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Detecting Celiac Disease in Patients With Down Syndrome

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The main purposes of this undertaking were to determine how often patients with Down syndrome (DS) are screened for celiac disease (CD) across five DS specialty clinics, which symptoms of CD are most often reported to DS specialty providers at these clinics, and, how many individuals were diagnosed with CD by these clinics. This was accomplished by following 663 individuals with DS for 1 year, across five clinics in different states specializing in the comprehensive care of people with DS. Of the 663 participants, 114 individuals were screened for CD at their visit to a DS specialty clinic. Protracted constipation (43.2%) and refractory behavioral problems (23.7%) were symptoms most often reported to DS specialty providers. During the 1 year study period, 13 patients screened positive for CD by serology. Of those, eight underwent duodenal biopsy, and three were diagnosed with CD. We conclude that CD is an important consideration in the comprehensive care of individuals with DS. However, while symptoms are common, diagnoses are infrequent in DS specialty clinics.

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Abbreviations: DS, Down syndrome; CD, celiac disease; AAP, American Academy of Pediatrics; DSMIG, Down Syndrome Medical Interest Group; tTG-IgA, anti-tissue transglutaminase IgA.

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INTRODUCTION

Down syndrome (DS) is associated with increased risk for celiac disease (CD), an immune-mediated gastrointestinal disorder characterized by inflammation of the small intestine on exposure to gluten, a protein found in wheat, barley, and rye [Walker and Murra, 2011; Ludvigsson et al., 2013]. Estimates for the prevalence of CD in individuals with DS have ranged between 3.2% in the United States and 16% in Sweden [Pueschel et al., 1999; Zachor et al., 2000; Book et al., 2001; Mackey et al., 2001; Bonamico, 2005; Nisihara et al., 2005]. Within the general population in the United States, CD occurs in 17 of every 100,000 persons, or less than 1% [Ludvigsson et al., 2013]. Clinical vigilance must be high in patients with DS to screen for, diagnose, and treat CD, yet symptoms of CD overlap with the natural history of DS, making its detection and diagnosis difficult [Mackey et al., 2001; Chicoine and McGuire, 2010]. For example, DS is associated with developmental delays and disruptive behavioral problems, which may mask symptoms of CD, especially in young patients, those with limited expressive language skills, or adults encountering health problems related to early aging such as dementia.

Symptoms of CD include diarrhea, bloating, large bulky stools, fatigue, growth failure, abdominal discomfort, excess flatus, and irritability [Zachor et al., 2000; Carnicer et al., 2001; Hill et al., 2005; Rubio-Tapia et al., 2013]. Symptoms vary and overlap with other conditions, making diagnosis based on recent medical history and clinical exam uncertain without further testing [Mackey et al., 2001]. Generally accepted screening tools for CD include serum serology studies: anti-tissue transglutaminase antibody (tTG-IgA) and total IgA (IgA) [Zachor et al., 2000]. Both tTG-IgA and IgA are considered highly sensitive and specific for CD in the absence of concomitant IgA deficiency, which can skew tTG-IgA results toward false-negative [Zachor et al., 2000; Aberg and Olcén, 2009]. To confirm the diagnosis, patients with positive serologic markers should have a small bowel biopsy (gold standard). Recent guidelines put forward by the European Society for Pediatric Gastroenterology, Hepatology, and Nutrition (ESPGHAN) eliminated the need for a biopsy for a final diagnosis of CD in the presence of certain clinical characteristics: high serology tTTG-IgA titers (at least 10 times the upper limit of normal), positive anti-endomysial antibodies, and positive HLA-DQ2 and HLA-DQ8 haplotypes [Husby et al., 2012]. For the purposes of this study, we compared current clinical practice among our centers with the guidelines put forward by the American Academy of Pediatrics for patients with DS [Bull, 2011].

Since the 1990s, the Down Syndrome Medical Interest Group (DSMIG), a panel of multidisciplinary clinical experts on DS, recommended that children with DS be screened for CD between age 2 and 3 years [Cohen, 1999]. These recommendations were retired in 2011 when the American Academy of Pediatrics published new guidelines, recommending serologic screening for CD only in symptomatic children with DS at each preventative care visit, beginning at age 1 year for children on a diet containing gluten [Bull, 2011]. For adults with DS, experts recommend similar screening in symptomatic patients at each preventative care visit [Chicoine and McGuire, 2010]. Celiac disease can develop at any age, so people with DS who have new or recurrent symptoms may need repeat testing, even after a previous negative test. Refractory developmental or behavioral problems may justify screening for CD in this population, whether these symptoms are concurrent with other gastrointestinal symptoms or as stand-alone changes in recent medical history [Bull, 2011].

Using a multi-center research patient database, we collected clinical data about CD in individuals with DS. The primary aim of this study was to assess how often participating clinics screen for and diagnose CD. We further examined reported symptoms associated with a CD diagnosis in patients with DS.

MATERIALS AND METHODS

Patients

We enrolled patients with DS in the multi-center research patient database ("Patient Database") compiled by five centers providing subspecialty care to individuals with DS: Boston Children's Hospital (BCH), Children's Hospital of Pittsburgh (CHP), Duke University Medical Center (DUMC), Levine Children's Hospital at Carolinas Medical Center (LCH), and Massachusetts General Hospital (MGH). Each center has a dedicated DS program with 4–10 clinics per month. The participating centers are herein called "specialty clinics."

Approval was obtained from the institutional review board (IRB) at each hospital. IRB submission materials were shared among specialty clinics to ensure consistency and to expedite IRB review. Consent was obtained from participants or their legal guardian to review medical records and to enter data related to secondary medical conditions into our research database.

Inclusion criteria were (i) diagnosis of DS by clinical examination or karyotype and (ii) enrollment as a patient at one of the participating specialty clinics. Individuals with DS and their families were excluded only when they were unable to complete the intake form, even with assistance, or unable to provide needed information by interview.

Data Collection

Data were collected prospectively and longitudinally during the 12-month study period (July 1, 2012, to June 30, 2013), as part of a larger multi-center research patient database effort [Lavigne et al., 2015].

A primary outcome of this study was CD testing status. This outcome was determined by caregiver response. Caregiver reports were confirmed with prior medical records when possible. If records were not available, we accepted caregiver report as credible.

We investigated which symptoms of CD were most often reported by patients and caregivers prior to their clinic visit. This outcome was determined by caregiver response to questions such as "Has child ever had constipation (diarrhea, nausea, etc.) in the past 12 months?" These questions were either asked on a clinic's intake form or by the provider. During the clinic visit, all reported symptoms were reviewed by the provider and a thorough history was obtained to clarify the severity and presentation of each symptom to decide whether to proceed with celiac screening. For example, constipation was considered to be clinically significant only if it presented as protracted or chronic constipation.

We asked if celiac screening labs were ordered at the patient's visit to a DS specialty clinic and if new diagnoses were made. This outcome was determined by review of provider documentation.

During each visit to a DS specialty clinic, participants were clinically assessed for CD according to the AAP guidelines for children and expert-based consensus for adults. Symptoms assessed were protracted constipation, diarrhea, vomiting, nausea, stomach complaints, refractory behavioral issues, and autoimmune problems (the presence of a pre-existing autoimmune disorder led to heightened suspicion for celiac disease) [Lundin and Wijmenga, 2015]. We ensured that patients being considered for screening were on a diet containing gluten in order to be of clinical significance and in accordance with guidelines. Specialty clinics consistently ordered serologic tests, consisting of tTG-IgA and IgA antibodies, for all patients with DS golder than 1 year who had symptoms associated with celiac disease. Serologic testing was performed at each specialty clinic's local CLIA-approved laboratory, per institutional standard operating procedures. Abnormalities were identified per each hospital's standard references ranges for tTG-IgA and IgA antibodies. Patients who screened positive for CD were referred for a duodenal biopsy. Celic disease was confirmed by review of biopsy reports.

Statistical Analyses

We used descriptive statistics, primarily frequencies, to report demographic and clinical characteristics. We considered inclusion of inferential statistics such as significance testing or confidence intervals, and decided that the current registry sample could not reasonably be construed as a random sample drawn from a well-defined larger population. We chose to report descriptive statistics in the form of frequencies and percentages.

RESULTS

Demographics

The 663 participants (ages 36 days to 70 years) were mostly infant and toddlers, ages 0–5 years (56.1%). The majority of participants were male (53.5%) and white (84.1%), although our dataset included individuals from diverse backgrounds and Hispanic ethnicities. A portion of patients declined to indicate their race (7.6%) and ethnicity (7.6%) (Table I).

Previous Screening for CD

Prior to their first appointment in this study period, 292 (47.2%) of patients had already been screened for CD with serology at least once, although this was not systematically and consistently validated in each patient (Table II). More than one third of patients younger than 5 years were screened for CD. Among older age groups (>5 years), more than half of patients in each age category (school age, adolescent, and adult) had been tested for CD.

Screening Ordered by Specialty Clinics

During their visits to the specialty clinics, many patients reported symptoms consistent with CD including protracted constipation and refractory behavioral problems (Table III). Screening labs for CD were ordered by providers at our specialty clinics for 114 (17.3%) patients (Table II). For 160 patients >1 year of age who had at least one symptom for CD listed in the AAP guidelines for DS, specialty clinics ordered CD screens for 45 patients (28.1%). Screening labs were ordered for 17.8% of pediatric and young adult patients (ages 0–21), compared with 9.3% of adult patients (Table II). Children and young adults (ages 5–21) accounted for 28.1% screened for CD (Table II).

Patients who had positive tTG-IgA screens were more likely to have symptoms of protracted constipation (75.0%) and diarrhea (41.7%) than those who screened negative (Table IV).

New Diagnoses

Of the patients screened for CD in a specialty clinic, 13 had positive results. Eight patients pursued duodenal biopsies. The remaining five did not pursue the biopsies: four preferred to adopt a gluten-free diet (GFD), and one opted for repeat celiac screening, which was subsequently negative. Of those with biopsies, three were confirmed to have CD (Table II), or <1% of our total original sample of 663 patients. The three individuals were from different age groups. Assuming that the four patients who waived the biopsy and initiated a GFD all had true CD, the new detection rate would be 1%.

DISCUSSION

Across the five collaborating specialty clinics, CD was frequently considered as a possible diagnosis, especially when patients with DS were experiencing persistent gastrointestinal symptoms or otherwise refractory behavior problems. While the symptoms are common (30.7% of patients older than 1 year experienced one or more

TABLE I. Patient Demographics for the Multi-Center Down Syndrome Patient Database as of July 1, 2013, Overall and by Site

Characteristic	All sites	BCH	MGH	DUMC	CHP	LCH
All patients	663	258	108	9	215	73
Age						
<1 year	127 (19.5%)	50 (19.5%)	13 (12.0%)	1 (11.1%)	47 (23.2%)	16 (21.9%)
1 to <5 yrs	238 (36.6%)	125 (48.6%)	7 (6.5%)	3 (33.3%)	65 (32.0%)	38 (52.1%)
5 to <13 yrs	184 (28.3%)	66 (25.7%)	20 (18.5%)	4 (44.4%)	79 (38.9%)	15 (20.5%)
13 to <21 yrs	47 (7.2%)	16 (6.2%)	14 (13.0%)	1 (11.1%)	12 (5.9%)	4 (5.5%)
21+ yrs	54 (8.3%)	0 (0%)	54 (50.0%)	0 (0%)	0 (0%)	0 (0%)
Missing	13 (1.9%)[a]	1 (0.4%)[a]	0 (0%)[a]	0 (0%)[a]	12 (5.6%)[a]	0 (0%)[a]
Gender						
Female	308 (46.5%)	120 (46.5%)	57 (52.8%)	1 (11.1%)	97 (45.3%)	33 (45.2%)
Male	354 (53.5%)	138 (53.5%)	51 (47.2%)	8 (88.9%)	117 (54.7%)	40 (54.8%)
Missing	1 (0.2%)[a]	0 (0%)[a]	0 (0%)[a]	0 (0%)[a]	1 (0.5%)[a]	0 (0%)[a]
Race						
White	517 (84.1%)	190 (80.9%)	86 (86.0%)	8 (88.9%)	189 (90.0%)	44 (72.1%)
Black/African American	37 (6.0%)	15 (6.4%)	3 (3.0%)	1 (11.1%)	9 (4.3%)	9 (14.8%)
Asian	5 (0.8%)	4 (1.7%)	0 (0%)	0 (0%)	1 (0.5%)	0 (0%)
Am Indian/Alaska native	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Hawaiian/Pac Islander	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Multiracial	25 (4.1%)	9 (3.8%)	3 (3.0%)	0 (0%)	8 (3.8%)	5 (8.2%)
Other race	16 (2.6%)	11 (4.7%)	4 (4.0%)	0 (0%)	0 (0%)	1 (1.6%)
Unknown/missing	15 (2.4%)	6 (2.6%)	4 (4.0%)	0 (0%)	3 (1.4%)	2 (3.3%)
Decline to participate	48 (7.6%)[a]	23 (8.9%)[a]	8 (7.4%)[a]	0 (0%)[a]	5 (2.3%)[a]	12 (16.4%)[a]
Ethnicity						
Hispanic/Latino	63 (10.2%)	33 (14.0%)	12 (12.0%)	2 (22.2%)	8 (3.9%)	8 (13.1%)
Not Hispanic/Latino	497 (75.7%)	178 (76.0%)	76 (76.0%)	7 (77.8%)	190 (91.8%)	46 (75.4%)
Unknown/missing	55 (8.9%)	24 (10.2%)	12 (12.0%)	0 (0%)	12 (5.7%)	7 (11.5%)
Decline to participate	48 (7.6%)[a]	23 (8.9%)[a]	8 (7.4%)[a]	0 (0%)[a]	5 (2.3%)[a]	12 (16.4%)[a]

BCH, Boston Children's Hospital; MGH, Massachusetts General Hospital; DUMC, Duke University Medical Center; CHP, Children's Hospital of Pittsburgh; LCH, Levine Children's Hospital at Carolinas Healthcare System.
Missing, respondent agreed to complete the demographic survey, but left a response unanswered; unknown, respondent agreed to complete the demographic survey, but selected "unknown" as a response; decline to participate, respondent declined to complete the optional demographic survey.
[a]Percentage of all patients.

symptoms) few new diagnoses were made (<1%). The fact that fewer cases were identified through specialty clinics may be the result of other health care practitioners (primary care providers or other specialty providers) identifying cases before they are seen at the clinics. This is suggested by the portion of our patients (292) who reported screening for CD prior to presenting at the specialty clinic. We are limited by not knowing how many of those screened already carried a diagnosis of CD.

Symptoms of constipation and diarrhea were more often associated with positive screens than negative. Since our data came from a clinic-based registry, and not a population-based one, further studies are necessary to determine if this trend is statistically significant, as well as to further determine whether or not there are symptom constellations that are particularly predictive for celiac disease. While approximately one third of patients from our referred sample sent for a biopsy received a positive result, due to the low overall numbers, definitive conclusions cannot be derived from this report alone.

These data raise the challenge of when physicians should screen for CD in patients with DS. Limited research has been conducted to answer this question. In 2000, a group of researchers assessed the accuracy and cost-effectiveness of current screening methods in the Netherlands. They proposed a new screening strategy including genetic testing of all individuals with DS to identify those 70% who may be excluded from future serologic CD screening based on HLA-DQ typing [Csizmadia et al., 2000]. Csizmadia et al. [2000] estimated that $44,820 could be saved per birth cohort of Dutch children with DS using their proposed screening protocol. In 2006, Swigonski et al. argued against universal screening for CD in asymptomatic children with DS, citing that a universal screening strategy "costs more than $500,000 per life-year gained" and "costs almost $5 million to prevent a single case of lymphoma" [Swigonski et al., 2006; Kawatu and LeLeiko, 2006]. The American Academy of Pediatrics guidelines currently recommend that tTG-IgA and total IgA screening be completed at each preventative care visit for symptomatic patients with DS, beginning at age 1 year in those on a gluten-containing diet [Bull, 2011]. Other guidelines, such as those put forth by the North American Society of Pediatric Gastroenterology, Hepatology, and Nutrition (NASPGHAN), recommend initial screening with tTG-IgA in asymptomatic children with Down syndrome beginning at age 3 provided that they had an adequate gluten-containing diet for a minimum of 1 year prior to

TABLE II. Celiac Screening and Diagnosis at Down Syndrome Specialty Clinics

Characteristic	tTG-IgA ever tested before?	tTG-IgA ordered at first visit to DS clinic?	Of tTG-IgA ordered in DS clinic, % positive	Of positive tTG-IgA results, % biopsy performed	Of biopsies performed, % positive
All patients	292/619 (47.2%)	114/660 (17.3%)	13/108 (12.0%)	8/13 (61.5%)	3/8 (37.5%)
Missing	43/662 (6.5% of total)[a]	2/662 (0.3% of total)	6/114 (5.3% of total)[b]		
Age					
<1 year	2/119 (1.7%)	2/126 (1.6%)	0/2 (0.0%)	0/0	0/0
1 to <5 yrs	81/227 (35.7%)	39/237 (16.5%)	1/37 (2.7%)	1/1 (100.0%)	1/1 (100.0%)
5 to <13 yrs	138/177 (78.0%)	49/184 (26.6%)	4/48 (8.3%)	3/4 (75.0%)	1/3 (33.3%)
13 to <21 yrs	39/46 (84.8%)	16/47 (34.0%)	4/14 (28.6%)	2/4 (50.0%)	0/2 (0.0%)
21+ yrs	24/38 (63.2%)	5/54 (9.3%)	4/5 (80.0%)	2/4 (50.0%)	1/2 (50.0%)
Gender					
Female	121/286 (42.3%)	49/306 (16.0%)	7/46 (15.2%)	3/7 (42.9%)	1/3 (33.3%)
Male	170/332 (51.2%)	64/353 (18.1%)	6/61 (9.8%)	5/6 (83.3%)	2/5 (40.0%)
Race					
White	244/481 (50.7%)	92/515 (17.9%)	9/88 (10.2%)	5/9 (55.6%)	3/5 (60.0%)
Black/African American	13/35 (37.1%)	5/36 (13.9%)	0/4 (0.0%)	0/0	0/0
Asian	3/5 (60.0%)	0/5 (0.0%)	0/0	0/0	0/0
American Indian/ Alaskan	0/0	0/0	0/0	0/0	0/0
Native Hawaiian/Pac Islander	0/0	0/0	0/0	0/0	0/0
Other race	4/16 (25.0%)	3/16 (18.8%)	2/3 (66.7%)	2/2 (100.0%)	0/2 (0.0%)
Unknown	0/1 (0.0%)	1/1 (100.0%)	1/1 (100.0%)	0/1 (0.0%)	0/0
Missing	4/14 (28.6%)	1/14 (7.1%)	0/1 (0.0%)	0/0	0/0
Multiracial	9/25 (36.0%)	5/25 (20.0%)	1/4 (25.0%)	1/1 (100.0%)	0/1 (0.0%)
Ethnicity					
Spanish/Hispanic/ Latino	24/61 (39.3%)	11/64 (17.2%)	1/11 (9.1%)	1/1 (100.0%)	0/1 (0.0%)
Not Spanish/ Hispanic/Latino	228/470 (48.5%)	89/497 (17.9%)	9/83 (10.8%)	5/9 (55.6%)	3/5 (60.0%)
Unknown	8/13 (61.5%)	4/13 (30.8%)	2/4 (50.0%)	1/2 (50.0%)	0/1 (0.0%)
Missing	32/75 (42.7%)	10/86 (11.6%)	1/10 (10.0%)	1/1 (100.0%)	0/1 (0.0%)

Missing, respondent agreed to complete the demographic survey, but left a response unanswered; unknown, respondent agreed to complete the demographic survey, but selected "unknown" as a response.
[a]Table I reports 663 total participants. One participant was lost to follow up; therefore, 662 are represented here.
[b]Six participants did not pursue tTG-IgA after it was ordered because they could not tolerate the blood draw at our clinics and/or they chose to have tTG-IgA drawn with a local provider.

TABLE III. Symptoms Reported by Patients and Their Caregivers at DS Specialty Care Visits

Characteristic	Constipation	Diarrhea	Vomiting	Nausea	Stomach complaints	Behavior problems	Autoimmune disorder(s)
All patients	257/595 (43.2%)	93/592 (15.7%)	76/596 (12.8%)	24/581 (4.1%)	63/571 (11.0%)	141/595 (23.7%)	13/574 (2.3%)
Age							
<1 year	40/112 (35.7%)	4/108 (3.7%)	15/110 (13.6%)	3/107 (2.8%)	9/105 (8.6%)	1/110 (0.9%)	0/106 (0.0%)
1–5 yrs	107/221 (48.4%)	43/222 (19.4%)	27/223 (12.1%)	6/214 (2.8%)	13/209 (6.2%)	44/224 (19.6%)	1/211 (0.5%)
5–13 yrs	82/177 (46.3%)	33/177 (18.6%)	26/177 (14.7%)	9/174 (5.2%)	28/172 (16.3%)	72/176 (40.9%)	11/171 (6.4%)
13–21 yrs	15/42 (35.7%)	7/42 (16.7%)	4/42 (9.5%)	4/42 (9.5%)	7/42 (16.7%)	13/41 (31.7%)	1/41 (2.4%)
21+ yrs	7/32 (21.9%)	6/31 (19.4%)	1/32 (3.1%)	2/32 (6.2%)	6/32 (18.8%)	10/32 (31.2%)	0/33 (0.0%)
Gender							
Female	115/272 (42.3%)	42/270 (15.6%)	33/273 (12.1%)	12/267 (4.5%)	31/264 (11.7%)	58/275 (21.1%)	4/262 (1.5%)
Male	141/322 (43.8%)	51/321 (15.9%)	43/322 (13.4%)	12/313 (3.8%)	32/306 (10.5%)	82/319 (25.7%)	9/311 (2.9%)
Race							
White	207/474 (43.7%)	75/469 (16.0%)	60/473 (12.7%)	17/460 (3.7%)	50/453 (11.0%)	113/474 (23.8%)	12/460 (2.6%)
Black/African American	7/31 (22.6%)	6/31 (19.4%)	5/31 (16.1%)	3/31 (9.7%)	3/31 (9.7%)	9/30 (30.0%)	0/28 (0.0%)
Asian	1/3 (33.3%)	1/4 (25.0%)	1/4 (25.0%)	0/3 (0.0%)	0/3 (0.0%)	0/5 (0.0%)	0/5 (0.0%)
Am Indian/Alaska native	0/0	0/0	0/0	0/0	0/0	0/0	0/0
Hawaiian/Pac Islander	0/0	0/0	0/0	0/0	0/0	0/0	0/0
Other race	9/15 (60.0%)	2/15 (13.3%)	2/15 (13.3%)	1/15 (6.7%)	1/15 (6.7%)	5/15 (33.3%)	0/14 (0.0%)
Multiracial	7/23 (30.4%)	4/23 (17.4%)	3/23 (13.0%)	0/23 (0.0%)	2/22 (9.1%)	5/23 (21.7%)	1/21 (4.8%)
Unknown/missing	5/12 (41.7%)	2/13 (15.4%)	0/13 (0.0%)	1/13 (7.7%)	2/13 (15.4%)	1/14 (7.1%)	0/13 (0.0%)
Ethnicity							
Hispanic/Latino	27/57 (47.4%)	7/57 (12.3%)	9/57 (15.8%)	5/55 (9.1%)	7/55 (12.7%)	13/58 (22.4%)	1/55 (1.8%)
Not Hispanic/Latino	191/457 (41.8%)	76/454 (16.7%)	57/456 (12.5%)	13/446 (2.9%)	47/439 (10.7%)	101/460 (22.0%)	12/444 (2.7%)
Unknown	4/10 (40.0%)	2/10 (20.0%)	2/11 (18.2%)	1/10 (10.0%)	1/10 (10.0%)	2/11 (18.2%)	0/8 (0.0%)
Missing	35/71 (49.3%)	8/71 (11.3%)	8/72 (11.1%)	5/70 (7.1%)	8/67 (11.9%)	25/66 (37.9%)	0/67 (0.0%)

TABLE IV. Patient/Caregiver-Reported Symptoms/Complaints Compared With Result of Serologic Screening for Celiac Disease

Symptom/complaint	"Positive result"[a] (%)	"Negative result" (%)
Constipation	9/12 (75.0)	47/93 (50.5)
Diarrhea	5/12 (41.7)	22/93 (23.7)
New behavioral issues	4/12 (33.3)	30/94 (31.9)
Nausea	1/12 (8.3)	5/92 (5.4)
Vomited	1/12 (8.3)	12/93 (12.9)
Autoimmune problems	1/12 (8.3)	5/93 (5.4)
Stomach complaints	0/12 (0.0)	18/90 (20.2)

[a]One patient's family did not complete intake forms and, therefore, symptom/complaint data due to language barrier. Above data represent 12 of 13 patients (Table II) with a positive screening result.

testing [Hill et al., 2005]. For both sets of guidelines, a confirmatory biopsy is required. Guidelines developed by the ESPGHAN recommend that serology screening include an anti-endomysial serology and HLA DQ2/DQ8 testing, and may not require a biopsy [Husby et al., 2012]. An evaluation of the ESPGHAN celiac guidelines in a North American pediatric population suggest that the ESPGHAN guidelines may be applied providing clinicians understand the performance of their celiac serology tests [Gidrewicz et al., 2015]. In adhering to AAP screening guidelines, celiac disease was confirmed in <1% of patients over a 12-month period, suggesting that application of the AAP guidelines leads to rare changes in clinical management.

Our physicians screened only 28.1% of patients who were at least 1 year of age and who reported at least one CD symptom. This could suggest that participating physicians made an active clinical judgment that CD screening was not necessary. Sometimes caregiver-reported symptoms on clinical intake forms change or resolve by the clinical visit. Clinicians might have chosen to focus on more pressing clinical needs, saving the discussion of CD screening for a subsequent visit. For example, the clinician might choose to exclude significant constipation by a radiograph or to make dietary changes to address diarrhea before screening for CD. Another possibility is that participating clinicians might not consistently apply the AAP guidelines. Our results represent the most conservative percentage of CD in our study population.

Further research is needed to guide CD screening among individuals with DS. Cost-effectiveness analyses should be undertaken to assess lifetime savings of CD screening, including costs avoided, such as the costs of medical consultations, blood draws, and hospitalizations for undiagnosed gastrointestinal symptoms.

One strength of our present study is its scale: these data include people with DS of all ages, with robust representation from the pediatric population, laying the groundwork for future longitudinal data collection. The age distribution of patients included in the patient database is consistent with the expected populations at our specialty clinics. Four clinics (BCH, CHP, DUMC, and LCH) see pediatric patients exclusively, and one clinic (MGH) sees patients of all ages. Our study reports novel prospective data about CD in adults with DS, a group that is historically under-studied. Longitudinal records of older individuals with DS are challenging to access due to variable caregiver arrangements; adults with DS often live with family members or in group living environments with support staff. The multi-center research patient database plans to expand over the coming years to include more of the 58 DS specialty clinics in 32 U.S. states.

Our study is also limited by variations between providers. Providers sometimes ordered tTG-IgA without total IgA. Total IgA is an important indicator for false-negative results on tTG-IgA, as outlined by the AAP healthcare guidelines for DS [Bull, 2011]. The NASPGHN guidelines recommend quantitative serum IgA when interpreting a low tTG-IgA, in the presence of symptoms suggestive of CD. The NASPGHN guidelines recommend testing for children with nongastrointestinal symptoms suggestive of CD (such as dermatitis herpetiformis, delayed puberty, short stature, failure to thrive), whereas our study did not consistently take these symptoms into account when considering testing (although behavioral manifestations were taken into consideration) [Hill et al., 2005]. While our clinics' providers might have ordered celiac screening for these purposes, they were not coded into our databases.

Our study is limited by recall bias. We most often collected patients' symptoms on our clinics' intake forms, completed up to a few months prior to the clinical visits. Some parents/caregivers might have listed symptoms that were no longer relevant at the time of the clinical visit. Others might not have mentioned symptoms that emerged since the intake was completed. If the healthcare provider did not probe these possibilities, an over-reporting or under-reporting of symptoms might have occurred. For the group ultimately diagnosed with CD, patients/caregivers were aware of their symptoms and communicated the possible symptoms of CD to their specialty providers.

Our study is limited by selection bias. Our DS specialty clinics primarily serve a referred population—often, patients who have been screened by primary care providers and judged to have complex medical needs or patients whose parents or caregivers are motivated to seek subspecialty care. Our patient population most likely does not represent patients who are either relatively well or who have limited access to preventative healthcare and specialty care. Our data should not be considered population-based. While our patient database represents populations from rural areas of North Carolina to urban populations in and around Boston, a population-based sample of individuals with DS would include patients from a wider geographical distribution. Patients from most racial groups were recruited to participate in our patient database; however, non-White patients were the minority. There are no population-based data available on the race and ethnicities of patients with DS in the areas served by our clinics to determine how representative our sample was.

To answer questions about prevalence of CD in patients with DS, a population-based registry is needed. DSConnect™, an online database spearheaded by the NIH, offers a secure location where people with DS and their families may enter health history and medical information. DSConnect™ provides authorized clinicians and researchers a connection to families interested in research

opportunities. DSConnect™ differs from our patient database in that our data is provider-entered, rather than patient-entered. Ideally, the patient database would be linked with DSConnect™ and a national DS biobank using a Global Unique Identification (GUID), allowing a powerful comparison of data entered by people with DS and their families to data entered by clinical providers.

Celiac disease is an important consideration in the comprehensive care of individuals with DS. While symptoms are common, diagnoses are rare in Down syndrome specialty clinics. Ultimately, more research is needed to answer key questions: which patient-reported symptoms in this population have predictive value for diagnosing CD, and at which ages? Is there a more cost-effective way to screen for CD in patients with DS without sacrificing detection rates?

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