

## Congenital Sucrase-Isomaltase Deficiency: What, When, and How?



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## Congenital Sucrase-Isomaltase Deficiency: What, When, and How?

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### Target Audience

This CME monograph will target gastroenterologists, primary care physicians, nurse practitioners, physician assistants, and nurses.

### Goal Statement

The goal of this journal supplement is to deliver focused, educational updates highlighting clinically relevant advances in the management of patients with CSID/SID.

### Educational Objectives

After completing this activity, participants should be better able to:

- Describe the role of intestinal disaccharidases in health and disease
- Summarize recent evidence regarding the epidemiology, presentation, and natural history of patients with CSID/SID
- Summarize the benefits and limitations of current diagnostic tests for CSID/SID
- Incorporate practical screening/diagnostic strategies to identify appropriate patients for screening, interpret test results accurately, and effectively differentiate CSID/SID from other common GI disorders seen in clinical practice
- Describe the role of dietary modification and enzyme supplementation in the management of patients with CSID/SID

### Accreditation Statement and Credit Designation

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# Congenital Sucrase-Isomaltase Deficiency: What, When, and How?

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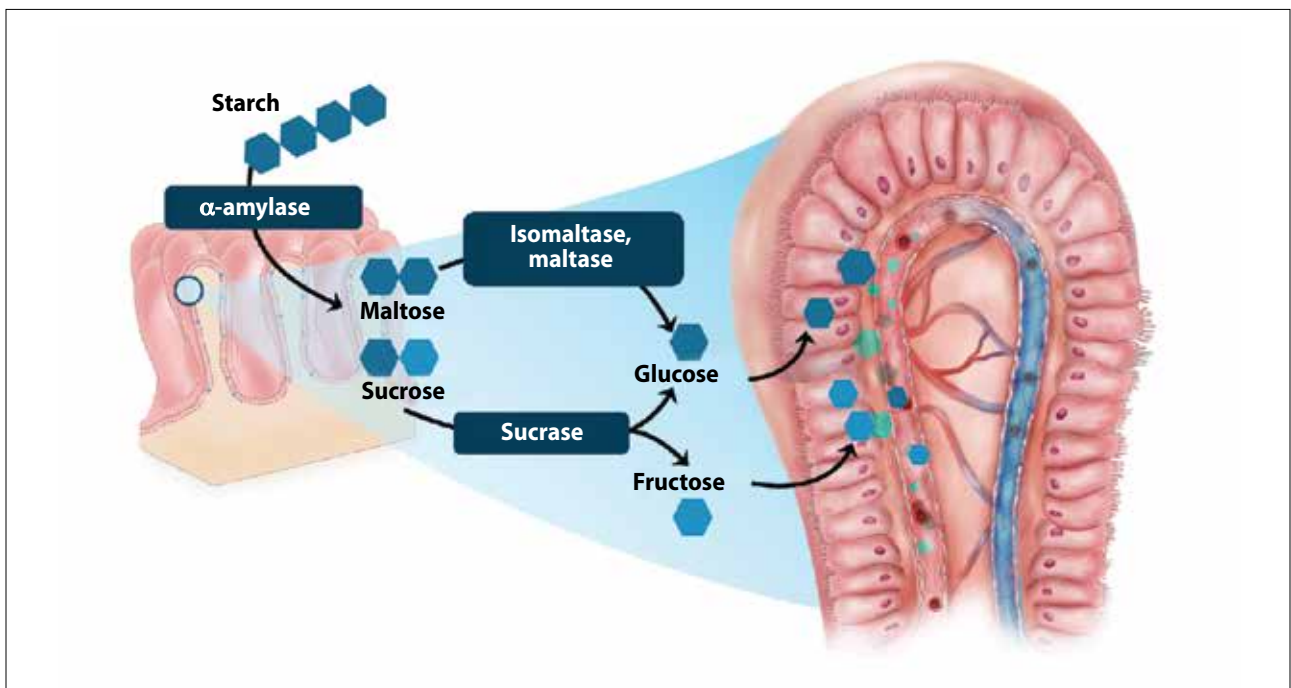
## Disaccharidase Deficiency: An Overview for Gastroenterologists Focusing on CSID

### Overview of Carbohydrate Metabolism

Nearly half of the average Western diet is composed of carbohydrates,<sup>1</sup> which are made up of simple and complex sugars. Simple sugars are monosaccharides (eg, glucose, fructose) or disaccharides (eg, sucrose, maltose, lactose), whereas complex sugars include starches, glycogen, and fibers, which are composed of multiple glucose

molecules with varying structures and bonds.<sup>2,3</sup> Because relevant transporters in the small intestine can only transport monosaccharides, disaccharides and polysaccharides must be hydrolyzed to monosaccharides for absorption to occur (Figure 1).<sup>2</sup> The digestion of starch is initiated by salivary and later pancreatic  $\alpha$ -amylases that hydrolyze it into smaller sugar residues, maltose and sucrose.<sup>2</sup> In the final step of starch digestion, enzymes in the brush border of the small intestine hydrolyze disaccharides into monosaccharides such as glucose and fructose, which are then transported across the epithelial brush

border for absorption and metabolism.<sup>2,4</sup> Isomaltase hydrolyzes branched  $\alpha$ -linked dextrans into 2 glucose molecules, while sucrase hydrolyzes sucrose to fructose and glucose.<sup>4,5</sup> Given its abundance and substrate specificity, the sucrase-isomaltase enzyme complex is responsible for nearly all sucrase activity and approximately 60% to 80% of maltase activity in the intestine.<sup>4,6</sup> Disaccharidase activities vary throughout the small intestine, with lower values in the proximal duodenum, peak activities in the mid-jejunum, and decreasing activities in the ileum.<sup>7</sup>



**Figure 1.** Normal carbohydrate digestion.<sup>6,8</sup> Starches must be hydrolyzed for absorption, a process that begins with pancreatic  $\alpha$ -amylase and is followed by  $\alpha$ -glucosidases. Disaccharides are hydrolyzed by disaccharidases in the small intestinal brush border to monosaccharides for absorption and metabolism.

**Table 1.** Phenotypes of CSID<sup>12</sup>

Phenotype	Cellular Localization	Enzymatic Activity	
		Sucrase	Maltase
I	ER	Completely inactive	Completely inactive
II	ER, ER-Golgi intermediate compartment, and <i>cis</i> -Golgi	Completely inactive	Completely inactive
III	Brush border membrane	Completely inactive	Completely inactive
IV	Random on apical and basolateral membranes	Active	Active
V	Intracellular cleavage, degradation of sucrase, isomaltase is correctly located at the apical membrane	Absent	Active
VI	Intracellular cleavage, enzyme secreted	Active	Active
VII	ER, random cell surface distribution at the apical and basolateral membranes	Decreased	Absent

CSID, congenital sucrase-isomaltase deficiency; ER, endoplasmic reticulum.

### What Is CSID?

First described in 1960,<sup>9</sup> congenital sucrase-isomaltase deficiency (CSID) is an inherited primary defect of sucrase-isomaltase caused by variants in the *sucrase-isomaltase (SI)* gene.<sup>6,10</sup> Patients with CSID harbor 2 defective copies of the *SI* gene due to recessive homozygous or compound heterozygous mutations, leading to the absence or diminished activity of sucrase-isomaltase at the brush border and the clinical symptoms of carbohydrate maldigestion.<sup>10,11</sup> At least 37 pathogenic mutations in the *SI* gene have been described that affect various aspects of gene function, resulting in multiple phenotypes with a broad range of enzymatic activity and clinical presentations (Table 1).<sup>5,12,13</sup> Sucrase activity in patients with CSID can range from completely absent to low residual activity, while isomaltase activity can range from absent to normal.<sup>6</sup> Maltase activity is also reduced significantly in most patients with CSID.<sup>6</sup>

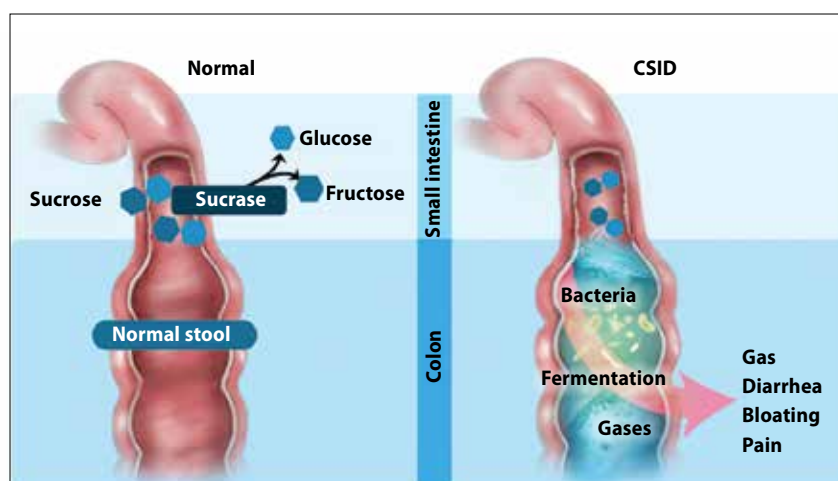
When sucrase-isomaltase is absent or deficient, nonabsorbed carbohydrates enter the distal small intestine and colon where they are fermented, leading to the excessive production of short-chain fatty acids and gases such as hydrogen, methane,

and hydrogen sulfide.<sup>6,10</sup> This in turn can lead to abdominal distension, cramping, pain, excessive flatulence, and osmotic diarrhea (Figure 2).<sup>6,10</sup> If left untreated, significant sucrase-isomaltase deficiency (SID) can result in inadequate growth and failure to thrive in children as well as weight loss in adults.<sup>10,14-16</sup>

### Other Causes of SID

In addition to the congenital forms

of the disorder, acquired or secondary forms of SID have been observed in patients with chronic diarrhea.<sup>4</sup> Decreased enzyme activity can result from generalized intestinal damage related to various etiologies involving villous atrophy, infection, and/or rapid transit (Table 2).<sup>4,17</sup> The clinical impact of SID on these disorders may be transient, with enzymatic activity returning to normal as the underlying disorder resolves.<sup>4</sup>



**Figure 2.** Clinical consequences of carbohydrate malabsorption.<sup>6,8</sup> When sucrase-isomaltase is absent or deficient, nonabsorbed carbohydrates enter the distal small intestine and colon causing excess bacterial fermentation and increased production of short-chain fatty acids and gases, leading to abdominal distension, cramping, pain, excessive flatulence, and osmotic diarrhea. CSID, congenital sucrase-isomaltase deficiency.

**Table 2.** Potential Causes of Secondary or Acquired SID<sup>4</sup>

Potential Cause	Conditions
<b>Villous Atrophy or Alteration</b>	Celiac disease Nontropical sprue Chemotherapy and radiation enteropathy Crohn's disease Allergic enteropathy Immunodeficiency Malnutrition
<b>Infection</b>	Acute gastroenteritis Giardiasis Tropical sprue HIV enteropathy SIBO/dysbiosis
<b>Rapid Transit</b>	Rapid gastric emptying Chronic nonspecific diarrhea Dumping syndrome Crohn's disease Ulcerative colitis, Crohn's colitis, lymphocytic colitis, and collagenous colitis Medications

SIBO, small intestinal bacterial overgrowth; SID, sucrase-isomaltase deficiency.

### Epidemiology and Clinical Presentation of CSID/SID

#### Reassessing the Prevalence of CSID

CSID has been historically considered a rare disease, with an estimated 0.2% prevalence in North American and European populations<sup>18</sup> and an even lower prevalence in African Americans and whites of Hispanic descent.<sup>6,19</sup> Higher estimates have been reported among certain populations,<sup>20,21</sup> with one study reporting a 10% prevalence among Inuit communities in Greenland.<sup>21</sup>

In contrast to these earlier reports, more recent studies demonstrating that heterozygous carriers of *SI* variants also experience symptoms suggest that CSID may be more common than once believed.<sup>4-6,22,23</sup> The true prevalence of CSID is likely underestimated due to a number of factors, including inconsistencies in nomenclature of the condition, diverse testing methodologies with unclear performance characteristics, the existence of multiple genomic abnormalities with broad phenotypic variability, symptom overlap with other gastrointestinal (GI)

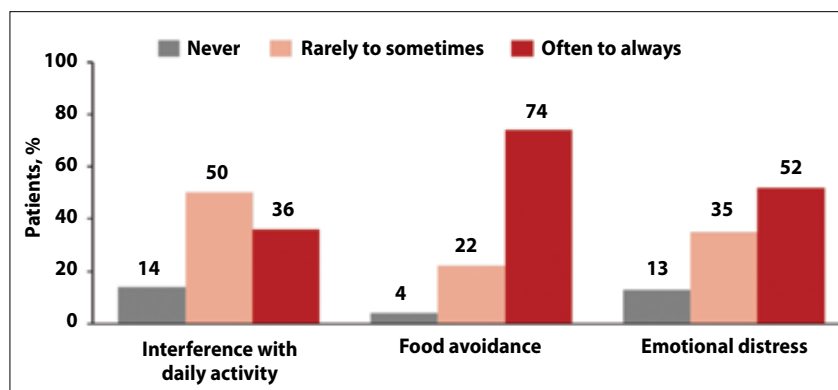
disorders, and lack of high-quality epidemiologic data in adults.<sup>5,11,22</sup> In a 6-year retrospective study involving disaccharidase assay of 27,875 mucosal biopsy tissue samples in symptomatic children, at least 1 disaccharidase deficiency was present in 45% of samples, with 9.3% deficient in sucrase and maltase.<sup>22</sup> A subsequent systematic review of 30 observational studies in children undergoing esophagogastroduodenoscopy (EGD) found similar results, with an overall prevalence of lactase, sucrase, and maltase deficiency

noted to be 39.2%, 9.0%, and 9.1%, respectively.<sup>24</sup>

#### Clinical Features

CSID has classically been thought to present with severe watery diarrhea, failure to gain weight, irritability, and diaper rash in infants who have been exposed to sucrose and starch in baby juices, baby food, fruits, teething biscuits, crackers, and other starches.<sup>6,25</sup> In a case series of 65 patients with CSID, diarrhea was the most frequently described symptom, followed by bloating/gas, abdominal pain, and irritability.<sup>6</sup> However, the clinical presentation and severity vary considerably depending on the nature and type of the *SI* gene mutations, as well as their homozygous or heterozygous combinations.<sup>11,26</sup> Other factors that can influence clinical presentation include the amount of sugar and starch being consumed and patient age, as children may be more susceptible to symptoms due to the shorter length of their small intestine and reduced reserve capacity of the colon to absorb excess luminal fluid.<sup>4,6</sup>

Although symptoms usually appear early in life, increasing reports demonstrate that CSID can present later in life, either in children with diagnoses of nonspecific diarrhea of childhood or in adolescents or adults often carrying diagnoses of diarrhea-predominant irritable bowel syndrome (IBS-D).<sup>5,6,26</sup> In either case, clinical features characteristic of CSID



**Figure 3.** Effects of symptoms on quality of life in adults with sucrase-isomaltase deficiency.<sup>3</sup>

**Table 3.** CSID Signs and Symptoms<sup>3-6,27,28</sup>

<b>Key Symptoms</b>	Frequent, lifelong, and postprandial GI symptoms <ul style="list-style-type: none"> <li>• Diarrhea</li> <li>• Loose stools</li> <li>• Gas</li> <li>• Bloating</li> <li>• Abdominal cramping</li> </ul>
<b>Other Potential Signs</b>	Family history Avoidance of carbohydrates and/or sweet foods Nausea Dyspepsia Low BMI IBS symptoms not responding to therapy

BMI, body mass index; CSID, congenital sucrase-isomaltase deficiency; GI, gastrointestinal; IBS, irritable bowel syndrome.

include symptoms that are lifelong, frequent (typically multiple events per day and multiple days per week), and occur postprandially (Table 3).<sup>3-6,27,28</sup> In a study involving 17 adults with a positive sucrose breath test suggestive of SID, more than 75% of patients reported experiencing abdominal pain, bloating, and gas, and over half had experienced symptoms for more than 2 years.<sup>3</sup> These symptoms had considerable impact on patients' quality of life, with over half of patients reporting that their symptoms led to food avoidance and emotional distress often to always (Figure 3).

### Exploring the Connection Between CSID/SID and FGIDs

Several studies have investigated the potential association between *SI* polymorphisms and irritable bowel syndrome (IBS), including the generation of symptoms in this disorder. To that end, several studies have identified *SI* variants that are linked with an increased risk of IBS.<sup>11,26</sup> In a study involving 1031 IBS cases from around the world, patients with IBS had a 1.84 odds ratio (OR) of having a genetic *SI* mutation compared with controls.<sup>11</sup> In a larger study involving 2207 patients with IBS, 4.2% of patients with IBS-D were found to carry *SI* pathogenic variants, a higher frequency relative to a large matched reference population.<sup>26</sup> Most recently, a study involving pedi-

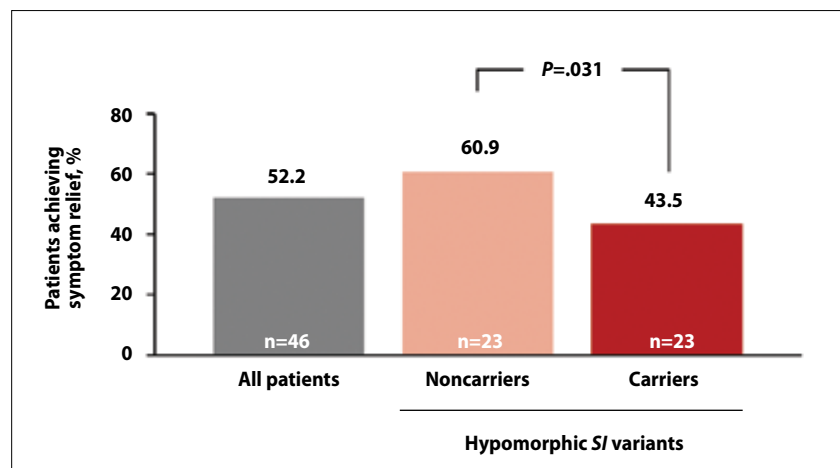
atric and young adult patients with symptoms of functional gastrointestinal disorders (FGIDs) found a higher prevalence of 13 known pathogenic *SI* variants in patients with abnormal sucrase activity via disaccharidase assay compared with those with moderate-normal or high-normal sucrase activity (29.0% vs 6.4% and 2.0%, respectively;  $P < .001$ ).<sup>28</sup>

In addition to an increased risk of FGID symptoms and diagnoses, *SI* polymorphisms have been linked to nonresponse to common dietary approaches to IBS.<sup>29</sup> In an analysis of data from 46 patients with IBS-D in a previous randomized,

controlled trial,<sup>30</sup> patient response to a low-fermentable oligosaccharide, disaccharide, monosaccharide, and polyol (FODMAP) diet was stratified by *SI* genotype data.<sup>29</sup> Patients who carried hypomorphic (pathogenic) *SI* variants were significantly less likely to experience adequate symptom relief from the low-FODMAP diet compared with noncarriers (43.5% vs 60.9%;  $P = .031$ ; OR, 4.66) (Figure 4). Although preliminary, data such as these characterizing the association of *SI* pathogenic variants with the risk of IBS and likelihood of response to various therapies may eventually pave the way for routine screening for *SI* genetic defects among patients with IBS-like symptoms to allow for more personalized diet management.

### Diagnosing CSID/SID

A diagnosis of CSID/SID is usually suggested by the patient's clinical history, paying particular attention to the pattern of symptoms in relation to meals.<sup>7</sup> As mentioned, symptoms can range from severe diarrhea in infancy to chronic, nonspecific diarrhea; gas; and bloating in adolescents to adults reporting dyspeptic or IBS symptoms.<sup>5,7,25</sup> A number of diagnostic tests are available to support the diagnosis of disaccharidase deficiency,



**Figure 4.** Adequate relief of IBS-D symptoms with a low-FODMAP diet.<sup>29</sup> FODMAP, fermentable oligosaccharide, disaccharide, monosaccharide, and polyol; IBS-D, diarrhea-predominant irritable bowel syndrome; *SI*, sucrase-isomaltase.

**Table 4.** Comparison of Diagnostic Tests for CSID/SID<sup>6,7,31,33,34,36</sup>

Test	Advantages	Limitations
<b>Disaccharidase Assay</b>		
<b>EGD With Disaccharidase Assay</b>	<ul style="list-style-type: none"> <li>• Ability to determine enzyme activity for all disaccharidases and glucoamylase</li> <li>• Increasingly, insurance payors are requiring disaccharidase assay prior to covering sacrosidase</li> </ul>	<ul style="list-style-type: none"> <li>• Invasive, requires sedation</li> <li>• Costly and time-consuming</li> <li>• Assay variability (27% coefficient variation)</li> <li>• False-positive results due to mishandled biopsy specimens, biopsy samples of the proximal duodenum, and patchy distribution of disaccharides in the brush border</li> </ul>
<b>Breath Tests</b>		
<b><sup>13</sup>C-Sucrose Breath Test</b>	<ul style="list-style-type: none"> <li>• Noninvasive</li> <li>• Safe (stable isotope—<sup>13</sup>C has never been observed to decay)</li> <li>• Well-tolerated (requires only 0.02 g/kg sucrose solution)</li> <li>• More specific than hydrogen-methane breath test</li> </ul>	<ul style="list-style-type: none"> <li>• False-positive results due to dumping syndrome</li> <li>• False-negative results due to delayed gastric emptying</li> <li>• Need for further validation</li> </ul>
<b>Hydrogen-Methane Breath Test</b>	<ul style="list-style-type: none"> <li>• Noninvasive</li> <li>• Safe</li> </ul>	<ul style="list-style-type: none"> <li>• Influenced by diet and motility agents</li> <li>• Indirect test (not specific for sucrose)</li> <li>• Time-consuming (3 hours)</li> <li>• False-positive results due to SBBO, dumping syndrome</li> <li>• False-negative results due to nonhydrogen producers, delayed gastric emptying</li> <li>• Large sucrose load (2 g/kg sucrose solution) can cause severe symptoms in CSID patients</li> </ul>
<b>Other Tests</b>		
<b>Sucrose Challenge Test</b>	<ul style="list-style-type: none"> <li>• Noninvasive</li> <li>• Simple and easy</li> <li>• Cost-effective</li> <li>• Theoretically sensitive, with high likelihood to cause CSID symptoms</li> </ul>	<ul style="list-style-type: none"> <li>• Lack of validation data</li> <li>• Unknown NPV and PPV</li> <li>• Severe symptoms likely in CSID patients</li> </ul>
<b>Empiric Trial of Sacrosidase</b>	<ul style="list-style-type: none"> <li>• Noninvasive</li> <li>• Simple and easy</li> <li>• Theoretically sensitive, with high likelihood of symptom resolution in CSID patients</li> </ul>	<ul style="list-style-type: none"> <li>• Costly (likely not covered by insurance without CSID being confirmed by an approved diagnostic test)</li> <li>• Lack of validation data</li> <li>• Unknown NPV and PPV</li> </ul>
<b>Empiric Trial of Low-Sucrose Diet</b>	<ul style="list-style-type: none"> <li>• Noninvasive</li> <li>• Theoretically sensitive, with high likelihood of symptom resolution in CSID patients</li> </ul>	<ul style="list-style-type: none"> <li>• Difficult to maintain such a restrictive diet—recommend GI dietitian to assist patient</li> <li>• Lack of validation data</li> <li>• Unknown NPV and PPV</li> </ul>
<b>Urinary Disaccharidase Test</b>	<ul style="list-style-type: none"> <li>• Noninvasive</li> <li>• Safe</li> </ul>	<ul style="list-style-type: none"> <li>• Influenced by diet</li> <li>• Time-consuming (10-hour urine collection)</li> <li>• Lack of validation data</li> </ul>
<b>Genetic Testing</b>	<ul style="list-style-type: none"> <li>• Noninvasive</li> <li>• If positive, confirms SID regardless of genotype</li> </ul>	<ul style="list-style-type: none"> <li>• Costly</li> <li>• Lengthy turnaround time</li> <li>• Normal test does not rule out CSID, as not all mutations have been identified</li> </ul>

CSID, congenital sucrase-isomaltase deficiency; EGD, esophagogastroduodenoscopy; GI, gastrointestinal; NPV, negative predictive value; PPV, positive predictive value; SBBO, small bowel bacterial overgrowth; SID, sucrase-isomaltase deficiency.

with disaccharidase assay of duodenal biopsy specimens considered the gold standard.<sup>6,17,24</sup> However, a number of noninvasive diagnostic tests can help establish the diagnosis. Despite the availability of multiple testing options, the optimal diagnostic strategy for CSID/SID remains unclear, as each option carries its own advantages and limitations (Table 4).

### Disaccharidase Assays

The gold standard for diagnosing intestinal disorders associated with carbohydrate metabolism is endoscopic small bowel biopsies assayed for disaccharidase activities (Table 5).<sup>2,6</sup> Given the distribution of sucrase-isomaltase, 2 to 4 biopsies should be obtained distal to the ampulla of Vater and placed into a container without formalin (Eppendorf tube). The Eppendorf tube with collected samples should be placed on ice immediately and stored at -20° C to -70° C within 2 hours of collection until disaccharidase assay is performed. The general diagnostic criteria for CSID/SID include normal small bowel morphology in the presence of absent or markedly reduced sucrase activity, isomaltase activity varying from no to full activity, and reduced maltase activity.<sup>6</sup> Lactase activity can be normal or reduced in children, in which case the sucrase:lactase ratio should be less than 1 to support a diagnosis of CSID. Histologic examination of the intestinal biopsy specimen can help differentiate secondary cases of SID from congenital deficiencies.<sup>2</sup> Clinical features can also help distinguish secondary deficiencies, with the recent onset of symptoms more typical in these patients compared with the frequent, lifelong, and postprandial symptoms experienced by patients with CSID.

Although disaccharidase assay remains the standard for diagnosing CSID/SID, the most widely used method (the Dahlqvist method) requires properly trained staff and typically requires resources of a specialty laboratory.<sup>17</sup> Additionally, the assay is limited by considerable variability,

**Table 5.** Normal Disaccharidase Values<sup>5</sup>

Disaccharidase	Normal Range
Lactase	15.0-45.5 μM/min/g protein
Sucrase	25.0-69.9 μM/min/g protein
Maltase	100.0-224.4 μM/min/g protein
Isomaltase	5.0-26.3 μM/min/g protein

with a demonstrated 27% coefficient of variation, and potential for false-positive results due to mishandled biopsy specimens, samples from the proximal rather than more distal duodenum, and/or patchy distribution of enzymes in the brush border.<sup>6,31,32</sup>

### Breath Testing

The hydrogen-methane breath test has been used in the evaluation of carbohydrate maldigestion for decades.<sup>7,33</sup> This test is based on the premise that when patients fail to digest carbohydrates in the small intestine, malabsorbed carbohydrates will be fermented by the intestinal flora and produce hydrogen and/or methane that diffuse into the circulation and are ultimately expired in the breath.<sup>7</sup> According to the North American Consensus Guidelines, a rise of at least 20 ppm from baseline in hydrogen is considered positive for carbohydrate maldigestion, while a rise of at least 10 ppm is positive for methane.<sup>33</sup> Although this test is safe and noninvasive, it is not specific for CSID/SID, and results can be compromised by contamination from a number of factors (eg, dumping syndrome, bacterial overgrowth, recent antibiotic use) that can produce either false-positive or false-negative results.<sup>6,34</sup> Further, given that patients must ingest a 2 g/kg

sucrose load, the test can cause severe symptoms in patients with CSID/SID.<sup>6</sup>

The use of isotope-labeled carbohydrates for breath testing was introduced in the 1970s and is a more specific methodology than the hydrogen-methane breath test.<sup>7,34</sup> Carbon-13 (<sup>13</sup>C) is a stable isotope of carbon that occurs naturally in sucrose, making it possible to track an individual's ability to digest and absorb sucrose by measuring the amount of <sup>13</sup>CO<sub>2</sub> exhaled after drinking a sucrose solution. The utility of the <sup>13</sup>C-sucrose breath test was prospectively evaluated in a case-control study involving 10 patients with confirmed CSID based on mucosal tissue biopsy samples and 10 controls with normal sucrase levels and histology.<sup>34</sup> Subjects received oral <sup>13</sup>C-glucose and <sup>13</sup>C-sucrose loads on consecutive study days, followed by breath collection and measurement of <sup>13</sup>CO<sub>2</sub> enrichment. The results of sucrose digestion and oxidation were expressed as the mean percentage of glucose oxidation (% CGO), which was found to correlate with biopsy-determined duodenal sucrase activity with 100% sensitivity and 100% specificity. Additionally, <sup>13</sup>C-sucrose breath test mean % CGO corrected to control levels in CSID patients after supple-

**Table 6.** Sucrose-Rich Foods<sup>39</sup>

<b>Fruits</b>	Apples, apricots, cantaloupe, dates, pineapple, mango, nectarine
<b>Vegetables</b>	Beets, carrots, chickpeas, corn, sweet potatoes
<b>Sweets/ Convenience Foods</b>	Breakfast cereal, granola bars, pastries, muffins, pudding, cookies, pies, jams, jellies
<b>Sugars</b>	Brown sugar, granulated sugar, maple syrup, cane juice, molasses



**Table 7.** Starch-Rich Foods<sup>39</sup>

Potatoes
Rice
Bread
Pasta
Dextrins
Maltodextrins
Glucose polymers

mentation with sacrosidase enzyme. Given the low dose of sucrose solution required (0.02 g/kg), patients with CSID tolerated the test well, without the symptoms of diarrhea, bloating, or cramping typically observed with the hydrogen-methane breath test.<sup>7,34</sup> Despite these encouraging results, more data are needed to validate the use of the <sup>13</sup>C-sucrose breath test and inform how and when it should be used in clinical practice.

**Other Strategies**

A sucrose 4-4-4 challenge is a simple test that consists of monitoring for the presence of symptoms (bloating, gas, diarrhea) for a 4- to 8-hour period after the patient drinks 4 ounces of water with 4 tablespoons of dissolved table sugar.<sup>4</sup> Although theoretically sensitive, this method has not been validated and is likely to cause significant symptoms in patients with severe CSID/SID. Other approaches that may be helpful in supporting a diagnosis of CSID/SID but have yet to be validated include a short (2-week) trial of enzyme (sacrosidase) replacement therapy, an empiric trial of a low-sucrose diet, and measurement of urinary disaccharides.<sup>4,6,35,36</sup> Although *SI* exome genetic sequencing can identify homozygous and compound heterozygous mutations responsible for CSID, a normal test does not exclude CSID, as all mutations have not yet been identified.<sup>4,13,37</sup>

**Is It CSID or IBS?**

The diagnosis of CSID/SID can be delayed or even missed because the symptoms are incorrectly attributed to other causes of recurrent diarrhea.<sup>12</sup>

Given the overlapping symptoms with IBS, it has been speculated that CSID/SID may be frequently misdiagnosed as IBS in clinical practice, particularly in patients with meal-related symptoms.<sup>3,5</sup> To explore this possibility, the prevalence of SID was investigated in 132 patients with chronic (>6 months) symptoms suggestive of the disorder (ie, diarrhea, bloating, nausea, early satiety, and/or abdominal pain).<sup>3</sup> Of these patients, 17% (n=22) had a positive sucrose breath test suggestive of SID, and more than half of patients (65%) had been diagnosed previously with IBS-D. In a subsequent pilot study, SID was found by disaccharidase testing in 11 of 31 (35%) patients undergoing EGD for presumed IBS-D or mixed IBS (IBS-M).<sup>5</sup> The higher-than-expected prevalence of SID in this study may have been related to selection and referral bias inherent to this population of patients with IBS undergoing EGD at a tertiary referral motility center. Taken collectively, however, these findings suggest that sucrose maldigestion may contribute to symptoms in patients with presumed IBS-D/M and should be considered in the differential diagnosis of such patients.<sup>5</sup>

**Managing CSID**

**Dietary Management**

Historically, the primary treatment option for CSID/SID has been implementing lifelong sucrose- and starch-restricted diets adapted to the requirements of the patient.<sup>2,6</sup> Given that all patients with CSID/SID are sucrose-intolerant, a sucrose-free diet should be implemented before starch intake is modified.<sup>38</sup> Common foods rich in sucrose include table sugar, brown sugar, and certain fruits, vegetables, and sweets/convenience foods (Table 6).<sup>39</sup> If symptoms persist after institution of a sucrose-free diet, starch consumption may need to be reduced. Starch tolerance may become more important in patients with severe symptoms and/or patients with low maltase activity.<sup>38</sup> Starch-rich foods include potatoes, rice, bread, pasta, dextrins, maltodextrins, and glucose polymers (Table 7).<sup>39</sup> Strategies for improving starch tolerance include chewing foods slowly to maximize salivary amylase exposure and eating starches with greater fiber content (eg, oats, barley, brown rice, whole grain flour) to prolong exposure to amylase

**Table 8.** Foods Low in Sucrose and Starch<sup>39</sup>

<b>Dairy<sup>a</sup></b>	Cow's milk, cream cheese, hard cheeses, plain cottage cheese, plain yogurt, sour cream
<b>Protein</b>	Beef, poultry, pork, lamb, firm tofu
<b>Vegetables</b>	Artichoke, asparagus, bamboo shoots, bell peppers, bok choy, broccoli, Brussels sprouts, cabbage, cauliflower, celery, collard greens, cucumber, eggplant, green beans, lettuce, bean sprouts, mustard greens, mushrooms, radish, rutabaga, spaghetti squash, spinach, tomatoes, turnips, summer squash, zucchini
<b>Fruits</b>	Avocado, blackberries, blueberries, boysenberries, cherries, cranberries, currants, figs, grapes, kiwifruit, lemon, lime, olive, papaya, pears, pomegranate, prunes, raspberries, rhubarb, strawberries
<b>Fats, Nuts, Seeds</b>	Olive oil, butter, other vegetable oils, <sup>b</sup> almond butter, <sup>c</sup> Brazil nuts, flax, peanuts, peanut butter <sup>c</sup>
<b>Sweeteners</b>	Granulated dextrose or fructose

<sup>a</sup>In patients with concomitant lactose intolerance, lactose-free or low-lactose foods (eg, hard cheeses, lactose-free milk, lactose-free yogurt) should be chosen as tolerated. <sup>b</sup>Caution should be used with margarine. <sup>c</sup>Without added sugar.

**Table 9.** Key Points

The majority of dietary carbohydrates are digested by sucrase-isomaltase.
CSID/SID are likely more common than previously believed. Current literature suggests an overall CSID prevalence of 4% to 5%, while approximately 10% of symptomatic children and adults have diminished sucrase-isomaltase activity (including secondary etiologies).
The optimal diagnostic strategy for CSID/SID remains unclear. While disaccharidase assay is the current gold standard, the <sup>13</sup> C-sucrose breath test offers a noninvasive, practical strategy to help establish the diagnosis. However, more data are needed to validate this test and determine how and when it is best used in clinical practice.
Although current evidence is insufficient to recommend early testing, CSID/SID should be included in the differential diagnosis of patients with presumed IBS who have unexplained, meal-related GI symptoms (diarrhea, bloating, flatulence, and abdominal pain), particularly those not responding to symptom-directed or dietary treatment.
Treatment of CSID/SID should be individualized based on patient preferences, using an iterative approach that incorporates dietary management and/or enzyme replacement therapy. Whenever possible, gastroenterologists should work with a registered dietitian who is knowledgeable about CSID/SID when managing these patients.

CSID, congenital sucrase-isomaltase deficiency; GI, gastrointestinal; IBS, irritable bowel syndrome; SID, sucrase-isomaltase deficiency.

throughout the GI tract.

Although dietary restriction alone should be theoretically effective, only a minority of patients remain consistently asymptomatic with this approach, with up to 75% of patients continuing to experience diarrhea, gas, and/or abdominal pain. Compliance even among younger patients can be suboptimal, with several studies suggesting that only half of children are typically compliant with the prescribed diet.<sup>6,14,40</sup>

Access to a registered dietitian who is knowledgeable about CSID/SID and maintaining a food diary are essential for guiding patients and their families in implementing dietary restrictions, ensuring adequate nutritional status, and introducing appropriate foods (Table 8)<sup>39</sup> safely in combination with sacrosidase to find tolerance levels.<sup>38</sup> Additionally, dietitians are instrumental in teaching patients and their families to understand food labels and recognize sucrose and starch in foods. Importantly, the amount of starch is not listed on food labels, but can be calculated by sub-

tracting the amount of fiber and sugar from the total carbohydrates.

### **Enzyme Replacement Therapy**

Treatment of CSID/SID has improved considerably with the availability of enzyme replacement therapy (sacrosidase), which allows liberalization of the sucrose-restrictive diet.<sup>6</sup> Derived from baker's yeast (*Saccharomyces cerevisiae*), sacrosidase is available as a solution containing 8500 IU of the enzyme/mL.<sup>41</sup> The efficacy of sacrosidase was demonstrated in a randomized, double-blind trial involving 28 children with confirmed CSID who received various concentrations of the enzyme following a baseline period of maintaining a sucrose-free, low-starch diet.<sup>42</sup> At the end of the 10-day treatment period, 81% of patients using full-strength sacrosidase were able to remain asymptomatic while consuming an unrestricted diet, which compared favorably with the experience of patients during the diet-restricted phase, during which 78% of patients were asymptomatic.<sup>42</sup> However, because sacrosidase does not

replace deficient isomaltase, restricting starch in the diet may still be necessary in some patients.<sup>41</sup>

Sacrosidase is usually taken with each meal or snack, mixed with 2 to 4 ounces of milk, water, or formula.<sup>41</sup> Dosing is weight-based, with 1 mL recommended in children of no more than 15 kg and 2 mL in patients over 15 kg (ie, older children and adults). In order to maintain enzyme viability, the solution should be refrigerated and should not be mixed in hot or acidic beverages, nor should it be heated after mixing. Because sacrosidase is derived from baker's yeast, it should not be given to people with a known hypersensitivity to yeast or yeast products. In addition, sacrosidase should be avoided or utilized with extreme caution in people with poorly controlled diabetes, as it can raise blood glucose levels through sucrose hydrolysis.

## **Conclusion**

Increasing clinical and genetic evidence indicates that CSID/SID, once believed to be rare, are more common than previously appreciated.<sup>4-6,22,23</sup> Given its broad phenotypic variability and shared symptoms with other causes of chronic diarrhea, it is likely that many patients with CSID/SID have been misdiagnosed with other GI conditions. This may be particularly true of patients diagnosed with IBS-D/M, in whom a high prevalence of *SI* mutations and sucrase deficiency has been reported.<sup>3,5,26,28</sup> Accordingly, clinicians should be alert to the possibility of CSID in patients of all ages who experience lifelong, frequent, and postprandial GI symptoms, particularly patients who carry a diagnosis of IBS-D/M. While duodenal biopsy and disaccharidase assay remain the gold standard for diagnosis of CSID/SID, the diagnosis can be supported by less-invasive methods such as breath testing, sucrose challenge, and a trial of enzyme replacement therapy.<sup>4,6,35</sup> Once diagnosed, the symptoms of CSID/SID can be improved through maintaining a low-sucrose, low-starch

diet, although it is difficult for patients to comply with the restrictiveness of such a diet.<sup>6,14,40</sup> Fortunately, the treatment of CSID/SID has improved considerably with the availability of enzyme replacement therapy, which allows patients to control their symptoms with less-restrictive dietary regimens.<sup>6,42</sup> The key points of CSID/SID are summarized in Table 9.

## References

- Seidelmann SB, Claggett B, Cheng S, et al. Dietary carbohydrate intake and mortality: a prospective cohort study and meta-analysis. *Lancet Public Health*. 2018;3(9):e419-e428.
- Gericke B, Amiri M, Naim HY. The multiple roles of sucrase-isomaltase in the intestinal physiology. *Mol Cell Pediatr*. 2016;3(1):2.
- Simmer S, Chey WD, Eswaran SL, Ranagan J, Petrucelli S. Is sucrase-isomaltase deficiency an under-recognized cause of IBS-D symptoms [abstract Mo1966]? *Gastroenterology*. 2018;154(6)(suppl 1):S-867.
- Cohen SA. The clinical consequences of sucrase-isomaltase deficiency. *Mol Cell Pediatr*. 2016;3(1):5.
- Kim SB, Calmer FH, Garrido J, Garcia-Buitrago MT, Moshiree B. Sucrase-isomaltase deficiency as a potential masquerader in irritable bowel syndrome. *Dig Dis Sci*. 2020;65(2):534-540.
- Treem WR. Clinical aspects and treatment of congenital sucrase-isomaltase deficiency. *J Pediatr Gastroenterol Nutr*. 2012;55(suppl 2):S7-S13.
- Robayo-Torres CC, Quezada-Calvillo R, Nichols BL. Disaccharide digestion: clinical and molecular aspects. *Clin Gastroenterol Hepatol*. 2006;4(3):276-287.
- Berni Canani R, Pezzella V, Amoroso A, Cozzolino T, Di Scala C, Passariello A. Diagnosing and treating intolerance to carbohydrates in children. *Nutrients*. 2016;8(3):157.
- Weijers HA, Van De Kamer JH, Mossel DA, Dicke WK. Diarrhoea caused by deficiency of sugar-splitting enzymes. *Lancet*. 1960;276(7145):296-297.
- Boney A, Elser HE, Silver HJ. Relationships among dietary intakes and persistent gastrointestinal symptoms in patients receiving enzyme treatment for genetic sucrase-isomaltase deficiency. *J Acad Nutr Diet*. 2018;118(3):440-447.
- Henström M, Diekmann L, Bonfiglio F, et al. Functional variants in the sucrase-isomaltase gene associate with increased risk of irritable bowel syndrome. *Gut*. 2018;67(2):263-270.
- Naim HY, Heine M, Zimmer K-P. Congenital sucrase-isomaltase deficiency: heterogeneity of inheritance, trafficking, and function of an intestinal enzyme complex. *J Pediatr Gastroenterol Nutr*. 2012;55(suppl 2):S13-S20.
- Chumpitazi BP, Robayo-Torres CC, Opekun AR, Nichols BL Jr, Naim HY. Congenital sucrase-isomaltase deficiency: summary of an evaluation in one family. *J Pediatr Gastroenterol Nutr*. 2012;55(suppl 2):S36.
- Antonowicz I, Lloyd-Still JD, Khaw KT, Shwachman H. Congenital sucrase-isomaltase deficiency. Observations over a period of 6 years. *Pediatrics*. 1972;49(6):847-853.
- Belmont JW, Reid B, Taylor W, et al. Congenital sucrase-isomaltase deficiency presenting with failure to thrive, hypercalcemia, and nephrocalcinosis. *BMC Pediatr*. 2002;2:4.
- Muldoon C, Maguire P, Gleeson F. Onset of sucrase-isomaltase deficiency in late adulthood. *Am J Gastroenterol*. 1999;94(8):2298-2299.
- He Z, Bolling L, Tonb D, Nadal T, Mehta DI. An automated method for the determination of intestinal disaccharidase and glucoamylase activities. *J Autom Methods Manag Chem*. 2006;2006:93947.
- Peterson ML, Herber R. Intestinal sucrase deficiency. *Trans Assoc Am Physicians*. 1967;80:275-283.
- Welsh JD, Poley JR, Bhatia M, Stevenson DE. Intestinal disaccharidase activities in relation to age, race, and mucosal damage. *Gastroenterology*. 1978;75(5):847-855.
- Ellestad-Sayed JJ, Haworth JC, Hildes JA. Disaccharide malabsorption and dietary patterns in two Canadian Eskimo communities. *Am J Clin Nutr*. 1978;31(8):1473-1478.
- Gudmand-Hoyer E, Fenger HJ, Kern-Hansen P, Madsen PR. Sucrase deficiency in Greenland. Incidence and genetic aspects. *Scand J Gastroenterol*. 1987;22(1):24-28.
- Nichols BL Jr, Adams B, Roach CM, Ma CX, Baker SS. Frequency of sucrase deficiency in mucosal biopsies. *J Pediatr Gastroenterol Nutr*. 2012;55(suppl 2):S28-S30.
- Chumpitazi BP, Lewis J, Cooper D, et al. Hypomorphic SI genetic variants are associated with childhood chronic loose stools. *PLoS One*. 2020;15(5):e0231891.
- Daileida T, Baek P, Sutter ME, Thakkar K. Disaccharidase activity in children undergoing esophagogastroduodenoscopy: a systematic review. *World J Gastrointest Pharmacol Ther*. 2016;7(2):283-293.
- Haberaman Y, Di Segni A, Loberman-Nachum N, et al. Congenital sucrase-isomaltase deficiency: a novel compound heterozygous mutation causing aberrant protein localization. *J Pediatr Gastroenterol Nutr*. 2017;64(5):770-776.
- Garcia-Etxebarria K, Zheng T, Bonfiglio F, et al. Increased prevalence of rare sucrase-isomaltase pathogenic variants in irritable bowel syndrome patients. *Clin Gastroenterol Hepatol*. 2018;16(10):1673-1676.
- Puertolas MV, Fifi AC. The role of disaccharidase deficiencies in functional abdominal pain disorders—a narrative review. *Nutrients*. 2018;10(12):1835.
- Deb C, Campion S, Derrick V, et al. Sucrase-isomaltase gene variants in patients with abnormal sucrase activity and functional GI disorders [published online July 28, 2020]. *J Pediatr Gastroenterol Nutr*. doi:10.1097/MPG.0000000000002852.
- Zheng T, Eswaran S, Pothenhauer AL, Merchant JL, Chey WD, D'Amato M. Reduced efficacy of low FODMAPs diet in patients with IBS-D carrying sucrase-isomaltase (SI) hypomorphic variants. *Gut*. 2020;69(2):397-398.
- Eswaran SL, Chey WD, Han-Markey T, Ball S, Jackson K. A randomized controlled trial comparing the low FODMAP diet vs. modified NICE guidelines in US adults with IBS-D. *Am J Gastroenterol*. 2016;111(12):1824-1832.
- Maiuri L, Raia V, Potter J, et al. Mosaic pattern of lactase expression by villous enterocytes in human adult-type hypolactasia. *Gastroenterology*. 1991;100(2):359-369.
- Smith JA, Mayberry JF, Ansell ID, Long RG. Small bowel biopsy for disaccharidase levels: evidence that endoscopic forceps biopsy can replace the Crosby capsule. *Clin Chim Acta*. 1989;183(3):317-321.
- Rezaie A, Buresi M, Lembo A, et al. Hydrogen and methane-based breath testing in gastrointestinal disorders: the North American Consensus. *Am J Gastroenterol*. 2017;112(5):775-784.
- Robayo-Torres CC, Opekun AR, Quezada-Calvillo R, et al. 13C-breath tests for sucrose digestion in congenital sucrase isomaltase-deficient and sacrosidase-supplemented patients. *J Pediatr Gastroenterol Nutr*. 2009;48(4):412-418.
- Puntis JW, Zamvar V. Congenital sucrase-isomaltase deficiency: diagnostic challenges and response to enzyme replacement therapy. *Arch Dis Child*. 2015;100(9):869-871.
- Bjarnason I, Batt R, Catt S, Macpherson A, Maxton D, Menzies IS. Evaluation of differential disaccharide excretion in urine for non-invasive investigation of altered intestinal disaccharidase activity caused by alpha-glucosidase inhibition, primary hypolactasia, and coeliac disease. *Gut*. 1996;39(3):374-381.
- Alfalal M, Keiser M, Leeb T, Zimmer KP, Naim HY. Compound heterozygous mutations affect protein folding and function in patients with congenital sucrase-isomaltase deficiency. *Gastroenterology*. 2009;136(3):883-892.
- McMeans AR. Congenital sucrase-isomaltase deficiency: diet assessment and education guidelines. *J Pediatr Gastroenterol Nutr*. 2012;55(suppl 2):S37-S39.
- Choosing your foods. CSIDCares. <https://www.csidcares.org/treatment/diet/>. Accessed September 5, 2020.
- Kilby A, Burgess EA, Wigglesworth S, Walker-Smith JA. Sucrase-isomaltase deficiency. A follow-up report. *Arch Dis Child*. 1978;53(8):677-679.
- Sucraid [prescribing information]. Vero Beach, FL: QOL Medical, LLC; 2019.
- Treem WR, McAdams L, Stanford L, Kastoff G, Justinich C, Hyams J. Sacrosidase therapy for congenital sucrase-isomaltase deficiency. *J Pediatr Gastroenterol Nutr*. 1999;28(2):137-142.

