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MEETING PROCEEDINGS

Gastroenterology

Conference proceedings: Inaugural meeting of the consortium for autism, genetic neurodevelopmental disorders, and digestive diseases

Alycia Halladay[1,2,3] | Joseph Croffie[4] | Julia Dallman[5] | Heidi Grabenstatter[3,6] | Calliope Holingue[7,8] | Katie Madgett[1,3] | Kara G. Margolis[9,10,11] | Kathleen J. Motil[12,13] | Andres Jimenez-Gomez[14,15] | Bradley J. Ferguson[16,17] | Baha Moshiree[18,19] | Kate Still[3,20] | Kent Williams[21] | Gerald Rick Upp[6] | William Bennett[3,4]

Correspondence

Alycia Halladay, 106 West 32nd St #118, New York, NY 10001, USA.
Email: ahalladay@autismsciencefoundation.org

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Abstract

Objectives: Individuals with neurodevelopmental disorders (NDDs), including autism spectrum disorder (ASD), often experience a higher prevalence of gastrointestinal (GI) symptoms but have complex medical and behavioral comorbidities that make diagnosis and treatment difficult. A multi-stakeholder conference was convened to (a) determine patient and family experiences related to GI symptoms in NDDs, (b) review the clinicians' and researchers' perspectives, and (c) determine actionable steps for future research.

Methods: The Consortium for Autism, Neurodevelopmental Disorders and Digestive Diseases (CANDID; www.candidgi.com) virtually over 2 days in 2022 and consisted of four key activities: (1) an electronic family survey to assess underlying NDDs and GI symptoms, (2) a session focused on family perspectives, (3) review current clinical care and research, and (4) discussion to identify key next steps. Survey results were obtained electronically via the REDCap platform, and descriptive statistics were generated. The sessions were recorded, and themes were identified.

Results: The pre-conference survey ran for ~2 months and 739 families provided responses, with 634 completing all items. 83% had a child with an NDD under age 18, and most patients were White (85%) and non-Hispanic (87%). Constipation (80%), gastrointestinal reflux disease (51%), and bloating (49%) were the most frequently reported symptoms. Families gave unstructured feedback that the measures used in the surveys were often difficult to answer for patients with NDDs or who were nonspeaking. Family and clinical/scientific sessions identified several common themes, including (1) the need for less invasive diagnostic modalities, (2) the need to validate or adapt existing diagnostic measures (e.g., the Rome IV criteria) and outcome assessments, and (3) the need for enhanced attention to parent and caregiver input in treatment plans.

Conclusions: Those providing care to children with NDDs, especially those with communication and cognitive challenges, should be aware of the differing

For affiliations refer to page 7.

needs in this community and consider family perspectives in managing, treating, and measuring GI issues. Future research should focus on adapting or creating diagnostic and research measures for those with NDDs, developing new diagnostic methods to account for diversity in neurodevelopment and communication, and improving methods for family and caregiver engagement in the care of GI disorders.

KEYWORDS
autism spectrum disorder, gastrointestinal, recommendations

1 | BACKGROUND

Neurodevelopmental disorders (NDDs) refer to a diverse group of diagnoses, including autism spectrum disorder (ASD), that emerge from changes in the physiologic and predicted process of development of cognitive and motor skills during early childhood.[1,2] They include, but are not limited to: ASD, attention-deficit/hyperactivity disorder, intellectual disability, learning disabilities, cerebral palsy, and a large number of genetic syndromes that are associated with developmental delay, intellectual disability, and epilepsy. Depending on the specific NDDs, their prevalences range from 0.6% to 17%.[3] NDDs are themselves heterogeneous[2,4] and result from the interaction of genetic and environmental factors. Over 100 highly penetrant rare variants have been associated with ASD.[5] Those with NDDs who are severely intellectually disabled, nonspeaking, and unable to communicate their pain and medical needs make up 27% of those with ASD, and may thus represent a particularly challenging population regarding gastrointestinal (GI) care.[6,7]

Up to 70% of those with NDDs also have GI symptoms or have received a GI diagnosis.[8] The majority of autistic individuals experience at least one GI symptom,[9] including abdominal pain, functional diarrhea or constipation, and gastroesophageal reflux.[10–17] Those with genetic causes of NDD have specifically been found to have constipation, diarrhea, and abdominal pain more commonly.[16,17] Little is known about the mechanisms behind GI symptoms in this population or how to support those who experience GI symptoms.[10] Given that many individuals with NDDs caused by rare genetic variants are either nonverbal or intellectually disabled,[5,18] physicians treating these children need awareness of specific challenges related to diagnosis and treatment in those with NDDs. While noninvasive methods of diagnosing or treating GI disorders are now more commonly used, many remain intensive or invasive.[19] In an effort to better understand the mechanism of GI dysfunction in NDDs, multiple animal models with NDD-associated genetic mutations have been created, many of which show GI dysmotility or impairment of enteric nervous system development,[20] but translational research from these models remains limited.

What is Known

- Gastrointestinal (GI) problems are common comorbidities in those with neurodevelopmental disorders (NDDs). These GI conditions can compound problems in neurodevelopment, leading to behavioral and psychiatric challenges like aggression, self-injury, anxiety, and withdrawn behavior.
- There is a dearth of data regarding the causes, course, diagnosis, and treatment of GI symptoms in this population.

What is New

- A multidisciplinary Consortium for Autism, Neurodevelopmental Disorders and Digestive Diseases (CANDID) was formed to bring together key stakeholders to discuss GI conditions in those with NDDs and autism spectrum disorder.
- CANDID identified three key areas for future work: (1) adaptation of diagnostic and research measures for those with NDDs, (2) improved diagnostic methods for those with developmental or communication deficits, and (3) enhanced focus on family/caregiver input in planning for diagnosis and treatment.

1.1 | Associations with other neurological symptoms and behaviors

GI symptoms may share common pathophysiology with other neurological symptoms, such as seizures and intellectual disability.[21] Furthermore, restrictive eating, oppositional behaviors, anxiety, and feeding disorders, all common in those with NDDs, are also highly associated with GI diagnoses.[22–24] Sensory processing dysfunction in those with NDDs may lead to impairments in oral intake (food refusal, aerophagia, and nonedible intake), oromotor swallowing dysfunction, exaggerated response to symptoms such as bloating

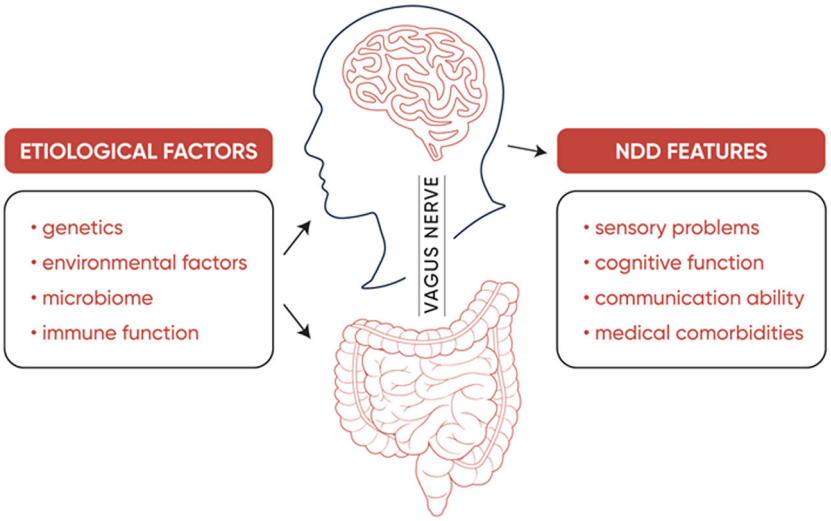

FIGURE 1 Schematic of the overlapping etiologies of gastrointestinal symptoms in people with neurodevelopmental disabilities. NDD, neurodevelopmental disorder.

and abdominal pain, and pelvic floor dysfunction contributing to constipation and encopresis Figure 1.[25]

1.2 | NDDs and nutrition

Growth failure, malnutrition, and bone fractures are common problems in NDDs,[26] often related to inadequate dietary intake of macronutrients, as well as micronutrients such as calcium and vitamin D.[27] There are currently no broadly utilized adapted clinical assessments of nutrition or specific therapeutic interventions tailored for those with NDDs. Furthermore, many genetic syndromes have growth trajectories, even in the setting of optimized nutrition, which diverge from the standard Center for Disease Control and Prevention and World Health Organization growth curves. While some syndromes (such as trisomy 21) have widely used adapted growth curves, most disorders do not, which can impede clinicians' ability to assess nutritional needs in those with NDDs. A schematic of the interaction between GI symptoms and expression of NDD features is found in Figure 1.

2 | CONFERENCE ACTIVITIES

To address these challenges, the Consortium for Autism, Neurodevelopmental Disorders and Digestive Diseases (CANDID; www.candidgi.com) convened a National Institutes of Health-funded conference in 2022 to bring together family members, clinicians, scientists, and industry partners focusing on GI disorders in individuals with NDDs. Because those with rare genetic syndromes associated with NDDs are more likely to be nonspeaking, experience cognitive disability, and have more complex medical comorbidities,[18] CANDID focused on genetic syndromes with more significant symptomology. Those who are minimally verbal and cognitively disabled often face more significant impairment from GI symptoms as well as additional challenges to diagnosis and management.[17] The conference agenda consisted of (1) a pre-conference survey of families, (2) a family panel describing the lived experience of severe GI symptoms concomitant with NDDs, (3) eight presentations by clinical and scientific experts, and (4) discussion of themes and identification of future directions for research (Table S1). A total of 304 participants (including experts in pediatric and adult GI, interventional endoscopy, nutrition, and motility), behavioral specialists, care providers, family members, researchers, industry representatives, and patient advocacy organization representatives attended.

2.1 | Pre-conference electronic survey

Before the conference, we created a family survey using REDCap, which was distributed through a number of patient advocacy groups such as AGENDA (Alliance for Genetic Neurodevelopmental Disorders and Autism), the Rare Epilepsy Network (REN), Simons Searchlight, and via social media on the channels of the Autism Science Foundation and Autism Speaks. The University of Indiana Institutional Review Board reviewed and approved the survey and consent to participate. These organizations interact with families who are diagnosed with ASD and have a rare genetic syndrome. Since there are overlapping groups in each network, we do not know how many individual families were recruited; however, 16 rare genetic disorders associated with NDDs or ASD as well as many with idiopathic autism were represented in the findings. Families were given an HTML link to complete the survey and completed questions related to age, race, ethnicity, specific NDD diagnosis, and two measures of

quality of life (patient reported outcomes measurement information system gastrointestinal scales).

There were 739 families who provided responses, with 634 completing all items. Eighty-three percent (83%) had a child with an NDD under age 18, and most patients were White (85%) and non-Hispanic (87%). Constipation (80%), gastrointestinal reflux disease (51%), and bloating (49%) were the most frequently reported symptoms, and only 5% reported no GI symptoms at all (Figure 2). Most patients indicated a specific genetic diagnosis (91%), and the remainder indicated that their child had an NDD or ASD without a genetic syndrome. The response rate by syndrome varied widely, since this survey was not designed to sample all NDDs uniformly and was distributed to a sample of convenience. Among the 91% who reported a specific genetic NDD, the most common specific diagnoses were Phelan-McDermid Syndrome (16%), duplication of 15q (9%), and SYNGAP mutations (8%). Over 50% of families ranked GI conditions among their "top three concerns," and less than 10% of families ranked GI conditions as low concern compared to other co-occurring diagnoses with NDDs (Figure 2). It should be noted that this sample was inherently biased toward families impacted by GI conditions, since the survey was solicited associated with the CANDID conference and was not a sampling of the general NDD population.

Families also provided unstructured free text feedback about the survey. Many families reported difficulty completing the survey instruments for a variety of reasons, most notably because some questions could not be answered (such as the presence or absence of a symptom in a nonspeaking individual). Others reported difficulty completing all questions, especially those that were not specifically relevant to their child, and felt that the number of questions was excessively burdensome.

2.2 | Session 1—Family lived experience

To explore the lived experience of families with children who have a rare genetic disorder with NDD, families presented descriptions of their child's GI symptoms

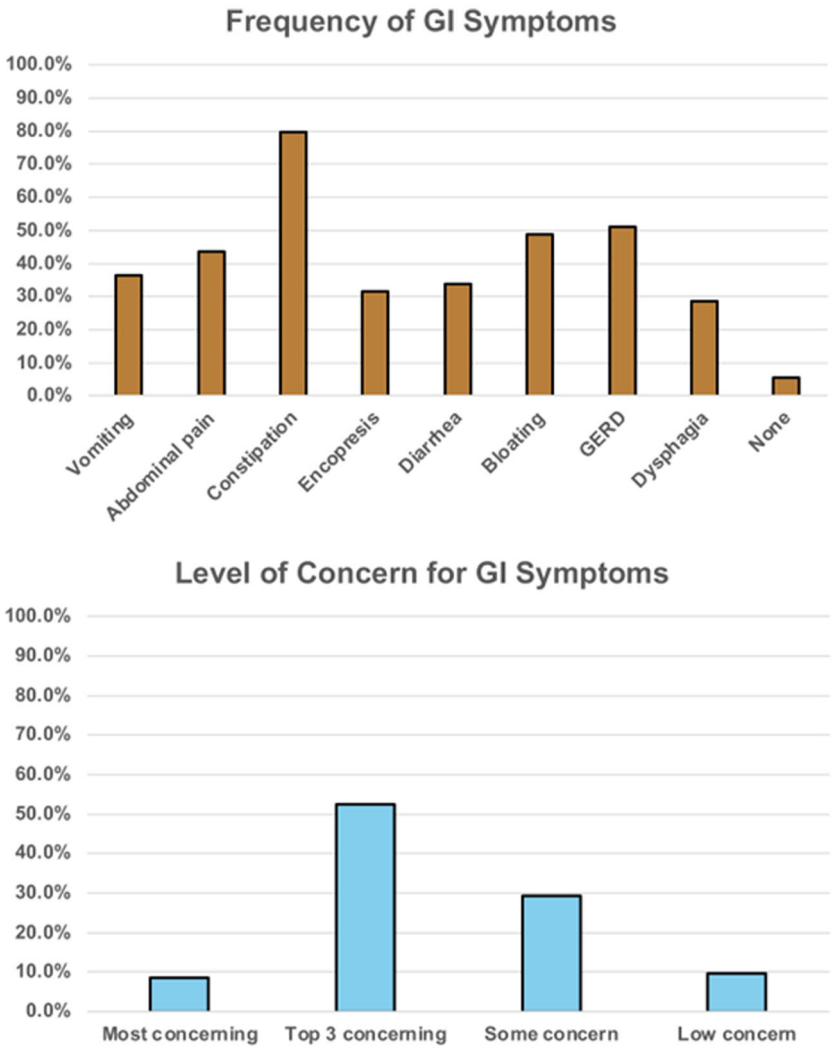

FIGURE 2 Frequency of reported symptoms (top panel) and level of concern for these symptoms (bottom panel) in a sample of parents surveyed before the CANDID conference. CANDID, Consortium for Autism, Neurodevelopmental Disorders and Digestive Diseases; GI, gastrointestinal.

and the impact on the families' lives and each affected patient's. Families reported constipation, which was debilitating and worsened seizure activity, caused dehydration, or necessitated more invasive intervention such as an appendicostomy. Families frequently described that worsening constipation was associated with decreased appetite or refusal to eat. They described how pain or difficulty stooling was also associated with challenging behaviors like aggression, self-injury, and "constant screaming" that prevented progress in developmental, learning, and social skills. Two detailed examples of family lived experience are shown in Table S2.

Challenges that many of the families expressed within the medical system included lack of history recall and limited treatment options despite a lack of improvement. Some families noted positive experiences with interventions like antidepressants, anal botulinum toxin (which one parent described as "life changing"), or other "outside the box" approaches. Treatments have also included biofeedback, diverting colostomy, and a wide variety of alternative feeding approaches such as gastrostomy, gastrojejunostomy, and nasogastric tubes. Feeding tubes, while they were generally regarded as helpful, often prevented the family from participating in the community and traveling as they desired.

From these varied patient experiences, we identified multiple general themes:

1. GI symptoms are pervasive, severe, and often happen early in life.
2. Nonverbal patients cannot communicate the nature of their pain and often respond with self-injury and other destructive behaviors.
3. The entire family is affected, as GI conditions can restrict everyday activities.
4. The first intervention tried by clinicians was rarely effective. Families had to try several procedures, therapies, medications, or a mix of all three, and often had to seek a second opinion.
5. Because the GI symptoms posed an immediate and disabilitating issues in their child, families often put other care like therapies or school "on the back burner" until the GI conditions resolved, which caused problems in itself.
6. Families reported that some physicians could be dismissive of these conditions or unprepared for the complexity of their child.
7. Once GI symptoms are effectively managed, the entire family experiences an improvement in their quality of life, and the child can make progress in areas that are held back because of pain.

A summary of some potential solutions and resources for physicians to help work with children experiencing challenges in communication and cognitive ability, and exhibiting severe and challenging behaviors can be found in Table 1.

2.3 | Session 2—Clinical and research experts

Research presentations were grouped under the following four categories: (1) the gut–brain connection, (2) the spectrum of GI disorders in neurodevelopmental conditions and their impacts, (3) detection and monitoring of GI disorders in people with neurodevelopmental conditions, and (4) new methods to study GI disorders in these populations.

Clinicians shared that those with NDDs may have difficulty communicating pain or other subjective experiences due to impairments in enteroception, language, and cognition.[9,10,28] This represents a particular challenge for clinicians without extensive experience with NDDs. Thus, to identify when children with NDDs are experiencing GI symptoms, parents often rely on detecting bodily signs (e.g., abdominal swelling, diarrhea, and lack of bowel movement) or nonverbal behaviors such as screaming and self-injury, and changes in other health domains (e.g., sleep conditions, irritability, and aggression).[10,29] Furthermore, expert clinicians across multiple subspecialties reviewed our current options for diagnosis (e.g., radiology, endoscopy, and manometry) and acknowledged the many challenges inherent in invasive diagnostic modalities in children with NDDs, similar to concerns voiced by families.

Researchers shared that many existing measures used in autism research do not incorporate nonverbal clinical data.[9] This has serious implications for the quality of research on GI health in those with NDDs and ASD, the ability to accurately screen and diagnose GI conditions in these patients, and the assessment of the safety and effectiveness of clinical trial interventions or inclusion of individuals with NDD in clinical trials at all.

Both researchers and clinicians identified a clear need for both clinical and research tools to diagnose and monitor the progression of GI disorders in patients with NDDs. This effort requires instruments that have been widely validated in individuals with cognitive or communication deficits and reflect not just clinical signs but overall impact on daily functioining. Despite the high proportion of those with NDDs who experience GI symptoms, few exist.

Researchers identified newer tools that may meet this need, such as the Gastrointestinal and Related Behaviors Inventory (GIRBI), which combines items from the Autism Treatment Network GI Inventory[15,30] and the Brief Autism Mealtime Behavior Inventory.[31–33] The measure was piloted in an online research registry, and preliminary psychometric performance was assessed, resulting in a 36-item tool

TABLE 1 Challenges, barriers, and potential solutions.

Challenges	Barrier	Solutions	Examples
Patients with NDDs may be MV	These individuals cannot express their GI pain precisely making diagnosis based on patient report difficult	Augmentative and alternative communication devices Objective caregiver-reported	Proloquo2 Go or other devices AS-ATN GI Signs and Symptoms Inventory-17 ASD-GIRBI
Tests requiring consumption are not palatable	Reluctance to consume liquids or solids due to pain	Development of more palatable methods	Tasteless tracers or palatable foods containing tracers
Complex medical issues prevent travel to clinics	Diagnostic tests requiring specialized equipment may be difficult to obtain	Mobile technologies for tracking GI activities at home in real time, integrated with EMR and medications	Blue muffin at-home tracking of motility, paired with phone application
Comorbid IDD diagnoses	These individuals may not be able to understand instructions given verbally or written. GI pain may be masked by other symptoms	Social stories explaining the procedure beforehand and what will happen Increased expertise of common outward signs of GI distress, and formation of specialist teams including GI expertise	https://paautism.org/resource/colonoscopy-social-stories/ Centers of Excellence for Clinical Care
Tests require immobility	Procedures may be challenging or not feasible	Extra time and patience by staff, additional education of medical staff, creation of enjoyable environment, which reduces stressors for the patient	Child-friendly and developmentally age-appropriate distractors, understanding of individual likes and dislikes during testing.
Tests are invasive	Can be not feasible in some people with NDDs, or require anesthesia	Use of minimally invasive measures whenever possible, and/or advent of new minimally invasive measures	Electrogastrography—noninvasive measure of myoelectric activity

Abbreviations: AS-ATN, autism speaks autism treatment network; ASD, autism spectrum disorder; ASD-GIRBI, ASD Gastrointestinal and Related Behaviors Inventory; EMR, electronic medical record; GI, gastrointestinal; IDD, Intellectual disability; MV, minimally verbal; NDD, neurodevelopmental disorder.

with seven domains.[29] GIRBI has high reliability, strong convergent validity, and high sensitivity in predicting parent-report GI diagnoses, though the specificity was low.

We identified multiple themes from the clinician/researcher sessions:

1. Improved clinical diagnostic methods are needed to help accurately diagnose GI disorders in those with NDDs and ASD. This includes both adapted or new diagnostic measures (e.g., the Rome IV criteria) and less-invasive or adapted diagnostic modalities.
2. Improved research measures are also needed to enhance inclusivity in clinical trials and validate measures in the broader NDD patient community. These tools are especially needed to sensitively document improvement in response to new therapies. Newer tools such as the GIRBI show promise, and efforts to validate such tools across NDD/ASD communities are key.
3. Treating patients with NDDs requires substantial experience across multiple clinical domains. Enhanced educational efforts to properly prepare trainees to care for this complex patient population are direly needed, and access to multidisciplinary expertise for both trainees and patients is limited.

2.4 | Session 3—Discussion and identification of themes for future research

In the final session of the conference, we convened the study team, clinicians, and researchers, and reviewed both the survey data and perspectives provided by all speakers. We formulated a set of themes from families and clinicians/researchers, as well as a set of recommendations for next steps. Audio and video for all sessions were posted on the CANDID website (www.candidgi.com) with public access. Transcripts were automatically generated with the conference software and reviewed by the study team. Based on discussions as well as questions raised during the meeting, we identified both clinical and research recommendations.

3 | MOVING FORWARD

To effectively manage symptoms of GI disorders in people with ASD specifically and NDDs more broadly, there is a pressing need for evidence-based therapies[7] as well as education and awareness as early as medical school in helping to enable broader physician awareness of GI problems in children with NDDs.[10,11] For communities impacted by NDDs, a significant

benefit of a genetic diagnosis is building community with shared goals of managing symptoms and advocacy,[34,35] as well as understanding the potential mechanism by which these GI disorders exist. These advocacy and research efforts have resulted in regularly updated consensus guidelines for families and clinicians (e.g., for Rett syndrome),[36] improving clinical care for children who would otherwise be isolated. Because affected individuals can be nonspeaking or have trouble describing symptoms, caregiver-assisted observations that rely on signs rather than self-reporting have been developed and continue to be refined with input from the broad community,[15,28] including those with and without communication and cognitive challenges.[29]

In addition to providing access to clinical expertise across NDDs, stakeholders have the opportunity to support widespread testing and validation of diagnostic tools and outcome measures. Gastroenterologists, including pediatric and adult specialists, often have limited training in the diagnosis or treatment of patients with NDDs, and the exposure can be highly variable depending on the site of training. Additional opportunities for awareness in this community are desperately needed. CANDID has created a large network of patients, patient advocate leaders, medical experts, and scientists dedicated to this cause. It is the responsibility of these stakeholders to improve measurements until they can sensitively detect GI symptoms most important to families. This will involve funding, recruitment, communication, and advocacy with the Food and Drug Administration and other agencies to create meaningful change.

4 | RECOMMENDATIONS FOR RESEARCH AND CLINICAL PRACTICE

4.1 | Clinical recommendations

1. Families should have enhanced participation in the development of measures used to best describe their GI symptoms.
2. Adapted or de novo clinical diagnostic measures (e.g., a version of the Rome IV criteria for those with NDDs) are necessary to assist clinicians in treating patients with limited communication or cognitive impairment.
3. Additional shared decision-making should be used when deciding on the best diagnostic tools or treatment options, with a preference for less-invasive GI testing protocols. Clinicians should consider the tolerability of diagnostic testing for those with NDDs before ordering.
4. Enhanced parental supports (e.g., social stories, low sensory rooms, and video conference visits for follow-ups to alleviate stress in the office visit) should be implemented for patients with NDDs (see Table 1).
5. Gastroenterologists should consider early referral for genetic testing based on the American College of Medical Genetics' clinical guidance on genetic testing for those with NDDs, if not yet conducted.[37]
6. While gastroenterologists often have experience with NDDs broadly, those with rare genetic forms of an NDD may require greater awareness and support.[7,38]
7. The role of a gastroenterologist in this care is essential, and they should work in collaboration and close communication with the person's behavioral health provider(s) and consider discussion with the relevant rare disease foundation that may have access to clinicians with more specific expertise.

4.2 | Research recommendations

1. Additional basic science research is needed to better characterize the mechanism of GI symptoms in those with NDDs. For example, animal models of NDDs need to focus on the role of gene mutations in regions of the body other than the brain, such as the GI tract.
2. Translational research involving interventions on the GI system should include potential modifiers of response that may be easily measured in those with limited communication, such as inflammatory markers, objective measures of feeding and eating behavior, genetics, and metabolomics.
3. Adapted or de novo validated clinical measures are needed to serve as outcomes to perform effective clinical trials in patients with NDDs. This may also serve to enhance the participation of those with NDDs in clinical trials.
4. Additional outcomes should be measured in clinical trials of GI disorders in NDDs that assess the effects of treatment on family and caregiver well-being.

AFFILIATIONS

[1]Autism Science Foundation, New York, New York, USA

[2]Rutgers University, New Brunswick, New Jersey, USA

[3]Alliance for Genetic Etiologies in Neurodevelopmental Disorders, New York, New York, USA

[4]Division of Pediatric Gastroenterology, Hepatology, and Nutrition, Indiana University School of Medicine/Riley Hospital for Children, Indianapolis, Indiana, USA

[5]Department of Biology, University of Miami, Miami, Florida, USA

[6]International Foundation for CDKL5 Research, Wadsworth, Ohio, USA

[7]Center for Autism and Related Disorders, Kennedy Krieger Institute, Baltimore, Maryland, USA

[8]Department of Mental Health, Johns Hopkins Bloomberg School of Public Health, Baltimore, Maryland, USA

[9]NYU Pain Research Center, New York, New York, USA

[10]NYU College of Dentistry, New York, New York, USA

[11]NYU Grossman School of Medicine, New York, New York, USA

[12]USDA/ARS Children's Nutrition Research Center, Houston, Texas, USA

[13]Department of Pediatrics, Baylor College of Medicine, Houston, Texas, USA

[14]Neuroscience Center, Joe DiMaggio Children's Hospital, Hollywood, Florida, USA

[15]Stiles-Nicholson Brain Institute, Florida Atlantic University, Boca Raton, Florida, USA

[16]Departments of Health Psychology and Radiology, University of Missouri, Columbia, Missouri, USA

[17]Thompson Center for Autism and Neurodevelopment, Columbia, Missouri, USA

[18]Wake Forest University, Winston-Salem, North Carolina, USA

[19]Atrium Health, Charlotte, North Carolina, USA

[20]Phelan-McDermid Syndrome Foundation, Osprey, Florida, USA

[21]Nationwide Children's Hospital, Columbus, Ohio, USA

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CONFLICT OF INTEREST STATEMENT

The authors declare no conflict of interest.

ORCID

Alycia Halladay https://orcid.org/0000-0002-8264-8753

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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