Variable Use of Disaccharidase Assays When Evaluating Abdominal Pain

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Abstract: ***Background and Aims:*** Patients with a disaccharidase deficiency typically present with abdominal discomfort and often with diarrhea. However, disaccharidase deficiency is often overlooked as a cause of these complaints. Therefore, we sought to determine the prevalence of lactase and sucrase deficiencies in a pediatric population undergoing diagnostic esophagogastroduodenoscopy (EGD) and to describe disaccharidase testing practices among pediatric gastroenterologists. ***Methods:*** Endoscopic records from patients undergoing diagnostic EGD and disaccharidase analysis (DA) were retrospectively reviewed. Diagnostic EGDs performed over a 5-year period (2010 through 2014) at a free-standing endoscopy center serving 13 pediatric gastroenterologists were assessed. Demographic and clinical data on patients were collected and grouped; patients with primary sucrase-isomaltase deficiency (SID) were the main focus. The data were stratified by the physician performing the procedures. ***Results:*** Over the 5-year study period, 5368 EGDs were performed, with abdominal pain as the primary indication in 3235 cases (60.2%). DAs were performed on 963 patients (17.9% of the total cohort; 29.8% of those with abdominal pain). Lactase deficiencies, sucrase deficiencies, and primary SID were found in 44.7%, 7.6%, and 3.5% of DAs, respectively. The number of DAs performed varied widely among physicians, ranging from 1.6% to 64.5% of EGDs evaluating patients with abdominal pain. Univariate regression analysis revealed significant correlations between the number of DAs performed and the number of SID and lactase deficiencies found ($P < .001$ for both). ***Conclusion:*** Rates of DAs vary widely among pediatric gastroenterologists performing diagnostic EGDs in children with abdominal pain. Physician education and clinical practice guidelines regarding the use of DAs are warranted.

Keywords
Sucrase-isomaltase deficiency, disaccharidase deficiency, lactase deficiency, physician variability

Primary sucrase-isomaltase deficiency (SID) is an inherited disorder resulting in reduced activity of these intestinal disaccharidases. Affected individuals have a relative inability to hydrolyze sucrose, maltose, short 1→4-linked glucose oligomers, branched (1→6-linked) α-limit dextrins, and starch.[1] Originally,

Table 1. Clinical Traits of Patients With Primary Sucrase-Isomaltase Deficiency

Clinical Traits	Number of Patients (N=34)	Percentage
Female	23	68
White	27	79
Abdominal Pain	29	85
Diarrhea	18	53
Without Pain	4	12
Constipation	9	26
Nausea	13	38
Poor Weight Gain	10	29
Flatulence	3	9

primary SID was thought to be a rare, homozygous condition presenting in infancy; subsequent investigations have revealed different genotypic and phenotypic patterns. Currently, 37 genetic alleles resulting in 7 SID phenotypes have been characterized.[2] Sucrase-isomaltase variants can occur on either sucrase or isomaltase subunits, resulting in differing effects on sucrase-isomaltase enzyme activity.[3] SID can occur secondarily as well, similar to secondary lactase deficiency. These occur when intestinal microvilli are disrupted by an enteric infection or due to conditions that cause intestinal injury (eg, celiac disease, Crohn's disease, other enteropathies affecting the small intestine).[4,5] SID also appears to accompany esophageal and gastric disorders such as eosinophilic esophagitis, acid-peptic disease, and *Helicobacter pylori* infection, although these disorders are likely unrelated, coexisting conditions.[6,7]

Clinically apparent symptoms are generally non-specific but consistently occur in affected individuals and may include diarrhea, bloating, flatulence, and abdominal pain, similar to lactose intolerance.[7-9] When sucrose is included in the diet, fermentation of undigested sugars by the intestinal microflora produces methane, hydrogen, and carbon dioxide, which contribute to bloating and abdominal pain, and often acidic, watery, and hyper-osmolar diarrhea.[10]

Symptom severity depends on several factors that are both host- and environment-specific, such as residual enzyme activity, colonic flora, and the amount of ingested sucrose and starch. In the classic presentation of SID, symptoms occur in infants soon after the introduction of sucrose and other starches into their diet.[1] Logically, the functional variants in the sucrase-isomaltase gene have been shown to extend into adulthood, typically presenting as irritable bowel syndrome (IBS).[11-13]

Methods for diagnosing SID include ^{13}C-sucrose breath tests,[14] sucrose hydrogen breath tests (HBTs), genetic tests,[2,11,15] or a trial of oral sucrase (sacrosidase; Sucraid, QOL Medical, LLC) therapy[16,17]; however, the gold standard for the diagnosis of SID remains procuring small intestinal biopsy specimens and performing a disaccharidase analysis (DA) along with routine duodenal histology.[5] The analysis measures the glucose released after incubating the tissue samples with the various disaccharides (ie, lactose, sucrose, maltose, and isomaltose, also called palatinose), indicating the enzymatic activity level. However, DA does not indicate which enzyme is hydrolyzing the substrate.[18]

Recent work suggests that lactase and sucrase deficiencies are more prevalent than previously thought[4,11,13,19]; thus, a retrospective study was conducted to determine the prevalence of disaccharidase deficiencies in a pediatric population undergoing diagnostic esophagogastroduodenoscopy (EGD) at a single center.[6] This article describes the varying disaccharidase testing practices among the pediatric gastroenterologists at that center.

Materials and Methods

Electronic endoscopic records (ProVation Medical) from patients undergoing diagnostic EGDs and biopsies for a variety of esophageal, gastric, and intestinal disorders were reviewed, including an assessment of DA procurement over a 5-year period (2010 through 2014) at a free-standing endoscopy center (GI Care for Kids Endoscopy) serving 13 pediatric gastroenterologists (Children's Center for Digestive Health Care, LLC). Biopsy-obtained tissue specimens from the distal duodenum were immediately frozen in the endoscopy center (-10° Fahrenheit to -20° Fahrenheit, with weekday monitoring), then collected and shipped overnight midweek on dry ice to ensure proper processing for DA (JOLI Diagnostic). The DAs were conducted by employing the modified Dahlqvist method[18] to determine enzyme activity. This method consists of measuring the quantity of glucose released over time per gram of tissue after incubation with the appropriate substrates. Glucoamylase assay was not available and, therefore, was not used.

The overall histopathologic diagnoses, including those involving the intestinal biopsies, were paired with the results of the DAs. Symptoms, clinical diagnosis, histologic impressions, treatment, and demographic variables were also obtained from patients found to have sucrase activity less than 25 µmol/min/g (Table 1). To understand the reasons for physician variability in obtaining DAs, treating physicians completed a questionnaire to determine their years of clinical practice, previous

Table 2. Physician Questionnaire

Initials ____
Years in practice ____
When you were trained, were disaccharidase biopsies commonly obtained when performing esophagogastroduodenoscopies? Yes No
What were your indication(s) for obtaining disaccharidase biopsies? Unexplained abdominal pain ____ Diarrhea ____ Only when both are present ____ Bloating ____ Flatulence ____ Not sure ____ Don't obtain ____ Other _____
What is your preferred method for diagnosing lactose intolerance? Breath test ____ Disaccharidase biopsy____ Stool-reducing sugar ____ Clinical history ____
What is your preferred method for diagnosing sucrose intolerance? Breath test ____ Disaccharidase biopsy ____ Stool-reducing sugar ____ Clinical history ____
Lactose intolerance is one of the most common conditions worldwide: Yes No
Begins at approximately age (years) ____
Sucrose intolerance is one of the most common conditions worldwide: Yes No
Begins at approximately age (years) ____
Can sucrose intolerance produce irritable bowel syndrome symptoms? Yes No
Is pandisaccharidase deficiency common? Yes No
Is pandisaccharidase deficiency merely the result of poorly prepped specimens? Yes No
What is the treatment for lactose intolerance? Lactose-free diet ____ Lactose-limited diet + lactase ____ Regular diet + lactase ____ Regular diet + probiotic ____
What is the treatment for sucrose intolerance? Sucrose-free diet ____ Sucrose- and starch-free diet ____ Sucrose-limited diet + sacrosidase ____ Regular diet + sacrosidase ____ Regular diet + probiotic ____

training, attitude toward the clinical entity of disaccharidase deficiency, and the methods utilized for diagnosing the conditions (Table 2).

Statistical analysis was conducted using statistical analysis software (Minitab 17 Statistical Software version 17.2.1, Minitab Inc). Descriptive procedures for continuous linear variables were fitted line plot and graphical summary statistics. Inferential regression procedures for continuous linear variables were univariate regression analysis and 1-way analysis of variance. Procedures for categoric data included descriptive statistics and chi-square tests for association. The criterion for further follow-up analysis of inferential analyses was an alpha less than 0.05%. Actual probability estimates are reported for statistically significant inferential analyses.

This study was conducted as approved by the Institutional Review Board (IRB) at Children's Healthcare of Atlanta (IRB #14-195).

Results

Among 5368 completed EGDs, DA was performed on 963 children (17.9%), with 646 patients (12.0%) undergoing complete enzyme analysis and 317 (5.9%) undergoing analyses for just lactase and sucrase. The primary indications for EGD were abdominal pain (n=3344; 62%) and diarrhea (n=529; 10%); however, the medical records software recognized patients with both symptoms independently, and some patients may have been counted in each group. Analysis was not performed on the total patient population to determine if individual patients had multiple procedures (which is likely among the 2024 patients who did not have pain as a primary indication, as repeat EGDs are often needed in patients with eosinophilic esophagitis). None of the patients with SID had repeat procedures.

Lactase deficiency, defined as enzyme activity less than 15 µmol/min/g, was observed in 430 patients (44.7% of the DA cohort; 8.0% of the total cohort). SID was observed in 73 patients (7.6% of the DA cohort; 1.3% of the total cohort). The presenting symptoms were abdominal pain (78%) and/or diarrhea (43%), followed by constipation, nausea, vomiting, weight loss or failure to thrive, flatulence, and bloating. Sucrase deficiency without lactase deficiency occurred in only 4 patients (5.6% of the DA cohort; 0.07% of the total cohort). When all of the disaccharidases were analyzed, pandisaccharidase deficiency (as determined by a reduction in all enzyme activity) was observed in 51 of 54 patients (94.4%) when sucrase was deficient.[6]

Thirty-nine patients with abnormal sucrase levels had normal duodenal histology; however, 2 patients had celiac disease with normal histology at the time of biopsy and 3

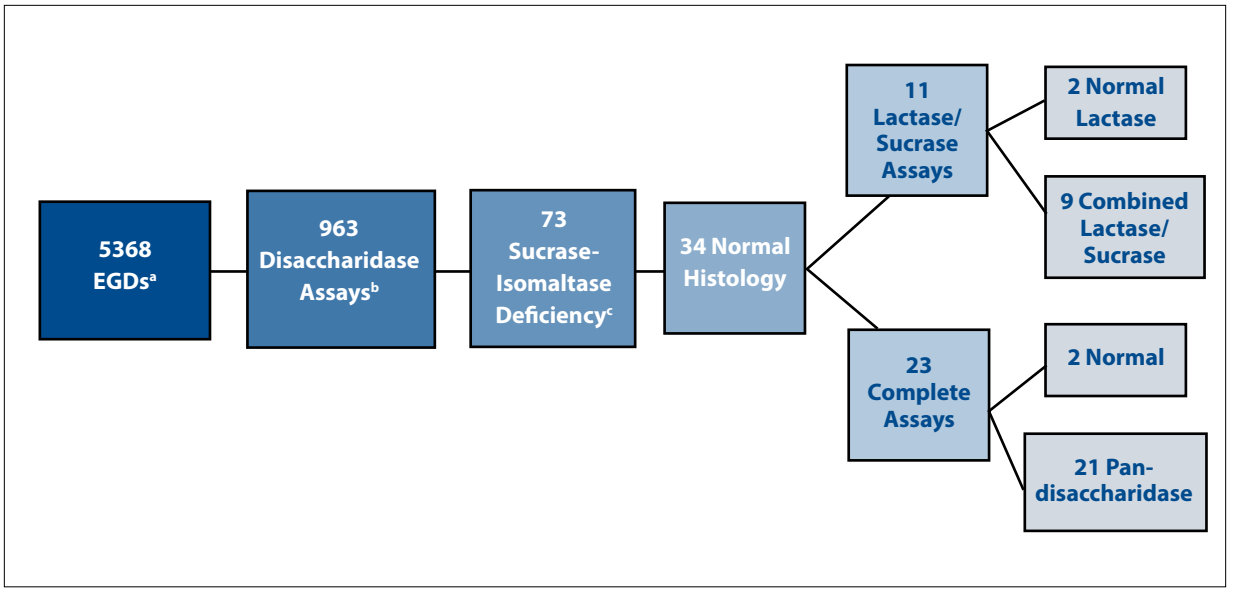

Figure 1. A breakdown of the cohort of pediatric patients with sucrase and pandisaccharidase deficiencies with normal histology who underwent esophagogastroduodenoscopies (EGDs) at a single center.

[a]Abdominal pain was the primary symptom in 3344 patients, and diarrhea with or without abdominal pain was the primary symptom in 529 patients.

[b]Of the 963 disaccharidase assays, lactase deficiency was observed in 430 (44.7%).

[c]Thirty-four of the sucrase-deficient disaccharidase assays displayed abnormal histology.

Adapted from Cohen SA, Oloyede H, Gold BD, Mohammed A, Elser H. Clinical characteristics of disaccharidase deficiencies among children undergoing upper endoscopy. *J Pediatr Gastroenterol Nutr*. In press.

had distal Crohn's disease. These 5 patients were excluded from analysis in order to have a clearer understanding of primary SID (Figure 1). The clinical characteristics of the 34 included patients are shown in Table 1. The other patients with sucrase deficiency had abnormal duodenal histology; 32 had inflammation described as acute (n=10) or chronic (n=5), 20 had diminished villous height, 9 had crypt hyperplasia, and 1 had eosinophils.

Among the physicians who performed a diagnostic EGD in patients with abdominal pain, the number of DAs performed varied widely among physicians, ranging from 1.6% to 64.5% (Table 3). When stratified by the physician performing the procedures for evaluation of abdominal pain, there was no relationship between EGDs performed and primary SID found (r=58.8%; R^2=34.6%; Figure 2A). However, regression analysis revealed a much closer relationship between the DA performed and the number of patients with lactase deficiencies and primary SID (r=90.4%; R^2=81.8%; Figure 2B). Regression analysis demonstrated similar relationships between DA and both sucrase and lactase deficiencies (r=90.1%; R^2=89.2% and r=99.5%; R^2=99.4%, respectively).

Diagnosis as noted at the visit following the procedure and treatment was as varied as DA obtainment. Of the 34 patients diagnosed with SID, 4 patients (4.6 ± 6.1 years old) had normal lactase. The 4 patients were all diagnosed with sucrose intolerance and placed on a sucrose-free diet, which included sacrosidase enzyme replacement. (Two of the patients on the enzyme replacement improved; the others did not, although dietary compliance was not noted.) Among the remaining 30 patients (13.8 ± 4.8 years old), 6 were diagnosed with lactose intolerance. Two were placed on a lactose-free diet alone, 2 were placed on a lactose-free diet plus a proton pump inhibitor, 1 was placed on a lactose-free diet with senna, and 1 was given metronidazole alone; all patients responded. Generalized disaccharidase deficiency was diagnosed in 9 patients. Three patients were placed on a proton pump inhibitor (1 with a gluten-free diet; improvement was seen in this patient as well as another). Four patients were placed on a lactose-free diet (2 received combined treatment with a proton pump inhibitor); 2 responded (including 1 on the combination treatment), and 1 was lost to follow-up. One patient was placed on a combined sucrose- and lactose-free diet, and another patient was placed on a fruit-free diet; both improved. Of note, IBS was diagnosed in 1 of the patients, who was then placed on nitazoxanide without improvement.

Table 3. Disaccharidase Test Results Among Patients With Abdominal Pain

		DA			LD	
Treating Physician	**EGDs**	**N**	**%**	**Primary SID, N**	**N**	**% EGDs**
1	148	72	48.6	2	37	25.0
2	645	419	64.5	11	149	23.1
3	557	9	1.6	0	4	0.7
4	164	14	8.5	0	3	1.8
5	212	8	3.8	0	3	1.4
6	205	106	51.7	4	39	19.0
7	203	43	21.2	2	16	7.8
8	181	8	4.4	0	2	1.1
9	27	4	14.8	0	3	11.1
10	449	97	21.6	7	46	10.2
11	92	22	23.9	1	12	13.0
12	213	134	62.9	7	57	26.8
13	248	27	10.9	0	9	3.6
Total	**3344**	**963**	**29.8**	**34 (3.5% DA)**	**430**	**12.9 (44.7 DA)**

DA, disaccharidase analysis; EGD, esophagogastroduodenoscopy; LD, lactase deficiency; SID, sucrase-isomaltase deficiency.

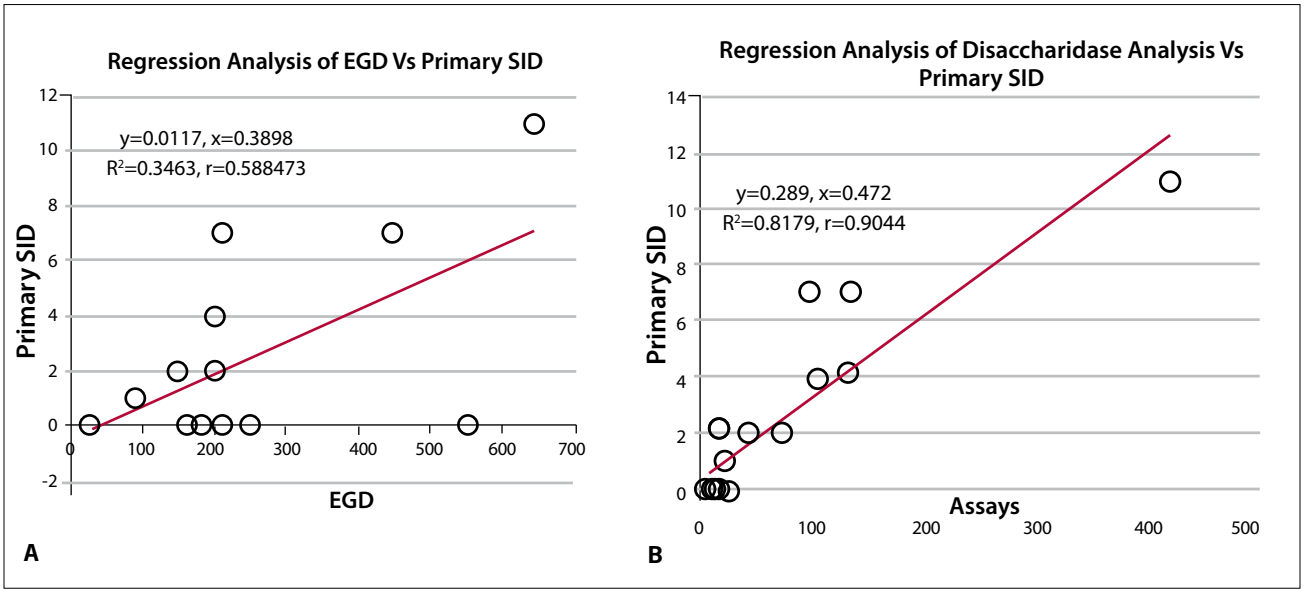

Figure 2. Regression analysis of EGDs (**A**) and disaccharidase analyses (**B**) vs findings of sucrase deficiency and normal histology (primary SID). There was a close relationship between the number of disaccharidase analyses obtained per physician and the diagnosis of primary SID.

EGD, esophagogastroduodenoscopy; SID, sucrase-isomaltase deficiency.

Discussion

Lactase deficiency has been reported in the majority of the world population, with estimates higher than 90% in some Asian and African countries.[16] In contrast, the prevalence of primary SID has been reported to range from 5% to 10% among Greenland Eskimos to as low as 0.05% to 0.2% among white Europeans.[1] However, recent evidence indicates that the prevalence of symptomatic, heterozygous carriers may be as high as 2% to 9% among Americans of European descent, suggesting that sucrase deficiency may be greatly underreported.[17] A 2016 report suggests that a single mutation, p.Val15Phe, reduced disaccharidase activity by 35% and increased the risk of IBS in case-control and population-based cohorts (*P*=.00012; odds ratio, 1.36).[11]

A retrospective review of 27,875 sucrase, maltase, and palatinase assays used on biopsy samples submitted to a reference laboratory for analysis showed that lactase deficiency occurred in 32% (n=8963), and pandisaccharidase deficiency occurred in 8% (n=2347).[15] Among patients who were sucrase- and maltase-deficient (9.3%), most (86.0%) had pandisaccharidase deficiency.

These findings are similar to the results of the current study, in which 7.6% of DA-tested patients were sucrase-deficient and 34 patients had primary SID (3.5% of the DA cohort). Our study focused on SID with normal histology rather than the totality of primary and secondary sucrase deficiency in order to gain more knowledge about the clinical features of the primary condition. The total lactase-deficient population (ie, patients with adult hypolactasia and secondary lactose intolerance) was included in order to compare with previous studies and provide a broader perspective of widely recognized disaccharidase deficiencies. Although patients with diarrhea might represent a SID-enriched population, making it tempting to conjecture that there would be a greater prevalence of SID among those with diarrhea (there being 6 times as many patients with pain compared to diarrhea), it is important to note that only 4 of the patients with SID had diarrhea without pain and 9 had constipation. Additionally, in an IBS-focused study,[11] a single SID genetic variant was seen with greater frequency along with a mixed-IBS stooling pattern compared to patients who had diarrhea-predominant IBS.

In addition to bringing attention to our finding that disaccharidase deficiencies may be missed or underreported, the present study also revealed substantial variation among pediatric gastroenterologists with respect to the use of intestinal DA as a diagnostic aid. Not surprisingly, physicians who obtained DA more frequently diagnosed a greater number of patients with SID and lactase deficiencies. This can be seen most dramatically by comparing the results for Physicians 5 and 12 in Table 3. Over the 5-year study period, the 2 physicians performed an almost identical number of EGDs for abdominal pain evaluation (212 vs 213, respectively), yet Physician 5 only obtained disaccharidase biopsies for DA 8 times (3.8% of the physician's EGDs for abdominal pain), finding 0 patients with primary SID and 3 with lactase deficiency. Physician 12 obtained 134 biopsies for DA (62.9% of EGDs for abdominal pain), finding 7 patients with primary SID and 57 with lactase deficiency. Similar discrepancies can also be seen between Physicians 3 and 10, who performed EGDs more frequently for evaluation of abdominal pain, with a marked disparity in the DAs obtained and disaccharidase deficiencies diagnosed.

The difference in diagnostic habits was explored post hoc by a survey distributed to the physicians (Table 2). The difference was not explained by previous training, practice duration, preference for HBT for lactose or sucrose intolerance (3/6 physicians who obtained the most DAs by percentage actually preferred HBT vs none of the bottom 6), recognition that SID may be associated with symptoms often linked to IBS, or emerging recognition of the frequency and variability of SID. Rather, the distinction seemed to reside in the indications for obtaining the biopsies. Whereas all but 1 physician obtained biopsies for DA when diarrhea or bloating was present, the 6 physicians who obtained the most biopsies for DA by percentage included unexplained abdominal pain as an indication for sampling. The 3 physicians who obtained the fewest biopsies for DA by percentage only did so when pain was accompanied by diarrhea. Of note, 9 of the 13 physicians discounted the results of samples showing pandisaccharidase deficiency as spurious, although pandisaccharidase is now suggested to be the second most common form of disaccharidase deficiency[4] and is inherent due to sucrase-isomaltase digestion of multiple carbohydrate linkages and the lack of enzyme specificity with the modified Dahlqvist method used to identity enzyme activity.[18]

The difference in diagnostic habits, the under-recognition of the clinical significance of SID and lactase deficiency,[20] and the resulting differences in treatment are likely to be clinically important, as ongoing symptoms may result in additional testing and repeated medical visits until the diagnosis is reached. As with other chronic gastrointestinal illnesses, quality of life may be impaired, which impacts school attendance and/or performance, extracurricular participation, and work attendance by parents. Potential consequences (eg, lower college aptitude and success, decreased promotions for the parents) could arise later from each of those disruptions.[21-23]

Although the data presented here regarding the overall frequency of disaccharidase deficiency in a pediatric

cohort typically seen in a tertiary care referral center who were undergoing diagnostic EGDs closely align with previous reports,[13,15] there are limitations to the present study. The study cohort derives from a single, referral-based pediatric gastroenterology practice. The overall epidemiology of primary SID in the highly diverse referral population of Metro Atlanta is unknown, and the comparison to lactase deficiency may not be equivalent. Furthermore, there is little known regarding the significance of primary SID or lactase deficiency in relationship to quality of life or studies that characterize the socioeconomic impact of primary SID and its subtypes, individually or as a whole, in pediatric or adult populations.

Conclusion

Based on our study findings, there appears to be a clear need for large, prospective, multicenter studies to determine the prevalence and significance of disaccharidase deficiencies as well as the most cost-effective, accurate diagnostic methods to use in order to establish the diagnosis of these enzyme deficiencies. Furthermore, there appears to be a great need for studies on practice variation among pediatric (and adult) gastroenterologists, as well as guidelines to lessen possible medical, social, and economic impacts of the practice variation observed by our study.

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Dr Stanley Cohen serves as a consultant and a disease state (noncommercial) speaker for QOL Medical, LLC, and as the CEO and director of the Medical Advisory Board for Nutrition4Kids.com. Ms Oloyede has no relevant conflicts of interest to disclose.

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