

The Gut-Brain Connection in Autism: from Research to Practice

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Center for Autism and Related Disorders
at Kennedy Krieger Institute

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ASHA Disclosure Slide

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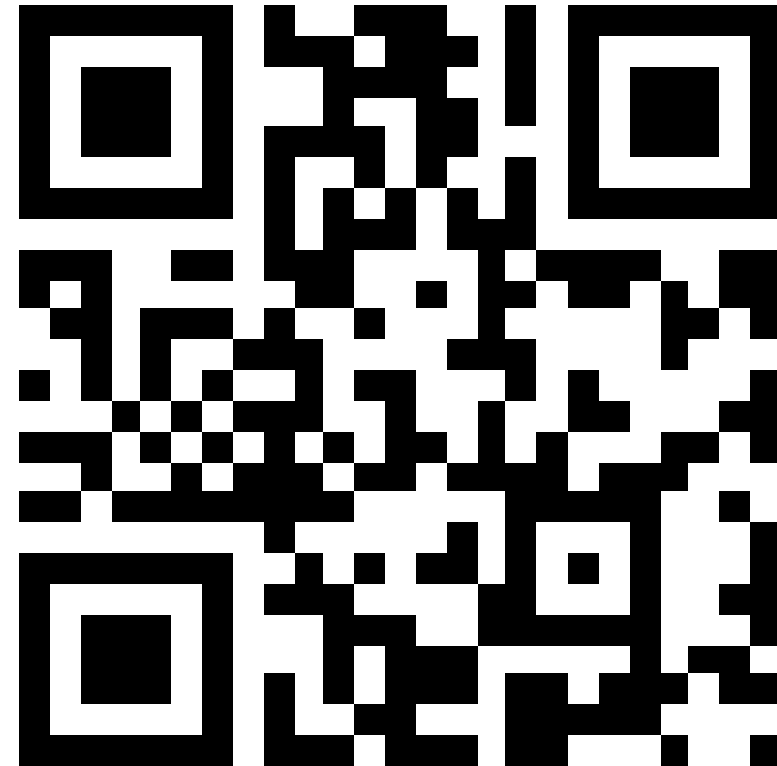


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Which group(s) do you belong to? Select all that apply:

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Objectives

1. Describe the potential pathways linking GI symptoms/gut dysregulation with ASD.
2. Learn about the latest gut-microbiome research in autism.
3. Identify approaches to identifying and managing GI symptoms in individuals with ASD.

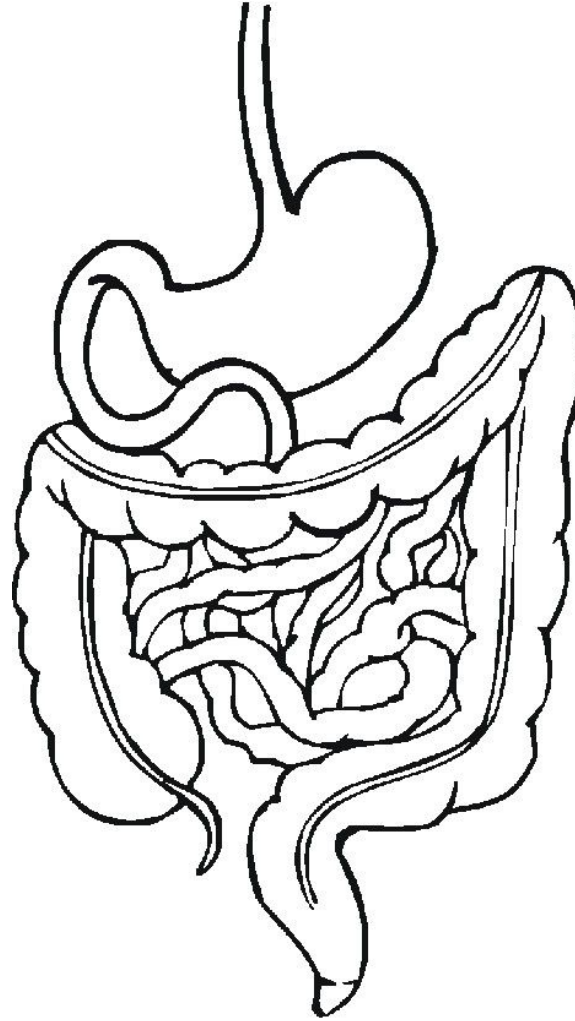


Outline

1. Why care about ASD and GI symptoms?
2. Pathways linking GI symptoms/gut dysregulation and ASD
3. Latest ASD gut-microbiome research
4. Identifying and managing GI symptoms in ASD



Why care about ASD and GI symptoms?



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
- Functional constipation linked with worse behavioral symptoms, stress, anxiety, increased cortisol
- Seizures, sleep disorders also associated with GI dysfunction



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



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.”



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."



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.”





What is one way in which having GI symptoms can affect a child with ASD?

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Pathways linking GI symptoms/gut dysregulation and ASD

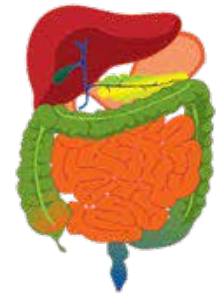


Having ASD may increase GI symptoms

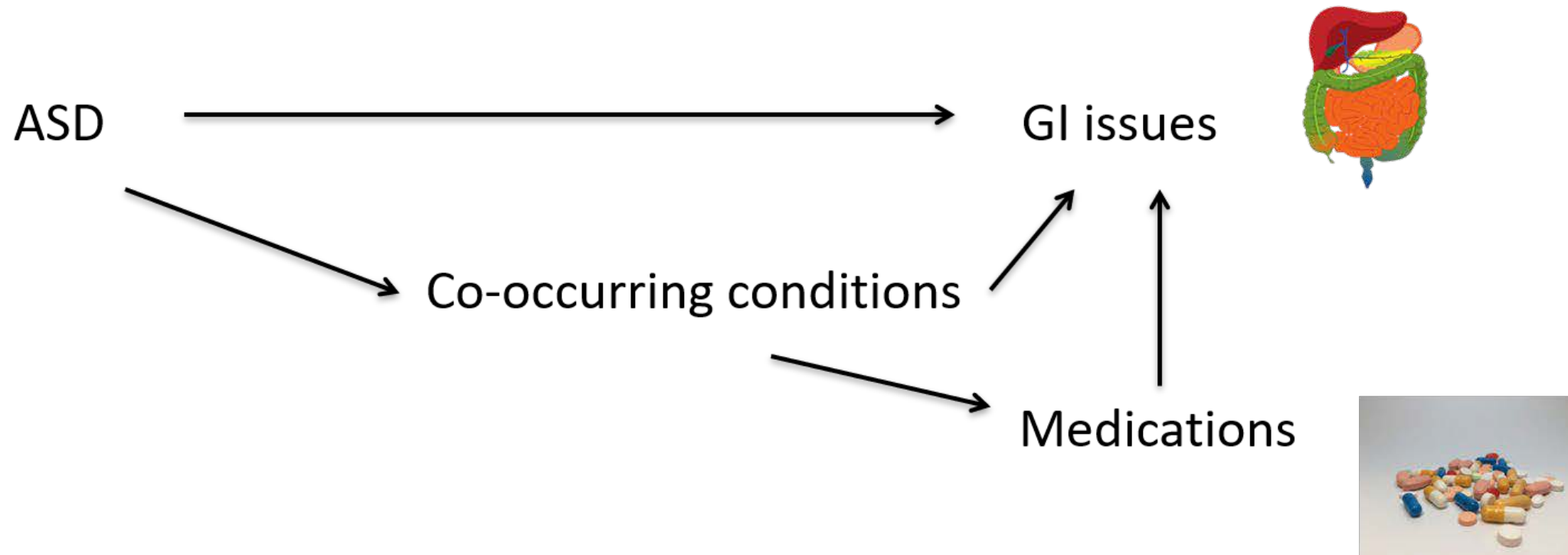
ASD



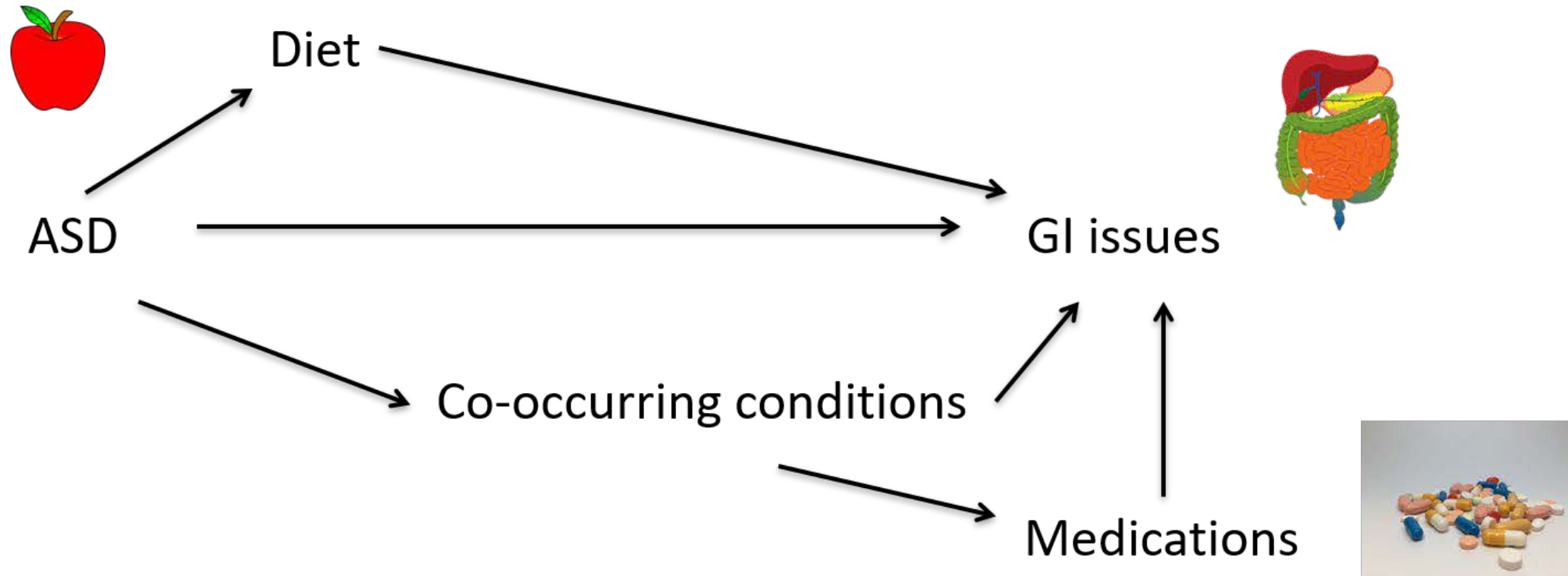
GI issues



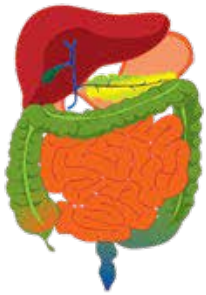
Co-occurring conditions and meds may increase GI symptoms



Dietary restrictions or preferences may increase GI symptoms



Having GI symptoms/gut dysfunction may influence ASD



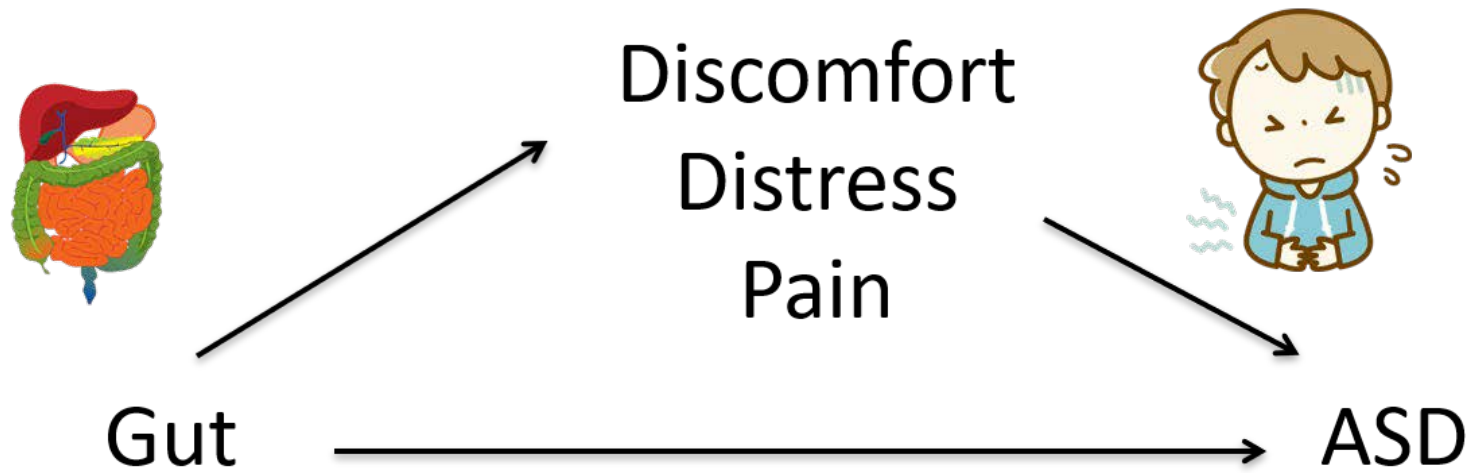
Gut



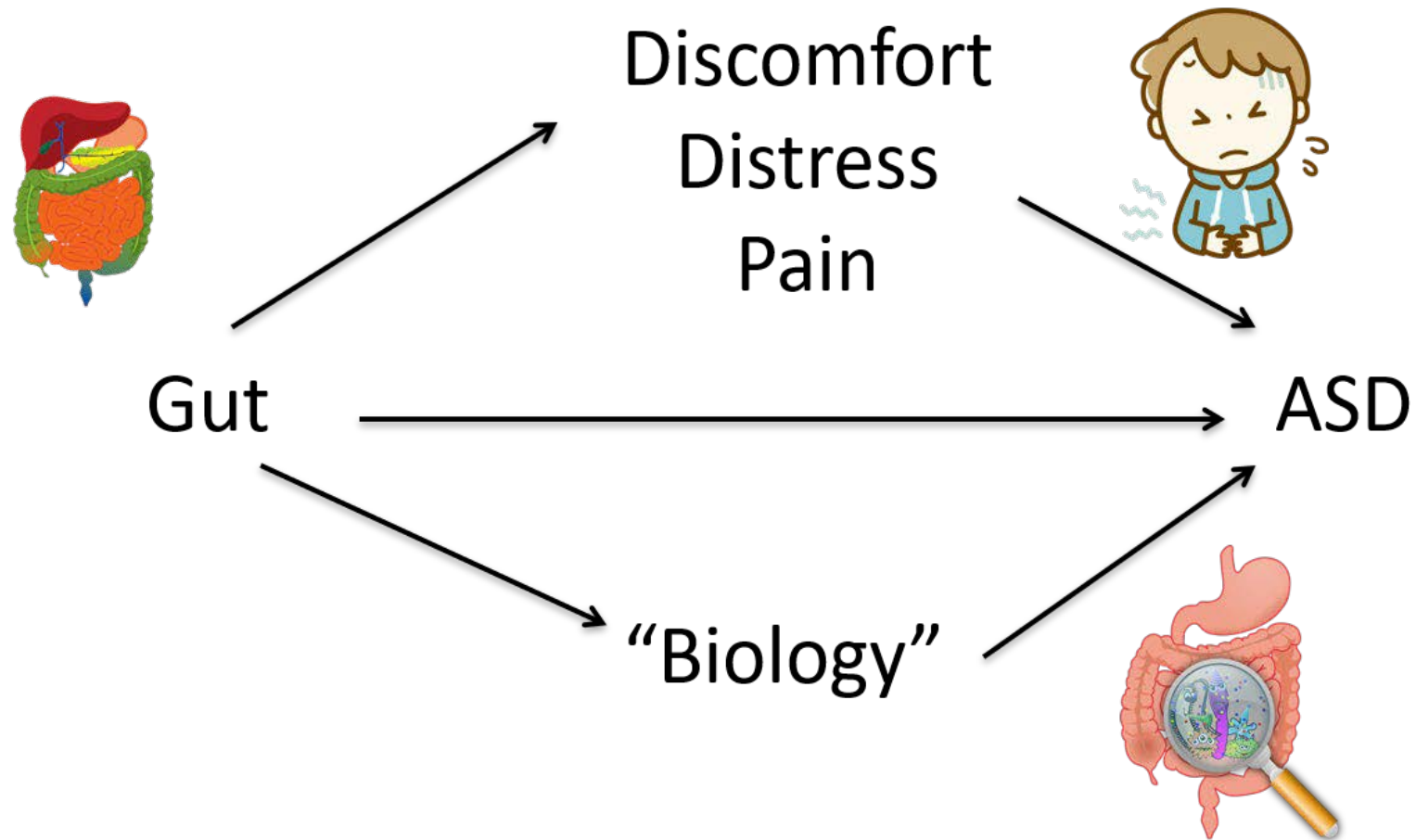
ASD



GI discomfort and pain may influence ASD and related conditions



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



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Which of the following factors may help explain why people with autism tend to have more GI symptoms?

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Latest ASD gut-microbiome research



History (1)

- Anecdotal reports of young children who developed regressive ASD after repeated exposures to antibiotics for chronic otitis media
- Eradication of Clostridiales through additional antibiotics improved ASD symptoms



History (2)

- Open label clinical trial
- Children with regression ASD
- 8-week course of vancomycin and 4 weeks of oral probiotics
- 8 of 11 children showed behavioral improvements, and then deterioration within 2 weeks of vancomycin cessation



History (3)

- Some individuals with ASD may have distinct Clostridial species relative to NT controls
- Clostridium (Lachnoclostridium) boltae associated with ASD & GI symptoms
- Clostridiales may produce neurotoxic metabolites, but not clear if these affect brain, gut development or function

Finegold et al 2002; Song et al 2004; Parracho et al 2005; Finegold et al 2010; Altieri et al 2011; Gondalia et al 2012; De Angelis et al 2013; Kang et al 2013; Wang et al 2013; Son et al 2015; Finegold et al 2017; Persico et al 2013; Saurman et al 2020



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



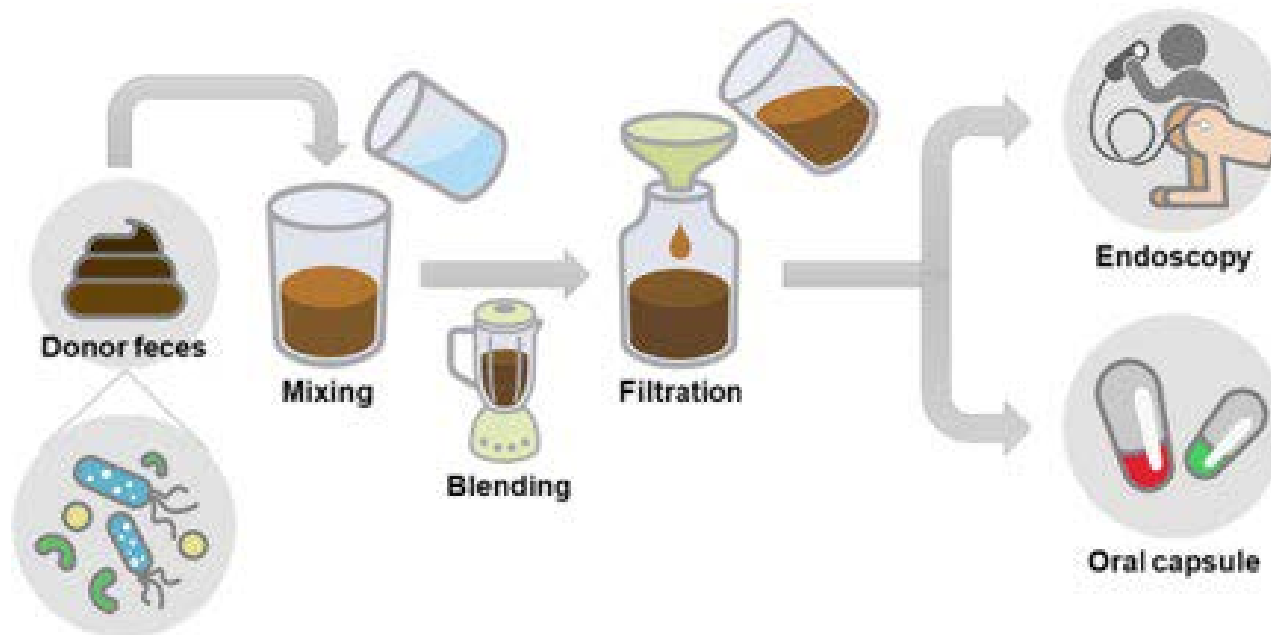
Types of Microbial Interventions

- 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 anus), pills



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Which of the following are reasons for the discrepancy in ASD microbiome findings across studies?

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ASD and Microbiota Transfer Therapy

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



Dae-Wook Kang^{1†}, James B. Adams^{2†}, Ann C. Gregory^{3,15†}, Thomas Borody⁴, Lauren Chittick^{5,15}, Alessio Fasano⁶, Alexander Khoruts^{7,8,9}, Elizabeth Geis², Juan Maldonado¹, Sharon McDonough-Means¹⁰, Elena L. Pollard², Simon Roux^{5,15}, Michael J. Sadowsky^{8,11}, Karen Schwarzborg Lipson¹², Matthew B. Sullivan^{3,5,15,16*}, J. Gregory Caporaso^{12,13*} and Rosa Krajmalnik-Brown^{1,14*} 

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

Dae-Wook Kang ^{1,2,8}, James B. Adams³, Devon M. Coleman³, Elena L. Pollard³, Juan Maldonado^{1,2}, Sharon McDonough-Means⁴, J. Gregory Caporaso ^{5,6} & Rosa Krajmalnik-Brown ^{1,2,7}



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 Caveats

- 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 and managing GI symptoms in ASD



Reminders

- Autism is a heterogeneous disorder
- There is no one single cause of autism
- There may be a subset of autism in which gut is implicated
- There is no one single cause of GI symptoms/gut dysfunction in autism
- This has implications for etiology, treatment, prevention
- Disclaimer: I'm not a medical doctor



Identifying GI Symptoms



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
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Theme A

- Children with ASD often had difficulty verbally communicating the presence of GI symptoms
 - Parents of children with ASD with fluent speech also experienced challenges identifying their child's GI symptoms.
 - Parents reported relying on bodily signs to identify when their child was experiencing GI symptoms.
 - Parents reported relying on non-verbal behaviors to identify when their child was experiencing GI symptoms.



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

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

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. Margolis¹ , Timothy M. Buie², J. Blake Turner³, Anna E. Silberman³, Judith F. Feldman³, Katherine F. Murray², Maureen McSwiggan-Hardin³, Joseph Levy¹, Margaret L. Bauman⁴, Jeremy Veenstra-VanderWeele³, Agnes H. Whitaker³, Harland S. Winter²

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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



What to look out for



Verbal Communication

- Direct verbalization ("ouch", "hurts", "bad", "tummy", "belly")
- Delayed echolalia that includes reference to pain/stomach (e.g. child repeating "Does your tummy hurt?")



Bodily signs

- Lack of bowel movements
- Diarrhea
- Grumbling belly
- Abdominal swelling
- Etc.



Non-verbal Behaviors

- Pointing to abdomen, sensitivity to being touch in abdominal area
- Facial grimacing, wincing, gritting teeth
- Constant eating/drinking/swallowing, clearing throat, chewing on clothes
- Applying pressure to abdomen (e.g., leaning against furniture)
- Unusual posturing (jaw thrust, neck torsion, arching back)
- Groaning, sighing, irritability, oppositional behavior, aggression, sleep disturbances



Managing GI Symptoms



Strategies for Parents & Individuals with ASD

- Take note of behaviors that child uses when communicating symptoms
- Keep a food, symptom, and toileting log to identify patterns.
- Remember the whole person – we all benefit from being able to move our bodies, eat well, stay hydrated, sleep well, etc.
- Trial and error



Dietary Strategies

- In effort to remove offending foods, sometimes diets become too restrictive and cause GI symptoms.
 - Monitor carefully and don't remove too much at once. Add food back in if not seeing improvement from removing it.
- Getting right amount of fiber is important for maintaining gut health and minimizing symptoms.
 - Fiber supplements (e.g. Benefiber, Citrucel) can be mixed in a drink. Start very slowly.
- Adequate hydration
- Work with medical provider



Build a "team"

- Primary care physician, nurse practitioner
- (Pediatric) gastroenterologist
- Psychiatrist – medications may be impacting GI symptoms
- Nutritionist – finding ways to incorporate more diversity in diet while avoiding offending foods
- Behavioral therapist – stool withholding, anxiety around sitting on toilet, general anxiety
- Discuss potential accommodations with school/employer



Challenges seeking GI care

- Long wait times
- Shortage of providers
- Financial & insurance obstacles
- Medication reconciliation
- Office environments not conducive to autism
- Prepping child for anxiety-inducing experience (travel, environment, tests, procedures, etc.)
- Not being taken seriously / Diagnostic overshadowing



Beware Diagnostic Overshadowing

- When symptoms of physical illness are attributed to person's neuropsychiatric/neurodevelopmental disorder
- Increases the risks of treatment delay and the development of complications
- May arise due to stigmatization, negative attitudes, lack of education/training/confidence among clinicians



Example of Diagnostic Overshadowing

“A lot of physicians seem uninterested...It's sort of like ‘your child has autism. This goes with it.’”




Working with medical providers

- Problem-focused visits may be helpful for focusing on one issue (e.g. reflux, headache, sleep)
- Bring videos, behavioral, diet/symptom/toileting log
- Discuss referral to specialist
- Advocate for the outcome you want, be mindful of diagnostic overshadowing as a common practice
- Keep in mind the autism context in terms of identifying, managing, treating symptoms, but also consider GI symptoms as possible distinct medical issue
- Talk to medical office & provider in advance about how to make child more comfortable at visit





What of the following are true regarding the phenomenon of diagnostic overshadowing?

 Start presenting to display the poll results on this slide.

Bring these to your healthcare visit

SUPPLEMENT ARTICLE

Evaluation, Diagnosis, and Treatment of Gastrointestinal Disorders in Individuals With ASDs: A Consensus Report

AUTHORS: Timothy Buie, MD,^{a,b,c} Daniel B. Campbell, PhD,^a George J. Fuchs, III, MD,^a Glenn T. Furuta, MD,^{1,8} Joseph Levy, MD,² Judy Van de Water, PhD,¹ Agnes H. Whitaker, MD,² Dan Atkins, MD,^{3,4} Margaret L. Bauman, MD,^{5,m,n} Arthur L. Beaudet, MD,⁶ Edward G. Carr, PhD,⁷ Michael D. Gershon, MD,⁹ Susan L. Hyman, MD,¹ Pipop Jirapinyo, MD,⁸ Harumi Jyonouchi, MD,¹ Koorosh Kooros, MD,¹⁰ Rafail Kushak, PhD, DrSc,^{a,m} Pat Levitt, PhD,¹ Susan E. Levy, MD,^w Jeffery D. Lewis, MD,^x Katherine F. Murray, BSN, RN,^c Marvin R. Natowicz, MD, PhD,⁷ Aderbal Sabra, MD, PhD,^z Barry K. Wershil, MD,^{aa} Sharon C. Weston, MS, RD, LDN,^{bb} Lonnie Zeltzer, MD,^{cc} and Harland Winter, MD^{a,c}

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abstract

Autism spectrum disorders (ASDs) are common and clinically heterogeneous neurodevelopmental disorders. Gastrointestinal disorders and associated symptoms are commonly reported in individuals with ASDs, but key issues such as the prevalence and best treatment of these conditions are incompletely understood. A central difficulty in recognizing and characterizing gastrointestinal dysfunction with ASDs is the communication difficulties experienced by many affected individuals. A multidisciplinary panel reviewed the medical literature with the aim of generating evidence-based recommendations for diagnostic evaluation and management of gastrointestinal problems in this patient population. The panel concluded that evidence-based recommendations are not yet available. The consensus expert opinion of the panel was that individuals with ASDs deserve the same thoroughness and standard of care in the diagnostic workup and treatment of gastrointestinal concerns as should occur for patients without ASDs. Care pro-

SUPPLEMENT ARTICLE

Recommendations for Evaluation and Treatment of Common Gastrointestinal Problems in Children With ASDs

AUTHORS: Timothy Buie, MD,^{a,b,c} George J. Fuchs, III, MD,^d Glenn T. Furuta, MD,^{e,f} Koorosh Kooros, MD,^g Joseph Levy, MD,^h Jeffery D. Lewis, MD,ⁱ Barry K. Wershil, MD,^j and Harland Winter, MD^{a,c}

^aDepartment of Pediatrics, Harvard Medical School, Boston, Massachusetts; ^bLearning and Development Disabilities Evaluation and Rehabilitation Services, Lexington, Massachusetts; ^cDivision of Pediatric Gastroenterology and Nutrition, MassGeneral Hospital for Children, Boston, Massachusetts; ^dDivision of Pediatric Gastroenterology, Hepatology, and Nutrition, University of Arkansas for Medical Sciences, UAMS College of Medicine and Arkansas Children's Hospital, Little Rock, Arkansas; ^eKeck School of Medicine of USC, Los Angeles, California; ^fSection of Pediatric Gastroenterology, Hepatology and Nutrition, Children's Hospital Denver, Aurora, Colorado; ^gDepartment of Pediatrics, National Jewish Health, Denver, Colorado; ^hDepartment of Pediatrics, University of Colorado Denver School of Medicine, Aurora, Colorado; ⁱDivision of Pediatric Gastroenterology and Nutrition, Golisano Children's Hospital at Strong, University of Rochester Medical Center, Rochester, New York; ^jDepartment of Pediatrics (Administration), NYU Lagone Medical Center, New York University School of Medicine, New York, New York; ^kChildren's Center for Digestive Health Care, LLC, Atlanta, Georgia; and

abstract

Children with autism spectrum disorders (ASDs) can benefit from adaptation of general pediatric guidelines for the diagnostic evaluation of abdominal pain, chronic constipation, and gastroesophageal reflux disease. These guidelines help health care providers determine when gastrointestinal symptoms are self-limited and when evaluation beyond a thorough medical history and physical examination should be considered. Children with ASDs who have gastrointestinal disorders may present with behavioral manifestations. Diagnostic and treatment recommendations for the general pediatric population are useful to consider until the development of evidence-based guidelines specifically for patients with ASDs. *Pediatrics* 2010;125:S19–S29



Remain skeptical!

B.C. naturopath's pricey fecal transplants for autism are experimental and risky, scientists say



Jason Klop says he's seen 'dramatic improvements,' but top doctor warns parents against therapy



Bethany Lindsay · CBC News · Posted: Jan 10, 2020 1:00 AM PT | Last Updated: January 10



B.C. naturopath Jason Klop claims he's seen 'dramatic improvements' in symptoms of autism spectrum disorder after performing fecal microbiota transplants on children. (drjasonklop.com)

A Vancouver naturopath who charges \$15,000 US for children with autism to have fecal transplants at a clinic near Tijuana, Mexico could put them at serious risk of infection with an unproven treatment, according to doctors and scientists.

- Gut-brain field growing rapidly
- Promising early results but need more research
- Microbial therapies have potential benefits and risks
- Remain skeptical; consult a **trusted** medical provider



Center for Autism and Related Disorders
at Kennedy Krieger Institute

Some Resources

- Autism Speaks Toolkits
 - Feeding Behavior
 - Constipation
 - Toilet Training
 - Blood Draws
 - And more!
 - <https://www.autismspeaks.org/tool-kit?state=All&page=0>
- SPARK – The gut's connection to autism
 - <https://www.spectrumnews.org/news/the-guts-connection-to-autism/>
- Articles featuring Dr. Tine Buie
 - https://www.autismspeaks.org/search?search_api_fulltext=tim%20buie



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- Tim Buie, MD (Boston Children's Hospital & Harvard Medical School)



Thank you!

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References 1

- Altieri, L., Neri, C., Sacco, R., Curatolo, P., Benvenuto, A., Muratori, F., ... & Persico, A. M. (2011). Urinary p-cresol is elevated in small children with severe autism spectrum disorder. *Biomarkers*, 16(3), 252-260.
- Buie, T., Campbell, D. B., Fuchs, G. J., Furuta, G. T., Levy, J., VandeWater, J., ... & Winter, H. (2010). Evaluation, diagnosis, and treatment of gastrointestinal disorders in individuals with ASDs: a consensus report. *Pediatrics*, 125(Supplement 1), S1-S18." *Pediatrics* 125.Supplement 1 (2010): S1-S18.
- Buie, T., Fuchs, G. J., Furuta, G. T., Kooros, K., Levy, J., Lewis, J. D., ... & Winter, H. (2010). Recommendations for evaluation and treatment of common gastrointestinal problems in children with ASDs. *Pediatrics*, 125(Supplement 1), S19-S29.
- De Angelis, M., Piccolo, M., Vannini, L., Siragusa, S., De Giacomo, A., Serrazzanetti, D. I., ... & Francavilla, R. (2013). Fecal microbiota and metabolome of children with autism and pervasive developmental disorder not otherwise specified. *PloS one*, 8(10), e76993.
- Finegold, S. M., Molitoris, D., Song, Y., Liu, C., Vaisanen, M. L., Bolte, E., ... & Kaul, A. (2002). Gastrointestinal microflora studies in late-onset autism. *Clinical Infectious Diseases*, 35(Supplement_1), S6-S16.
- Finegold, S. M., Summanen, P. H., Downes, J., Corbett, K., & Komoriya, T. (2017). Detection of *Clostridium perfringens* toxin genes in the gut microbiota of autistic children. *Anaerobe*, 45, 133-137.



References 2

- Gondalia, S. V., Palombo, E. A., Knowles, S. R., Cox, S. B., Meyer, D., & Austin, D. W. (2012). Molecular characterisation of gastrointestinal microbiota of children with autism (with and without gastrointestinal dysfunction) and their neurotypical siblings. *Autism Research*, 5(6), 419-427.
- Holingue, C., Newill, C., Lee, L. C., Pasricha, P. J., & Daniele Fallin, M. (2018). Gastrointestinal symptoms in autism spectrum disorder: A review of the literature on ascertainment and prevalence. *Autism Research*, 11(1), 24-36.
- Holingue, C., Poku, O., Murray, S., Fallin, M.D. Children with Autism Spectrum Disorder and Gastrointestinal Concerns: A Qualitative Study of Family Experiences. Under Revision.
- Hsiao, E. Y., McBride, S. W., Chow, J., Mazmanian, S. K., & Patterson, P. H. (2012). Modeling an autism risk factor in mice leads to permanent immune dysregulation. *Proceedings of the National Academy of Sciences*, 109(31), 12776-12781.
- Hsiao, E. Y., McBride, S. W., Hsien, S., Sharon, G., Hyde, E. R., McCue, T., ... & Mazmanian, S. K. (2013). Microbiota modulate behavioral and physiological abnormalities associated with neurodevelopmental disorders. *Cell*, 155(7), 1451-1463.



References 3

- Kang, D. W., Adams, J. B., Gregory, A. C., Borody, T., Chittick, L., Fasano, A., ... & Krajmalnik-Brown, R. (2017). Microbiota transfer therapy alters gut ecosystem and improves gastrointestinal and autism symptoms: an open-label study. *Microbiome*, 5(1), 1-16.
- Kang, D. W., Adams, J. B., Coleman, D. M., Pollard, E. L., Maldonado, J., McDonough-Means, S., ... & Krajmalnik-Brown, R. (2019). Long-term benefit of microbiota transfer therapy on autism symptoms and gut microbiota. *Scientific reports*, 9(1), 1-9.
- Kang, D. W., Park, J. G., Ilhan, Z. E., Wallstrom, G., LaBaer, J., Adams, J. B., & Krajmalnik-Brown, R. (2013). Reduced incidence of *Prevotella* and other fermenters in intestinal microflora of autistic children. *PloS one*, 8(7), e68322.
- Kim, S., Kim, H., Yim, Y. S., Ha, S., Atarashi, K., Tan, T. G., ... & Huh, J. R. (2017). Maternal gut bacteria promote neurodevelopmental abnormalities in mouse offspring. *Nature*, 549(7673), 528-532.
- Lindsay, B. (2020, January 10). B.C. naturopath's pricey fecal transplants for autism are experimental and risky, scientists say | CBC News. CBCnews. <https://www.cbc.ca/news/canada/british-columbia/bc-naturopath-fecal-transplants-autism-1.5420048>.
- Margolis, K. G., Buie, T. M., Turner, J. B., Silberman, A. E., Feldman, J. F., Murray, K. F., ... & Winter, H. S. (2019). Development of a brief parent-report screen for common gastrointestinal disorders in autism spectrum disorder. *Journal of autism and developmental disorders*, 49(1), 349-362



References 4

- Nash, M. (2013). Diagnostic overshadowing: a potential barrier to physical health care for mental health service users. *Mental Health Practice*, 17(4).
- Parracho, H. M., Bingham, M. O., Gibson, G. R., & McCartney, A. L. (2005). Differences between the gut microflora of children with autistic spectrum disorders and that of healthy children. *Journal of medical microbiology*, 54(10), 987-991.
- Persico AM, Napolioni V. Urinary p-cresol in autism spectrum disorder. *Neurotoxicol Teratol*. 2013;36:82–90
- Rodakis, J. (2015). An n= 1 case report of a child with autism improving on antibiotics and a father's quest to understand what it may mean. *Microbial ecology in health and disease*, 26(1), 26382.
- Sandler, R. H., Finegold, S. M., Bolte, E. R., Buchanan, C. P., Maxwell, A. P., Väisänen, M. L., ... & Wexler, H. M. (2000). Short-term benefit from oral vancomycin treatment of regressive-onset autism. *Journal of child neurology*, 15(7), 429-435.
- Saurman, V., Margolis, K. G., & Luna, R. A. (2020). Autism spectrum disorder as a brain-gut-microbiome axis disorder. *Digestive diseases and sciences*, 65(3), 818-828.
- Son, J. S., Zheng, L. J., Rowehl, L. M., Tian, X., Zhang, Y., Zhu, W., ... & Li, E. (2015). Comparison of fecal microbiota in children with autism spectrum disorders and neurotypical siblings in the simons simplex collection. *PloS one*, 10(10), e0137725.



References 5

- Song, Y., Liu, C., & Finegold, S. M. (2004). Real-time PCR quantitation of clostridia in feces of autistic children. *Applied and environmental microbiology*, 70(11), 6459-6465.
- Vuong, H. E., & Hsiao, E. Y. (2017). Emerging roles for the gut microbiome in autism spectrum disorder. *Biological psychiatry*, 81(5), 411-423.
- Wang, L., Christophersen, C. T., Sorich, M. J., Gerber, J. P., Angley, M. T., & Conlon, M. A. (2013). Increased abundance of *Sutterella* spp. and *Ruminococcus torques* in feces of children with autism spectrum disorder. *Molecular autism*, 4(1), 1-4.
- Wimberley, T., Agerbo, E., Pedersen, C. B., Dalsgaard, S., Horsdal, H. T., Mortensen, P. B., ... & Yolken, R. H. (2018). Otitis media, antibiotics, and risk of autism spectrum disorder. *Autism Research*, 11(10), 1432-1440.



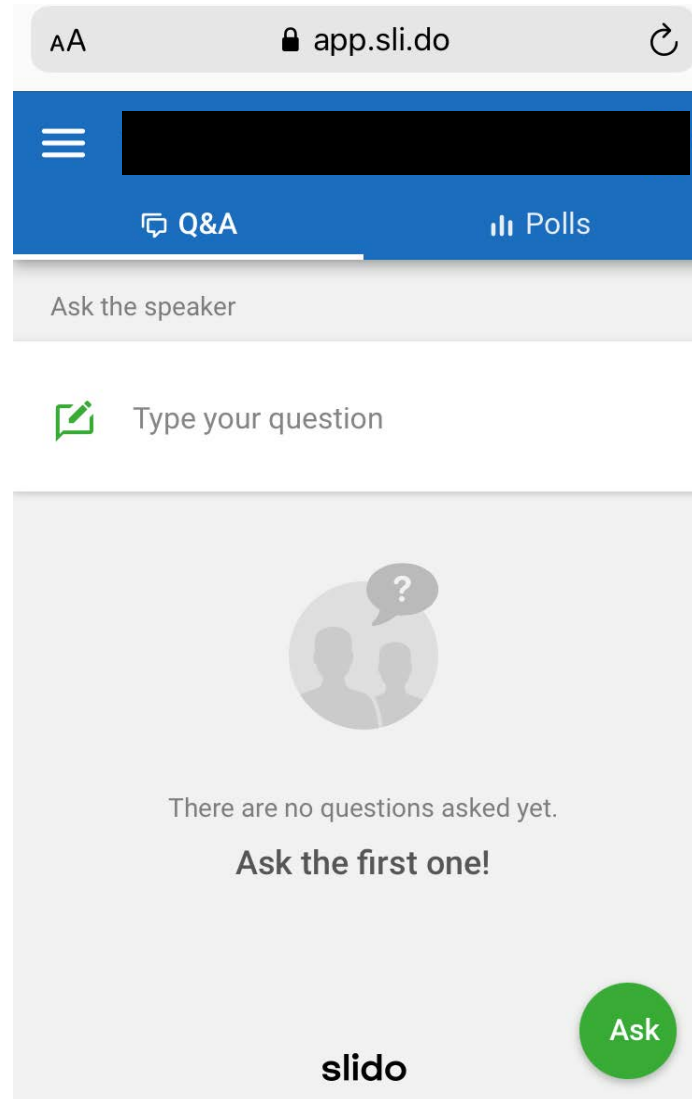
Question & Answer (Q&A) Segment.

Instructions: Toggle over to the Q&A section in Slido to enter questions.

Questions are selected **at random** by the moderator. We cannot guarantee your question will be answered during the Q&A segment.

The moderator may make small changes to a question for clarification purposes.

The Q&A segment is not anonymous.
Please refrain from sharing any personal health information (PHI) or any other identifying information.





Audience Q&A Session

 Start presenting to display the audience questions on this slide.