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Gastrointestinal Conditions in Children With Autism Spectrum Disorder: Developing a Research Agenda

Autism spectrum disorders (ASDs) are a set of complex neurodevelopmental disorders defined behaviorally by impaired social interaction, delayed and disordered language, repetitive or stereotypic behavior, and a restricted range of interests. ASDs represent a significant public health issue with recent estimates indicating that as many as 1% of children in the United States are diagnosed with an ASD.^{1,2} Many individuals with ASDs have symptoms of associated medical conditions, including seizures, sleep problems, metabolic conditions, and gastrointestinal (GI) disorders, which have significant health, developmental, social, and educational impacts. Gastrointestinal complaints are a commonly reported concern for parents and may be related to problem behaviors and other medical issues such as dysregulated sleep (ATN Annual Registry Report, unpublished data, November 2009).³ Despite the magnitude of these issues, potential GI problems are not routinely considered in ASD evaluations. This likely reflects several factors, including variability in reported rates of GI disorders, controversies regarding the relationship between GI symptoms and the putative causes of autism, the limited verbal capacity of many ASD patients, and the lack of recognition by clinicians that certain behavioral manifestations in children with ASDs are indicators of GI problems (eg, pain, discomfort, or nausea).^{4–10}

Whether GI issues in this population are directly related to the pathophysiology of autism, or are strictly a comorbid condition of ASD remains to be determined, but clinical practice and research to date indicate the important role of GI conditions in ASDs and their impact on children as well as their parents and clinicians.⁹

On November 15, 2009, a symposium addressing these issues was organized as an adjunct to the annual meeting of the North American Society for Pediatric Gastroenterology, Hepatology, and Nutrition. A panel of international experts presented the latest scientific information on pathophysiology, evaluation, and treatment strategies for GI conditions in children and adolescents with ASDs. One aim of the meeting was to raise awareness among gastroenterologists and GI researchers of GI disorders in the ASD population and to provide clinicians with information to improve their clinical practice for these children. The symposium addressed 4 major areas of concern for children with ASDs: reflux, constipation, diarrhea, and nutrition. Each session reviewed the state of the evidence, the latest findings on issues such as intestinal permeability, inflammatory processes, innervation, motility, nutrition, and the epidemiology, presentation, and clinical management of GI issues.

The symposium also set the context for a follow-up workshop on November 16 that focused on identifying and prioritizing the key research topics for further investigation. The 1-day workshop brought together

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KEY WORDS

autism, gastrointestinal disease, research

ABBREVIATIONS

ASD—autism spectrum disorder

GI—gastrointestinal

5-HT—serotonin

Drs Ashwood, Fasano, Fuchs, Geraghty, Kaul, Mawe, and Patterson contributed equally to this work.

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a group of symposium participants and speakers with a broad range of expertise in GI and autism clinical practice, and clinical as well as basic science research.

This report provides an overview of findings in GI and ASDs as presented in the symposium and highlights the key conclusions from the workshop. Specifically, the group identified the following 4 topics as priority areas for further study: epidemiology of GI conditions in ASDs, underlying pathology (gut-brain connection, immune function, animal models and genome-microbiome interaction), treatment and outcome, and nutrition. A recent consensus report on GI conditions in ASDs published in *Pediatrics* in 2010⁹ put forth 23 recommendations for the evaluation and management of GI conditions in ASDs. Although ASDs are behaviorally defined disorders, current thinking suggests multiple “autisms” with varying biological underpinnings. Some of these may eventually be identified as having associated GI symptoms, as has been seen with the MET gene. Pending new evidence on any such relationships, the recommendations in this current article expand upon several of the key recommendations made in the consensus statement highlighting areas in need of new knowledge.

EPIDEMIOLOGY OF GI CONDITIONS IN ASDs

Several studies have assessed the prevalence and types of GI disorders in children with ASDs. The reported prevalence of any GI disorder in children with ASDs ranges from 9% to 91% (see Fig 1), abdominal pain or discomfort ranges from 2% to 41%, constipation from 6% to 45%, diarrhea from 3% to 77%, and persistent diarrhea from 8% to 19%^{3,9,11–21}. Although all the studies have significant methodological limitations, they collectively indicate unusually high rates of GI disorders or certain GI symptoms

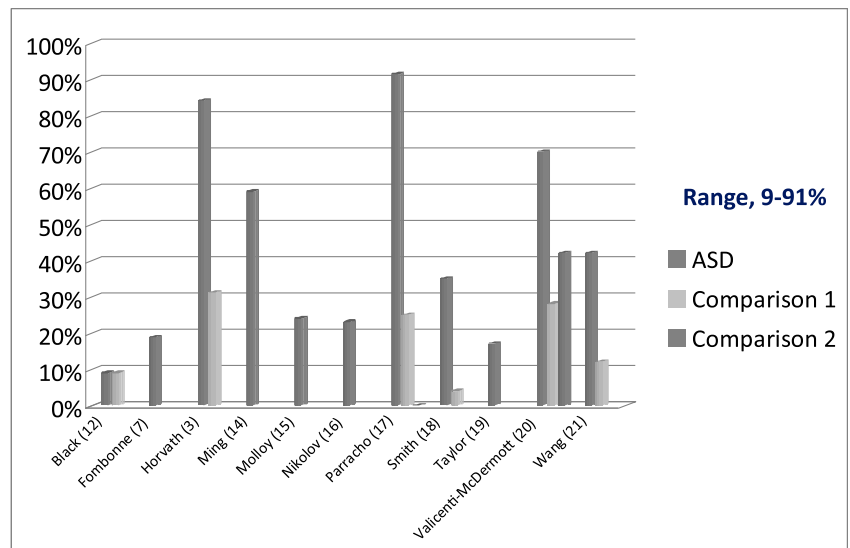


FIGURE 1
Reported prevalence of gastrointestinal disorders in children with ASD.

in children with ASDs and higher rates in all but one study when a control population was used.¹⁰

Recommendations

Accurately determining the rates of GI disorders will require addressing the significant methodological limitations of previous studies. These limitations include suboptimal or, in some cases, lack of controls, variability in the control groups used across studies, inclusion of populations of children with ASDs that are heterogeneous, retrospective approaches, bias (selection, referral, or recall), and/or reliance on parent report only.²² Developing rigorously designed, prospective population-based prevalence studies of defined GI symptoms and disorders in ASD is a high priority, and a shared data set would enable:

1. Identification of risk factors including clinical and behavioral indicators of GI problems
2. Identification of atypical presentations of GI disorders in ASDs
3. Identification of subpopulations within ASD that have GI symptoms
4. Correlation with biomarkers
5. Stratification of treatment groups

UNDERLYING BIOLOGY OF GI DYSFUNCTION IN ASDs

Current State of Knowledge

The underlying nature of GI dysfunction in ASDs and its relationship to etiology and ASD symptoms are poorly understood, and systematic research in this area has been limited. There is, however, emerging evidence relevant to ASDs in the areas of immune function, the relationship between signaling pathways of the gut and brain, and genome–GI microbiome interactions. Increasingly, evidence supports a combination of changes in gut microflora, intestinal permeability, inappropriate immune response, activation of specific metabolic pathways, and behavioral changes in genetically predisposed individuals. Integrating findings across these areas into a unifying theory will be critical to understanding the mechanisms and manifestations of GI disorders in ASDs.

Immune Function

Many reports have described immune abnormalities in ASDs including changes in immune-related gene expression, skewed cytokine production, altered T-cell function, and enhanced innate

immune responses.^{23,24} Mucosal immune cells make up ~70% of the immune cells within the body, and dysfunction in these cells may have adverse consequences for GI function. Endoscopic analyses of children with ASD and GI symptoms have revealed the presence of a subtle, diffuse inflammation of the intestinal tract (reviewed in refs 9 and 25). Characterizing the nature of this inflammation remains an area in need of further investigation to fully understand and to provide further evidence of its relationship to GI symptoms in individuals with ASDs.

Autoimmune responses in children with ASDs and a familial history of autoimmunity have been reported.^{25–28} Among the most common findings in ASD subjects and their mothers is an increased presence of autoantibodies directed toward central nervous system proteins.^{29–33} In addition, autoantibodies that bind to basement membranes of epithelial cells and colocalize with complement proteins are observed in the intestinal mucosa of children with ASD and GI symptoms.³⁴ It has been speculated that these autoantibodies could indicate the presence of inflammatory processes and/or an autoimmune component that could affect the integrity of the mucosal barrier and contribute to decreased mucosal barrier integrity; it is also possible that they indicate previous mucosal inflammation.

Gut–Brain Connection and Serotonin Signaling in the Gut

The digestive system has its own complex (enteric) nervous system that regulates gut functions such as motility and mucosal secretion. It is now well accepted that the gut–brain axis is a 2-way street. For example, in addition to traditional autonomic projections that regulate digestive reflexes, signals traveling from the gut to the brain influence satiety, and stress and anxiety

affect gut function and sensitivity.³⁵ Recently, studies involving germ-free mice inoculated with selective bacteria have made clear that commensal and probiotic gut microbes can have an influence on brain function and behavior.³⁶

Serotonin (5-HT), a highly prevalent signaling molecule in the gut (80%–95% of 5-HT receptors are found in the gut), is critical for GI function, and alterations in 5-HT signaling are implicated in a number of GI disorders. In both human and animal studies, altered 5-HT signaling has been implicated in inflammatory bowel diseases such as Crohn disease and ulcerative colitis and in functional disorders such as irritable bowel syndrome and chronic constipation.^{37–42} Recent studies have demonstrated that 5-HT acts as a proinflammatory modulator in the intestinal mucosa,^{43,44} and that circulating 5-HT arising from the gut affects bone growth, with elevated 5-HT levels leading to decreased bone density. Because both GI and bone disorders have been observed in ASD, altered gut 5-HT signaling may be associated with these changes.⁴⁵ The 5-HT system within the gut may be an important factor contributing to GI problems in children with ASD (see also Nutrition below).

Animal Models

Several environmental factors that increase the risk for the development of autistic features, including maternal infection and valproate exposure, have been used successfully in rodents to generate animal models of these ASD environmental risk factors (reviewed in ref 46). There is also a non-human primate model involving administration of antibrain antibodies to pregnant monkeys⁴⁷ and activating the maternal immune system.⁴⁸ These environmental and genetic models exhibit various characteristics of autism including

neophobia, deficits in social interaction and verbal and olfactory communication, increased stereotyped and repetitive motor behaviors, enhanced anxiety, abnormal pain sensitivity and eye blink conditioning, disturbed sleep patterns, seizures, and deficits in sensorimotor gating. Some animal models also exhibit neuropathology that is frequently seen in autism such as a spatially restricted Purkinje cell deficit, as well as characteristic neurochemical changes (5-HT abnormalities) and alterations in the immune status in the brain and periphery.^{46,49} It is critically important that these animal models of ASD environmental and genetic risk factors also be examined for GI symptoms. It should be noted that treatment with potential probiotic bacteria can normalize anxiety-like behavior in colitis and infection mouse models,⁵⁰ whereas such treatments in normal mice can induce anxiolytic-like effects in some tests and anxiogenic effects in other tests.^{51–53}

Intestinal Permeability and Gut Microbiome

It has been hypothesized that altered intestinal permeability (“leaky gut”) may play a pathogenic role in autism. Indeed, several studies have reported impaired intestinal barrier function in ASD.^{54,55} Moreover, Altieri and colleagues⁵⁶ recently reported a significant ($P < .01$) elevation in the level of a bacterial product in the urine of young autistic children. This molecule, *p*-cresol, is produced by bacterial strains that are found to be elevated in ASD. ASD children have higher counts and more species of Clostridia, Bacteroidetes, and Firmicutes than controls.^{57,58}

One critical feature of the GI tract is its ability to regulate the trafficking of macromolecules between the environment and the host through a barrier mechanism. Together with gut-associated lymphoid tissue and the neuroendocrine network, the intestinal epithelial barrier,

with its intercellular tight junctions, controls the trafficking of macromolecules.⁵⁹ The protein zonulin is a component of intercellular tight junctions that is involved in regulating gut permeability.^{60,61} Small-intestinal exposure to bacteria and gluten are 2 of the more powerful triggers for zonulin-induced tight junction disassembly. Enteric infections have been implicated in the pathogenesis of several pathologic conditions, including allergic, autoimmune, and inflammatory diseases, by causing impairment of the intestinal barrier. In addition to bacterial exposure, gliadin, the environmental trigger of celiac disease, has been shown to alter the intestinal barrier function by releasing zonulin.⁶¹ Moreover, there is increasing evidence supporting an association of gut microbiota with behavioral abnormalities such as anxiety and emotional reactivity^{51,62–65} and potentially affecting 5-HT metabolism.⁶⁶ When considered as a whole, there is much to learn regarding the integrity of the intestinal mucosa, its response to various gut microbiota, and the resultant effects on the body systemically.

Recommendations

Current evidence indicates the importance of better characterizing the underlying pathology of GI problems in ASD and determining if there are any unique characteristics of GI dysfunction specific to autism. Two recommendations are made for research in this area. The first is to determine whether children with ASD differ from typically developing children in terms of the GI microbiome, metabolites, inflammation, neurotransmitters, immune response, and mucosal integrity. Second, it is important to determine if any confirmed differences in these factors could be used to identify those with or at risk for developing ASD by using appropriate control groups. For example, 1 critical area would include determining if mucosal 5HT

availability is altered in ASD children with GI symptoms versus age-matched controls with GI symptoms. Another critical need is the determination of unique biomarkers (eg, cytokines, glutathione redox, antibodies, and zonulin) in the plasma, urine, or stool associated with the development of ASD in high-risk populations.

Animal Models

The work in human subjects will be enhanced by capitalizing on animal models to investigate the mechanisms of altered GI function and sensation in ASDs. The outcome measures would include the histochemical and immunologic abnormalities seen in subsets of ASD children, as well as the changes in gut microbial composition observed in ASD. Specifically, animal models for ASD can be used to determine if there is a distinct GI phenotype in autism and if such GI conditions lead to behaviors associated with ASD. Animal models can also be used to examine potential therapeutic options, for instance by experimentally altering the gut microbial composition.^{53,67} Outcome measures here would include behavior, immune status, neuropathology, as well as GI motility and sensitivity.

Nutrition

Current State of Knowledge

Several factors affect the nutritional status in children with ASDs, with most falling into 2 main categories: (1) medical/nutritional factors and (2) behavioral factors.^{68–73} Medical/nutritional factors encompass GI symptoms/problems, food allergies, metabolic abnormalities, and/or pre-existing nutrient deficiencies, as well as nutrition-related medication side effects. Behavioral factors include problem eating or idiosyncratic eating behaviors, sensory-processing difficulties, and family factors.⁶⁸ In this section, we focus on the medical

and nutritional factors affecting nutrition.

Nutritional status and nutrient intake are inextricably related in children with autism. The assessment of nutritional status in ASDs has been recently discussed in terms of anthropometric, biochemical, and clinical parameters.⁷⁴ Current literature that addresses overall nutrient intakes in ASD does not indicate a definitive consensus either toward evidence for differing nutritional intake or similar nutritional intake in children with ASD compared with typically developing children. There is also a body of studies targeted specifically on intake and status of nutrients related to bone health.⁶⁸ Problems in comparing existing studies include: (1) lack of adequate control groups in some studies; (2) variations in assessment tools and nutrient analysis programs; (3) different time frames postdiagnosis; and (4) different reference values and “cutoffs” defining inadequate. Table 1 summarizes existing studies and significant findings.

Hediger et al⁴⁵ reported that dairy-free diets and unconventional food preferences could place boys with autism and ASDs at high risk for thinner, less dense bones (based on bone cortical thickness measures) in comparison with a standardized reference based on age-matched typical boys. This occurred even for those not on dairy-restricted diets, although the differences were greater for those on casein-free diets. Several factors have been implicated in the higher risk for suboptimal bone development in children with ASDs, including lack of exercise, GI problems, and compromised vitamin D and calcium intake owing to either sensory/texture issues, idiosyncratic eating patterns, and restricted diets, particularly the gluten-free, casein-free diets.^{45,68,85} A recent nutrient intake study (based on 3-day food records) in

TABLE 1 Studies Investigating Nutritional Quality in Children with Autism

Study	No. of ASD subjects	No. of Control/ Typical Subjects	Dietary Tool	Significant Findings
Raiten and Massaro, 1986 ⁷⁵	40	34	7-d Diet Record	<ol style="list-style-type: none"> ASD group had significantly greater intake of protein, carbohydrates, niacin, thiamin, riboflavin, calcium, phosphorus, and iron ($P < .02$) No significant difference in vitamin A, vitamin C, or fat.
Ho et al, 1997 ⁷⁶	54	N/A	3-d Diet Record	<ol style="list-style-type: none"> Only 4 subjects with ASD (7.4%) met recommended servings from all food groups. All subjects had adequate protein intake, but had lower fat intake and higher carbohydrate intake than recommended nutrient intake for Canadians (RNI). 42.6% of subjects were obese.
Cornish, 1998 ⁷⁷	17	N/A	3-d Dietary Recall Food Frequency Questionnaire (FFQ)	<ol style="list-style-type: none"> Nutrient intakes below RNI levels in 53% of children for one or more of following: vitamin C, vitamin D, niacin, riboflavin, vitamin B₆, calcium, and zinc. Calcium and niacin levels >200% or RNI in those children who drank milk.
Lindsay et al, 2006 ⁷⁸	20	N/A	FFQ	<ol style="list-style-type: none"> <80% Recommended Dietary Allowance (RDA)/dietary reference intake (DRI) considered inadequate 45% consumed ↓calcium, 30% ↓pantothenic acid, 25% ↓ vitamin D, 40% ↓vitamin K
Levy et al, 2007 ⁷⁹	52	N/A	3-d Diet Record	<ol style="list-style-type: none"> The ASD subjects met 95%–101% of RDA guidelines for calories, carbohydrates, and fat ASD subjects overconsumed protein at 211% of RDA with a range of 67%–436% RDA among subjects This study used 77% of RDA consumption as adequate diet
Lockner et al, 2008 ⁸⁰	20	20	3-d Diet Record	<ol style="list-style-type: none"> Vitamins E and A were the least likely to be met by Estimated Average Requirement (EAR) for both groups ASD subjects consumed less calcium and fiber, but with no established EAR, significance was not determined
Schmitt et al, 2008 ⁸¹	20	18	3-d Diet Record	<ol style="list-style-type: none"> This study defined adequate consumption as >67% of DRI Both groups consumed <67% for fiber ASD group consumed <67% for vitamins E and K
Johnson et al, 2008 ⁷¹	19	15	24-h Recall	<ol style="list-style-type: none"> This study considered <80% of RDAs or DRIs as inadequate ASD group consumed significantly less vitamin K and significantly fewer food choices from the vegetable group
Herndon et al, 2009 ⁸²	46	31	3-d Diet Record	<ol style="list-style-type: none"> ASD children consumed significantly less calcium but consumed increasingly more vitamins B₆ and E than controls. ASD children consumed significantly more nondairy proteins and fewer dairy items. Both groups did not meet RDI for fiber, calcium, iron, vitamin D, and vitamin E
Xia et al, 2010 ⁸³	111	N/A	3-d Diet Record	<ol style="list-style-type: none"> Comparison with Dietary Reference Intakes (DRI) for Chinese children. Vitamin E and niacin exceeded 100% of DRI Intakes were below DRI for vitamins A, B₆ and C, Folic acid, calcium and zinc
Bandini et al, 2010 ⁷¹	53	58	Parent Interview FFQ 3-d Diet Diary	<ol style="list-style-type: none"> For both groups, fiber intake was inadequate as was intake of vitamin D, vitamin E, and calcium For ASD children, inadequate intake of vitamin D and calcium was more frequent ASD children had a higher number of nutrients at inadequate intake levels. A limited food repertoire, but not food refusal, was associated with higher nutritional inadequacy for both groups
Zimmer et al, 2011 ⁸⁴	22	22	FFQ	<ol style="list-style-type: none"> ASD children had higher intakes of magnesium ASD children had lower intakes of protein, calcium, vitamin B₁₂, and vitamin D. Selective eaters with ASD had greater likelihood of inadequate intake of calcium, vitamin B₁₂, zinc, and vitamin D Selective eaters with ASD compared with nonselective eaters with ASD had greater likelihood of inadequate intake of calcium. ASD children had less food variety than typically developing children

children with ASDs ages 3 to 9 years revealed that the nutrients commonly analyzed as inadequate were those important for bone health (vitamins A, D, and K) with 58.3%, 58.3%, and 91.7% of the children consuming intakes <80% dietary reference intake, respectively.⁸⁶

Collectively to date, these studies indicate a trend for clinically significant suboptimal nutrient intake in children with ASDs, with particular concern related to bone health nutrients. In general, nutritional status parameters need to be refined and tailored for this population.

Recommendations

Standardize Nutrient Assessment

Nutrient intake studies in ASDs should be standardized by: (1) including control groups with typical children, (2) using consistent nutrient assessment tools and analysis programs, (3) accounting for the time frame post-diagnosis, and (4) establishing consistent reference values and acceptable cutoffs for defining inadequate intake.

Correlations With Nutritional Status

Research should address the relationships between baseline nutritional status (by using standardized nutrient intake study principles and a thorough nutrition assessment) and health status, GI symptoms (constipation, diarrhea, flatulence, bloating, and nausea), bone cortical thickness/bone mineral density, behavior, sleep latency, food selectivity/idiosyncratic behaviors, sensory-processing difficulties (hypersensitivity to certain food textures, tastes, or smells), and measures of inflammation (eg, cytokines, c-reactive protein).

Efficacy of Nutritional Intervention

Studies should determine the effectiveness of nutritional interventions

on correcting identified deficiencies and any additional benefits to the individual's ASD symptoms. Further elucidation of the interrelationships among these variables will assist in the establishment of clinical algorithms for categorization and effective treatment.

TREATMENT AND OUTCOME

Current State of Knowledge

As highlighted in the previous sections, children with ASDs frequently experience GI symptoms, but their prevalence, nature and, therefore, best treatments remain elusive. Limited understanding of the underlying pathology of GI conditions in ASD limits the scientific rationale for many of the interventions (eg, antifungal therapy, enzymes, and nutritional supplements) aimed at correcting these GI dysfunctions.^{9,10} A possible theory unifying all the factors mentioned above would link changes in the gut microbiome with GI inflammation and other immunologic changes.

The most common GI diagnoses identified in children with ASDs include constipation, diarrhea, and gastroesophageal reflux, and these are usually treated in a standard manner.^{9,10} Children with ASDs may not present with the typical symptoms of a GI disorder, however, and an alteration of their baseline behavior may be the only indicator of its existence. There is a serious dearth of adequately designed studies on treatments for documented GI disorders and their outcomes, including behavioral changes, in children with ASDs.

Recommendations

Treatment Guidance

Although general pediatric guidelines exist for specific GI conditions, the recommendations may not always

address the particular needs of an ASD population. Evidence-based algorithms specific for ASD should be developed for each of the most common diagnoses that would address both management as well as treatment outcomes, tested rigorously, and subsequently refined to optimize outcomes (see this issue). These algorithms will provide the basis for comprehensive guidelines and final recommendations provided to clinicians caring for children with ASD.

Placebo-Controlled Trials

The positive impact of treatments aimed at the GI problems in ASD children is widely reported by parents, but there is little well-designed, controlled research to validate these interventions. It will also help substantially to stratify the ASD population to identify specific subgroups of children who may better benefit from interventions. Many of these approaches involve life-long interventions (such as implementation of a gluten-free diet), so better identifying the individuals likely to respond to particular treatments can reduce the costs and burden on families associated with nonefficacious treatments. Stratification might be conducted by using clinical phenotypes or through the identification and use of specific biomarkers (see Table 2).

The identification of specific ASD microbiome and metabolic phenotypes

TABLE 2 Biomarkers as Potential Outcome Measures

Biomarker	Clinical Significance
Intestinal permeability	Leaky gut
Calprotectin	Intestinal inflammation
Celiac disease serology tests	Celiac disease and gluten sensitivity
Food allergy panel	Food allergies
Organic acid testing	Vitamin B ₁₂ or folic acid deficiencies
Analysis gut microbiota	Gut dysbiosis

TABLE 3 Key Takeaway Messages**Epidemiology**

- Gastrointestinal conditions in ASD are at least as common as in typically developing population
- It is less clear whether GI conditions are more common in children with ASD
- Individuals with ASDs should receive diagnostic evaluations and medical treatments for GI disorders just as children without ASD do

Biology

- Several studies identify abnormalities of the immune system in ASD
- Some GI conditions in ASD may have an immunologic basis
- Some individuals with ASD have abnormalities in serum concentrations of the neurotransmitter serotonin
- Alterations in serotonin may be associated with anxiety, GI symptoms, and bone density abnormalities

Nutrition

- Several studies have identified abnormalities of diet and altered bone mineral density, but the cause (dietary preference, allergic issues, or absorptive problems) remains uncertain.

Treatment

- No treatments for GI problems specific to children with ASD currently exist.
- Individuals with ASD and GI conditions appear to respond to treatment much as people with typical development do.
- Studies that can lead to management that addresses specific challenges of the disorder are still needed.

TABLE 4 Key Research Objectives for an Integrated Approach to Addressing Knowledge Gaps

1. Determine the pathology of gastrointestinal conditions in ASDs through integrated studies of the gut microbiome, metabolism, inflammation, immunity, and mucosal integrity. The outcome measures would include the histochemical and immunologic abnormalities seen in subsets of ASD children, as well as the changes in gut microbial composition observed in ASDs.
2. Increase the use of animal models to better understand the underlying pathology. Studies manipulating the microbiome in animal models may help promote better understanding of these conditions.
3. Identify biomarkers for assessing the status of these conditions and to guide identification and treatment.
4. Identify biomarkers of nutritional status that will not only guide monitoring of response to treatment but help identify those requiring intervention.
5. Identify behavioral phenotypes related to poor nutritional status to better identify and treat this population.
6. Develop evidence-based clinical algorithms to help guide clinicians in the evaluation and treatment of gastrointestinal problems in individuals with ASDs.

can also help to define additional diagnostic tools, biomarkers, and therapeutic interventions such as the use of probiotics to change the intestinal

microbiota composition. These findings may have a far-reaching impact not only on our understanding of the role of specific allergens, leaky gut, and

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Developing a Research Agenda**

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