Khoruts<sup>7,8,9</sup>, Elizabeth Geis<sup>2</sup>, Juan Maldonado<sup>1</sup>, Sharon McDonough-Means<sup>10</sup>, Elena L. Pollard<sup>2</sup>, Simon Roux<sup>5,15</sup>, Michael J. Sadowsky<sup>8,11</sup>, Karen Schwarzberg Lipson<sup>12</sup>, Matthew B. Sullivan<sup>3,5,15,16\*</sup>, J. Gregory Caporaso<sup>12,13\*</sup> and Rosa Krajmalnik-Brown<sup>1,14\*</sup> 

## Long-term benefit of Microbiota Transfer Therapy on autism symptoms and gut microbiota

Dae-Wook Kang <sup>1,2,8</sup>, James B. Adams<sup>3</sup>, Devon M. Coleman<sup>3</sup>, Elena L. Pollard<sup>3</sup>, Juan Maldonado<sup>1,2</sup>, Sharon McDonough-Means<sup>4</sup>, J. Gregory Caporaso <sup>5,6</sup> & Rosa Krajmalnik-Brown <sup>1,2,7</sup>



# See prior Autism Research Institute webinars for more info!

Dr. Rosa Krajmalnik-Brown, Ph.D., discusses her recent studies on gut microbiota in individuals with autism who have gastrointestinal (GI) problems. She outlines what we know about human microbiomes, how they interact with our bodies, and the potential they hold for treating autism symptoms. The presenter reviews a 2017 open-label trial of Microbiota Transfer Therapy (MTT) and a 2019 follow-up study. Both studies showed GI and behavioral symptom improvements and positive changes in the gut microbiome environment. Krajmalnik-Brown asserts the need for double-blind, placebo-controlled clinical trials and urges listeners not to attempt such treatments at home. She outlines other relevant studies before closing with a question-and-answer session.

Take the knowledge quiz for this presentation [HERE](#)  
Learn more about our speaker, Dr. Rosa Rosa Krajmalnik-Brown [HERE](#)

<https://autism.org/category/webinar/gastrointestinal-webinar/>





## Purpose of study

- Goal was to assess whether modified fecal microbiota transplant (FMT)
  - Is safe and tolerable in ASD population ?
  - Improves GI and ASD symptoms ?



# Methods

- Open-label clinical trial
- Treatment Group: 18 children with ASD, moderate-to-severe GI problems (7-16 yrs)
- Control Group: 20 Typically Developing children, no GI disorders, same age & sex
- Intervention: 14-day course Vancomycin + Moviprep + Microbiota (oral/rectal) + Prilosec
- Parents collect stool samples, GI symptoms, ASD symptoms, global impressions



## Results: Microbiome Changes

- ASD gut bacteria less diverse at baseline but increased by the end of treatment, similar to control group
- Donor bacterial community partially engrafted in recipient gut
- Specific genera that changed significantly with treatment included *Bifidobacterium*, *Prevotella*, and *Desulfovibrio*



## Results: ASD and GI Symptoms

- Abdominal pain, indigestion, constipation, diarrhea improved; average Gastrointestinal Symptom Rating Scale, days with abnormal and no stools decreased
- Improvement in social responsiveness, autism severity, parent global impression
- Significant negative correlation between change in GI and ASD scores
- Average 1.4 year increase in developmental age (VABS-II)
- Treatment generally well tolerated, temporary adverse effects like hyperactivity, tantrums, aggression



## Limitations and Interpretation

- Not placebo controlled, blinded, or randomized
- Disentangling effects of parts of treatment (Vancomycin vs MoviPrep vs FMT vs Prilosec)
- Assessment of GI symptoms is challenging
- Subgroups of ASD & Generalizability
- **Are improvements in ASD symptoms due to microbiota influencing brain?**
- **Or due to FMT reducing GI symptoms which makes child feel better?**



# Identifying GI Symptoms in Autistic Individuals



# Symptoms and Signs

- *Symptoms*: phenomena that can only be described by the person feeling them (abdominal pain, nausea, or a burning sensation in the throat).
  - Communicated to others (e.g., “my belly hurts”) or indicated by signs
- *Signs* can be observed by someone else, either with their own eyes (e.g., diarrhea, vomiting, sweaty forehead, clutching stomach)



# Obstacles to having GI symptoms recognized

- Children, in general, may have trouble communicating pain and other subjective experiences
- Impairments in interoception (perception of internal sensations)
- Language impairments (naming and communicating those sensations)
- Intellectual disability
- Social world context: diagnostic overshadowing, lack of accommodations and trained providers
- We need NDD-specific tools for assessing GI symptoms






# Measurement Challenge in Autism Literature

## REVIEW ARTICLE

### Gastrointestinal Symptoms in Autism Spectrum Disorder: A Review of the Literature on Ascertainment and Prevalence

Calliope Holingue , Carol Newill, Li-Ching Lee, Pankaj J. Pasricha, and M. Daniele Fallin

There is no standard approach to measuring GI symptoms in individuals with ASD, despite postulated interactions. The objectives of this study were to (a) describe the range of GI symptom ascertainment approaches in studies of ASD, (b) describe the range of prevalence estimates across studies, and (c) assess associations between ascertainment approach and prevalence estimates. Studies published from 1/1/1980 to 1/31/2017 were collected via PubMed. Eligibility included studies with at least ten individuals with ASD that measured GI symptoms or conditions. We excluded review and hypothesis papers. We extracted information on study design, GI symptom ascertainment method, demographics, and ASD diagnostic criteria. From a subset of studies, we extracted GI symptom estimates. Out of a possible 386 titles, 144 were included. The prevalence range for constipation was 4.3–45.5% (median 22%), for diarrhea was 2.3–75.6% (median 13.0%), and for any or more than one symptom was 4.2–96.8% (median 46.8%). GI symptoms differed significantly by age of individuals, primary goal of study, study design, study sample, and who reported symptoms ( $P < .05$ ). Due to small sample size, we were not able to test for associations between every GI symptom and study characteristic of interest, or examine associations between GI symptoms and intellectual or verbal disability. Studies used a broad range of methods to ascertain GI symptoms in ASD. GI symptoms varied widely across these studies, with significant differences by study characteristics. Our findings highlight the need for a reliable, valid GI assessment tool to be used consistently across studies of ASD. *Autism Res* 2018, 11: 24–36. © 2017 International Society for Autism Research, Wiley Periodicals, Inc.

**Lay Summary:** We reviewed studies having to do with autism spectrum disorder and the gastrointestinal system, dating back to 1980. We found that the median prevalence of constipation was 22.2%, diarrhea 13.0%, and any symptom 46.8%. All symptoms had a wide range of estimates across studies. GI symptoms were associated with characteristics of the study, including who measured the GI symptoms. We call for the development of a reliable and valid GI questionnaire for studies of ASD.

**Keywords:** co-morbid conditions; exposure assessment/exposomics; psychometrics

Holingue et al 2018 *Autism Research*  
<https://doi.org/10.1002/aur.1854>

- Many assessment approaches, mostly parent-report pediatric questionnaires
- Wide range of symptom estimates (e.g., diarrhea ranged from 2.3% to 75.6% [median 13%])
- Symptom estimates depend on type of assessment approach
- Lack of psychometric data on available measures
- Existing measures have important limitations (e.g., lack of mealtime/diet related items, non-verbal signs)



# Qualitative Study

- What are the experiences that children with ASD & GI symptoms (& families) face?
- Advertised qualitative study to local ASD groups
- Recruited parents of child with ASD with history of GI Symptoms
- 12 interviews (in-person, video, phone)
- Inductive analysis, derived themes



## A major theme from qualitative research

- Children with NDDs (even those with fluent speech) often had difficulty verbally communicating the presence of GI symptoms
- To identify when child was having GI distress, parents relied on detecting:
  - Bodily signs (e.g., abdominal swelling, diarrhea, lack of bowel movement)
  - Non-verbal behaviors or changes in other health domains (e.g., sleep issues, irritability, aggression)



# Challenges Detecting GI Symptoms – Even in Verbal Children

*“He is verbal to the extent where he can talk to you about things but when something about his body or his feelings or anything that makes him uncomfortable, he doesn't have any words for it.”*



## Challenges Detecting GI Symptoms – Bodily Signs

*“Well, he had them [GI symptoms] starting as a baby. And so I mean something as simple as putting my hand on his stomach, I could feel everything moving and growling...he had severe gas...you could see it in his movements...sometimes I would have to bring him to the doctor, and they would basically have to assist because it would become so dried out [stool] that it would no longer move through his system.”*



## Challenges Detecting GI Symptoms – Non-Verbal Behavior

*“He gets angry. Short, kind of semi belligerent with really basic questions, very atypical for him on a daily basis and then find out that he had just had to go to the bathroom. That's how he kind of presents. But then if you ask him, “Do you need to go to the bathroom”... ‘No, I'm fine.’”*

*“When the stomach hurts, there's an almost immediate physical reaction. She could scream, she could throw things. And after she calms down then she tells us 'My tummy hurts'. Every time the police had to come out because she was really being destructive, first thing she would say as she regained her composure was 'my tummy hurts’”*



# Why we need ASD-specific GI instruments

- Measurement of GI symptoms challenging; tools used in neurotypical pediatric population may not be appropriate for ASD population
- Limitation of existing ASD-specific GI tools:
  - No psychometric studies (as of 2018)
  - Little inclusion of mealtime, dietary, or behavioral items
- Hinders research and clinical care



# Efforts ongoing to develop & validate parent-report GI screeners

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Journal of Autism and Developmental Disorders (2019) 49:349–362  
<https://doi.org/10.1007/s10803-018-3767-7>

## ORIGINAL PAPER



### Development of a Brief Parent-Report Screen for Common Gastrointestinal Disorders in Autism Spectrum Disorder

Kara G. Margolis<sup>1</sup>  · Timothy M. Buie<sup>2</sup> · J. Blake Turner<sup>3</sup> · Anna E. Silberman<sup>3</sup> · Judith F. Feldman<sup>3</sup> · Katherine F. Murray<sup>2</sup> · Maureen McSwiggan-Hardin<sup>3</sup> · Joseph Levy<sup>1</sup> · Margaret L. Bauman<sup>4</sup> · Jeremy Veenstra-VanderWeele<sup>3</sup> · Agnes H. Whitaker<sup>3</sup> · Harland S. Winter<sup>2</sup>

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#### Abstract

Gastrointestinal dysfunction in children with autism spectrum disorder (ASD) is common and associated with problem behaviors. This study describes the development of a brief, parent-report screen that relies minimally upon the child's ability to report or localize pain for identifying children with ASD at risk for one of three common gastrointestinal disorders (functional constipation, functional diarrhea, and gastroesophageal reflux disease). In a clinical sample of children with ASD, this 17-item screen identified children having one or more of these disorders with a sensitivity of 84%, specificity of 43%, and a positive predictive value of 67%. If found to be valid in an independent sample of children with ASD, the screen will be useful in both clinical practice and research.

**Keywords** Autism · Screen · Gastrointestinal · GI · Comorbidities · Behavior





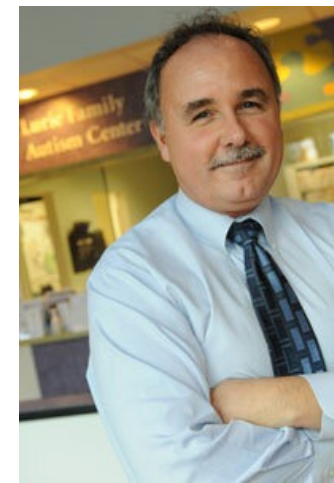
# Gastrointestinal and Related Behavior Inventory (GIRBI)



Literature review



Talking to families



Dr. Tim Buie  
*ATN GI Inventory*



Dr. Colleen Lukens  
*Brief Autism  
Mealtime Behavior  
Inventory (BAMBI)*

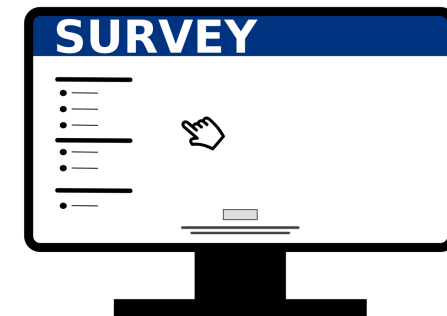
# Autism Gastrointestinal and Related Behaviors Inventory (ASD-GIRBI)

- Specific GI symptoms (e.g. nausea, constipation)
- Frequency of bowel movements, stool consistency, toileting behaviors
- Mealtime/dietary behaviors (e.g. picky, self injury at mealtimes)
- Motor & other behaviors (e.g. arching back, gritting teeth, coughing)
  
- Parent-report diagnoses of GI disorders



# Piloting GI Questionnaire

- Online Kennedy Krieger Institute CAARE Research Registry
- Parents completed ASD-GIRBI and Child Behavior Checklist
- N=334 children, ages 6-17 years



## Results

- 36 items
- Cronbach's  $\alpha=0.88$
- Strong convergent validity
- Developed with stakeholders; high content validity
- High sensitivity in predicting parent-report GI diagnoses

### **7-factor solution**

1. Abdominal Pain & Upset Stomach
2. Pain during Bowel Movements
3. Constipation & Encopresis
4. Aggressive/Disruptive during Mealtimes
5. Refusing Food
6. Particular with Food
7. Motor or Other Behaviors



# Future Work on GI Measurement

- Creating multiple versions of GIRBI to reach people across spectrum and across life course
  - 3 years+
  - Self-report and caregiver-report versions
- Clinical validation
- Expanding to other neurodevelopmental conditions (e.g., Angelman, Dup15q, Phelan-McDermid)
- Incorporation of biospecimens (fecal samples, cytokines, heart rate)
- Need for both questionnaires and biological measures



# Thank you to Collaborators

## Kennedy Krieger Institute

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Xiumei Hong

Jamie Dahm Kaczaniuk

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Michelle Landrum

Li-Ching Lee

Noel Mueller

Rashelle Musci

Sarah Murray

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Heather Volk

## Other Institutions

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Kara Margolis (Columbia/ NYU)

Zachary Williams (Vanderbilt)



# Thank you to Funders



Kennedy Krieger Institute  
UNLOCKING POTENTIAL



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& Developmental Disabilities



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5T32MH014592



National Institutes  
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U01AI090727, R21AI079872,  
R01HD086013, 2R01HD041702,  
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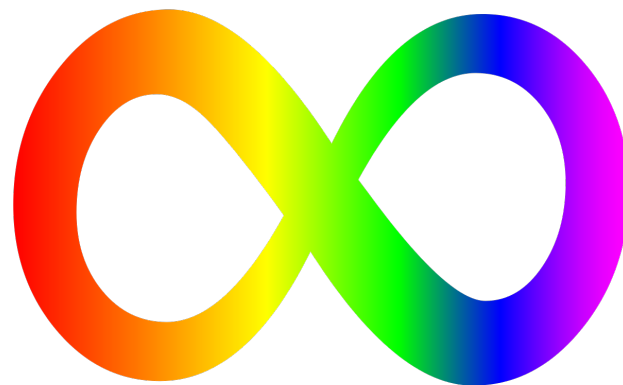


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Questions?

Calliope Holingue  
[holingue@kennedykrieger.org](mailto:holingue@kennedykrieger.org)  
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