

Utility of Diagnostic Tests in Children With Functional Abdominal Pain Disorders

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Abstract: Functional gastrointestinal disorders (FGIDs) and functional abdominal pain disorders (FAPDs) are common in pediatric patients. The prevalence of FGIDs using the Rome IV criteria ranges from 21.1% to 25.0% in children. The Rome IV criteria specify that the decision of testing is left to the clinician, giving him or her freedom to decide on the necessary workup. The clinician should consider all of the functional and organic diseases that manifest with chronic abdominal pain, as well as alarm features that should prompt testing. Societal guidelines and reports do not recommend routine evaluations for FAPDs, particularly in the absence of alarm features. Studies have reported variable results upon assessing the diagnostic yields of different tests. Furthermore, these evaluations considerably increase costs for the health care system. This article examines the current evidence on the utility of diagnostic testing in pediatric patients with FAPDs.

Functional abdominal pain disorders (FAPDs) are common in children.¹⁻⁵ More than 50% of new-patient visits to gastrointestinal (GI) clinics meet the criteria for 1 or more functional gastrointestinal disorder (FGID). FAPDs represent a large proportion of these consults.⁶

The pathogenesis and pathophysiology of FAPDs are yet to be fully uncovered. FAPDs are thought to result from the interaction of various elements that include genetic predisposition, adverse early-life events, abnormal sensory input and processing, and psychosocial and environmental factors.⁷⁻⁹ The incomplete understanding of the pathophysiology of FAPDs precludes the identification of clinically actionable biomarkers to diagnose this group of disorders.⁷ In the absence of biomarkers, diagnosis relies on the history obtained from patients and their families.

The Rome criteria are a diagnostic tool that allows for the clinical diagnosis of FGIDs. The criteria were initially created to diagnose FGIDs in adults. In 1999, the second iteration of the Rome criteria (Rome II) established pediatric diagnostic criteria for the first time.¹⁰ The latest edition of the Rome criteria (Rome IV), issued in 2016,¹¹ modified the previous diagnostic criteria, created new diagnoses and terminology, and provided recommendations for clinical management. One of these changes included the substitution of

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the previously used term abdominal pain–predominant FGIDs with the term FAPDs. The Rome IV criteria also divided FAPDs into abdominal migraine, irritable bowel syndrome (IBS), functional dyspepsia (FD), and functional abdominal pain—not otherwise specified.¹¹ Within FD, 3 groups were defined: epigastric pain syndrome, postprandial distress syndrome, and the overlap between them. IBS is now divided into subcategories based on the characteristics of bowel movements, same as in the adult version of the criteria.¹¹

These modifications to the Rome IV diagnostic criteria were associated with changes in the prevalence of FAPDs. Using the Rome IV criteria, studies conducted in the United States and in Colombia found FAPDs in 16.9% and 8.2% of children, respectively.^{12,13} When using the Rome III criteria in the same US population, Robin and colleagues reported a lower frequency of FAPDs (13.3%).¹² Conversely, the Colombia-based study by Saps and colleagues found a higher prevalence (10.4%) when using the Rome III criteria.¹³ The changes in prevalence using different versions of the Rome criteria can be viewed as a result of improvements of the new version or interpreted as a reflection of the shortcomings of diagnosing disorders on clinical grounds alone. Furthermore, previous editions of the Rome criteria (Rome II and III) showed poor diagnostic agreement among and between pediatric gastroenterologists and trainees.^{14,15}

The aforementioned limitations of exclusively clinical diagnoses have led some practitioners to routinely order tests to rule out organic diseases, even in the setting of a presumed FGID, leading to extremely high health care costs¹⁶ and occasional life-threatening complications.^{17,18} There are no recent comprehensive guidelines or reviews on the indication, yield, and costs of testing in children with FAPDs. This article reviews the current evidence on the utility of diagnostic testing in pediatric patients with FAPDs.

Diagnostic Approach

The Rome IV criteria no longer state that the diagnosis of a FAPD is made in the absence of anatomic, biochemical, or structural changes, as this was thought to be misunderstood by clinicians, leading to excessive testing. The criteria now state that the decision of testing is left to the clinician.¹¹ A common perception by some practitioners is that families would be unlikely to accept a functional diagnosis without prior investigations.¹⁹ However, this is not shared by all clinicians, with some practitioners arguing that most families, through education, can be reassured that there is no need to conduct extensive testing in cases of clear functional diagnoses.¹⁹ To that end, the clinician should consider all of the functional and

Table 1. Differential Diagnosis for Recurrent Abdominal Pain²⁰

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| <p>Gastrointestinal Tract Disorders: Esophagitis, gastroesophageal reflux disease, gastritis, peptic ulcer disease, celiac disease, disaccharidase deficiency, parasitic infection, intestinal malrotation, intussusception, Meckel diverticulum, chronic appendicitis, epiploic appendagitis, inflammatory bowel disease</p> |
| <p>Hepatic, Biliary, and Pancreatic Disorders: Cholelithiasis, choledocal cyst, chronic hepatitis, liver abscess, recurrent and chronic pancreatitis</p> |
| <p>Urogenital Disorders: Urinary tract infection, urolithiasis, hydronephrosis, dysmenorrhea, pelvic inflammatory disease, endometriosis</p> |
| <p>Other Disorders: Familial Mediterranean fever, malignancy, vasculitis, porphyria, hereditary angioedema, sickle cell disease, lead poisoning</p> |

organic diseases that manifest with recurrent abdominal pain (RAP) (Table 1)²⁰ and consider alarm features that should prompt testing.

A technical report from the American Academy of Pediatrics (AAP) and the North American Society for Pediatric Gastroenterology, Hepatology and Nutrition (NASPGHAN) published in 2005 concluded that, in the absence of alarm features, there was no basis for testing.²¹ More than 10 years later, the Rome IV criteria reviewed these alarm features and limited their number (Table 2). Arthralgia and nocturnal abdominal pain are no longer considered symptoms that suggest an organic disease, as both were found equally present in children with FAPDs and organic diseases.^{11,20} Gijsbers and colleagues reported that the Rome III alarm features alone were not able to differentiate between organic causes and RAP.²² There are no studies specifically evaluating the significance of the Rome IV alarm features alone or grouped as biomarkers. Recently, the Rome committee published an online pediatric tool kit to guide the diagnosis and workup of children with FGIDs.²³ The Rome committee's recommendations were mostly based on expert opinion, as their review of the literature found few studies investigating the evidence and yield of testing in children with FAPDs.¹¹ Some of the data on diagnostic evaluations and procedures that helped the Rome committee provide recommendations are presented below.

Routine Testing

Care providers frequently request laboratory examinations for complete blood count, basic biochemistry, inflammatory markers, and urinalysis when dealing with

Table 2. Alarm Features for Potential Organic Disease in Chronic Abdominal Pain¹¹

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| • Dysphagia |
| • Odynophagia |
| • Persistent vomiting |
| • Gastrointestinal bleeding |
| • Persistent right upper or right lower quadrant pain |
| • Nocturnal diarrhea |
| • Perirectal disease |
| • Involuntary weight loss |
| • Deceleration of linear growth |
| • Delayed puberty |
| • Unexplained fever |
| • Arthritis |
| • Family history of inflammatory bowel disease, celiac disease, or peptic ulcer disease |

a patient with features of a FAPD. These investigations have not shown diagnostic utility, so their use is still debatable.^{16,24} A study found that primary care physicians favor limited organ-specific testing for children with chronic abdominal pain (CAP), mostly using urinalysis. Abdominal ultrasound is the imaging modality most commonly employed, and its use is thought to be related to a need for reassurance rather than the expectation of finding a specific etiology.²⁵ Studies looking at the utility of abdominal ultrasonography in RAP concluded that it does not significantly contribute to diagnosis.^{26,27} A retrospective cohort of children with abdominal pain in primary care practices found that 17% and 14% of patients had laboratory and imaging testing ordered at their initial visit, respectively, with a diagnostic yield of only 3%.²⁸

The Rome IV criteria do not specifically discuss the need for parasite stool testing. As demonstrated in studies from Pakistan, Turkey, Egypt, and Poland, based on the geographic location, the prevalence of parasitic infections may justify testing.²⁹⁻³³ The presence of alarm signs (ie, nausea, vomiting, abdominal distention) and risk factors such as poor hygiene or toilet training was associated with *Giardia lamblia* infection in Pakistani children with RAP.²⁹ On the other hand, in developed countries, the prevalence of parasitic infections was not significantly different in children with and without CAI.^{34,35}

Stool Biomarkers

Even though an enzyme-linked immunosorbent assay for fecal calprotectin (FC) has been available since 1994,³⁶

FC assays have only been used in daily clinical practice in the United States over the last few years. Calprotectin is a calcium-binding protein that is found primarily in the cytosol of neutrophils, monocytes, and activated macrophages.³⁷ After it binds to calcium, calprotectin is stable and can remain in stool for 7 days at room temperature.³⁸ Elevation of FC reflects granulocyte migration through the intestinal wall in active inflammation.³⁹ Studies have suggested that FC is a versatile and useful tool in differentiating FAPDs and FGIDs from other inflammatory disorders, especially inflammatory bowel disease (IBD), at the time of diagnosis and in differentiating IBD flare-ups from IBS in the absence of active disease.^{40,41} A study in Norway described a significant difference in FC levels between children with functional abdominal pain (FAP) and patients with IBD.⁴⁰ Similarly, a study involving 142 children with various FGIDs demonstrated FC concentrations within normal limits.⁴¹ Diagnostic accuracy has been shown to be higher in children compared with adults.⁴² In adult patients, using a cutoff value of 50 µg/g, FC had a sensitivity of 64%, specificity of 80%, positive predictive value of 70%, and negative predictive value of 74% for organic causes. In comparison, FC in pediatric patients had a sensitivity of 70%, specificity of 93%, positive predictive value of 96%, and negative predictive value of 56% for organic causes.⁴² A meta-analysis reported that FC had a sensitivity of 97.8%, specificity of 68.2%, positive likelihood ratio of 3.07, and negative likelihood ratio of 0.03 for the diagnosis of suspected IBD in children. Cutoff values were not consistent among the evaluated studies (n=8).⁴³ Another study suggested that in cases of normal FC (<40 µg/g), there is no need to conduct endoscopic assessment. The study found that the probability of having IBD in adults with IBS was no more than 1%.⁴⁴ A pediatric meta-analysis reported that FC was the biomarker that added the greatest diagnostic value to symptoms suggestive of IBD and helped stratify risk.⁴⁵ However, at the time of interpreting FC values, the practitioner should be cognizant that FC is not devoid of false-positive results. FC is usually grossly elevated in cases of IBD, and discrete elevated values are unlikely to reflect inflammation secondary to IBD. False-positive values that can be misinterpreted as IBD can be found in cases of polyps, use of proton pump inhibitors or nonsteroidal anti-inflammatory drugs, and other inflammatory processes.⁴² The utility of FC has not been reported in dyspepsia or reflux disease. FC values also vary by age, and normal limits are higher in children up to 3 or 4 years of age.^{46,47} The Rome committee tool kit, an online resource for the diagnosis and management of FGIDs, currently recommends the use of FC to differentiate FGIDs from organic disorders in cases of unclear differential diagnosis.²³

Similarly, lactoferrin, an iron-binding glycoprotein, is a major component of neutrophils' secondary granules and is secreted by most mucosal membranes. As leukocytes infiltrate the intestinal mucosa during inflammation, the concentration of stool lactoferrin (SL) increases.⁴⁸ Even though there are fewer studies for SL in comparison to FC, testing for SL has shown similar sensitivity and specificity to FC in IBD,⁴⁹⁻⁵¹ including studies in children.⁵² The optimum cutoff value has been defined as 7.25 µg/mL based on individual study estimates and summary receiver operating characteristic curves.⁵⁰ Nevertheless, the utility of SL in differentiating IBD from IBS has not been clearly established, as studies have not reported consistent information.^{44,49,53} Kane and colleagues reported that elevated SL was 100% specific in ruling out IBS, and patients with IBS had almost identical SL levels as healthy controls.⁴⁹ On the other hand, a meta-analysis showed that elevated SL was more predictive of IBS than IBD. The overlap of positive SL for IBS and IBD reduces its ability to properly identify IBS patients.⁴⁴ SL has been used most in research settings, likely influenced by its reportedly shorter stability at room temperature when compared with FC.⁵⁴

Celiac Disease Screening

Celiac disease (CD) is an autoimmune chronic enteropathy that can develop in genetically predisposed individuals exposed to dietary gluten.⁵⁵ Clinical manifestations of CD vary and include abdominal pain, bloating, diarrhea, and constipation, which could mimic a FAPD (most commonly IBS).⁵⁶⁻⁵⁸ Although some studies have reported increased rates of CD in patients with IBS at the time of diagnosis,⁵⁹⁻⁶¹ the evidence is not conclusive.⁶²⁻⁶⁴ A prospective cohort study in children showed a 4-fold greater likelihood of CD among patients with a presumed diagnosis of IBS.⁶⁵ A meta-analysis also described an increased prevalence of biopsy-proven CD and positive serum serology in patients with symptoms suggestive of IBS compared with controls.⁶⁶ However, population-based studies showed no increase in odds ratio for any CD evaluation,^{67,68} and a Turkish cohort study found that CD was as common in children with FAP or FD as in the general population.⁶⁹ In light of the inconsistency of data, and to avoid missing potential cases of CD, the Rome IV committee recommends serologic screening for CD in children with a presumed diagnosis of IBS.¹¹

The controversy on the association between FAPD and CD is not limited to the time of diagnosis. Even in CD patients complying with a gluten-free diet (GFD), GI symptoms such as abdominal pain or discomfort (35%), diarrhea (22%), and constipation (46%) do not always resolve.⁷⁰ Persistence of symptoms after a GFD seems to be more common in adults than in children.⁷¹ An Italian study found that FGIDs were more common among

patients with CD on a GFD than in healthy controls.⁶⁴ In contrast, 2 studies have not shown an increase of FAPDs in children adhering to a GFD compared with controls.^{72,73}

Endoscopic Evaluation

One of the considerations that the clinician encounters at the time of diagnosis is whether to conduct endoscopies. At times, this can be a challenging decision in which the clinician has to balance parental expectations, possible diagnostic uncertainties, and his or her ability to convincingly communicate the unnecessary need for testing when the FAPD diagnosis is clear.²⁴ Additionally, physicians who want to base their decision on evidence need to consider that some of the published data related to the utility of endoscopic testing are retrospective, do not use clear diagnostic criteria, and/or arrive at conclusions not based on scientific evidence.

A prospective cohort study at a US tertiary care center involved 290 children who underwent esophago-gastroduodenoscopy (EGD) for the primary indication of CAP. Ninety-three percent of patients fulfilled the Rome III criteria for a FAPD, including 40% of children with FD. One hundred and nine cases (38%) yielded a diagnosis that prompted the authors to propose that EGD should be widely used in children with CAP.⁷⁴ However, in this study, the presence of 2 or more alarm signs was statistically different in patients with a diagnostic EGD compared with a nondiagnostic EGD.⁷⁴ The study found that reflux esophagitis was the most common finding (21%), whereas other children were found to have *Helicobacter pylori* infection and a few children had an increased number of eosinophils.⁷⁴ Nonetheless, the article received some criticism.^{75,76} The study design could have led to selection bias resulting in overestimation of the utility of EGD in CAP.⁷⁴ Moreover, other noninvasive examinations (ie, *H pylori* stool antigen or FC) were not considered prior to the endoscopic procedure,^{75,76} and there was an unclear definition of gastroesophageal reflux. Although the study proposes that the findings confirm the wide need for EGD, the AAP/NASPGHAN technical report for CAP stated that the coexistence of abdominal pain and an abnormal test result for a common GI disorder, such as *H pylori* infection, does not necessarily indicate a causal relationship between them.²¹ Societal guidelines also do not recommend EGD for the diagnosis of reflux and/or *H pylori* infection.^{77,78} Recent European Society for Paediatric Gastroenterology, Hepatology and Nutrition (ESPGHAN)/NASPGHAN guidelines for the management of *H pylori* infection in children and adolescents recommend against a test-and-treat strategy for this condition, as well as testing for it in patients with FAPD (strong recommendation, high quality of evidence).⁷⁸

Along the same lines, a Czech prospective observational study showed that *H pylori* infection diagnosed by EGD was significantly associated with abdominal pain-related FGIDs, especially FD but not with FAP,⁷⁹ and the frequent finding of *H pylori* was also used to recommend testing in children with CAP. The diagnostic yield of EGD in a 398-child Turkish prospective cohort study was 65.1% in patients with alarm symptoms compared to 45.2% in patients without alarm symptoms ($P=.001$; odds ratio, 2.26; 95% CI, 1.49-3.44). *H pylori* gastritis was positive in 35.2% of patients.⁸⁰ However, both studies ignore the high prevalence of *H pylori* infection in children even in cases without abdominal pain. Spee and colleagues reported that in high-prevalence areas, similar to Turkey and the Czech Republic, the prevalence of *H pylori* infection ranged from 15.8% to 56.6%, with a mean prevalence of 37.0%.⁸¹ In low-prevalence regions, the prevalence of *H pylori* infection ranged from 9.4% to 28.9%, with a mean of 16.1%. This study did not find an association between *H pylori* infection and RAP.⁸¹

Another consideration in children with CAP is the differential diagnosis of eosinophilic esophagitis (EoE). However, it is important to remember that CAP is much more prevalent than EoE and that only a small minority of cases of EoE present with abdominal pain alone. The pediatric prevalence of EoE is 0.2 to 43.0 cases per 100,000,⁸² whereas the prevalence of FAPDs is 8.2% to 16.9%.^{12,13} In a large database study in the United States, the main reported symptom of pediatric patients with EoE was heartburn in 38.1% and abdominal pain or dyspepsia in 31%.⁸³ In pediatric patients undergoing an EGD for CAP, the frequency of EoE was 3.8% to 7.0% based on the study methodology,^{74,84,85} yet current guidelines do not address the use of EGD to differentiate EoE from FAPDs.⁸⁶⁻⁸⁸ Because cases of EoE with abdominal pain as the most bothersome symptom usually respond to the same treatment as FAPDs,⁸⁹ it seems reasonable to recommend using EGD in cases of a high index of suspicion for EoE and in recalcitrant cases of CAP that do not respond to treatment.

In a similar fashion, the usefulness of colonoscopy in CAP is unclear. Studies in pediatric patients have demonstrated colonoscopy findings ranging from normal results to nonsignificant differences in children with CAP.^{90,91} An Australian retrospective study found that 10% of colonoscopies for RAP had abnormal findings. However, all patients had previously abnormal FC and elevated serum inflammatory markers. Rectal bleeding was the only factor associated with an abnormal histology ($P=.019$).⁹²

The recent guidelines by the ESPGHAN and the European Society of Gastrointestinal Endoscopy recom-

mend performing EGD and colonoscopy in pediatric patients with alarm symptoms, but not in the case of FGIDs (both weak recommendations, low quality of evidence).⁹³ Mark and colleagues developed an evaluation algorithm to categorize children with CAP into low or high suspicion of having intestinal pathology on endoscopy.⁹⁴ The algorithm considered standard workup with ancillary evaluations if some alarm signs were present. Based on signs, symptoms, and/or noninvasive test results, patients were categorized as having high- or low-risk features. This algorithm was applied retrospectively to categorize 150 outpatients with CAP, and endoscopic findings were examined. The low-suspicion group included normal values for laboratory tests such as FC. Organic diagnoses were less frequent in the low-suspicion group (6%) compared with the high-suspicion group (34%) ($P<.001$). In addition to abdominal pain, patients with 3 or more indications (eg, pain, weight loss, diarrhea) or with 1 more high-risk laboratory or imaging finding had significantly increased odds of diagnostic endoscopic findings.⁹⁴ Interestingly, the authors considered peptic irritation, lactase deficiency, and *H pylori* without peptic ulcer disease to be nonrelevant findings because the first 2 can be empirically treated without the need for endoscopy,⁹⁴ and for the third, treatment is not recommended.⁷⁸ Another study found that the presence of anemia, hematochezia, and weight loss could help identify children with CAP who could benefit from colonoscopy.⁹⁰

In the search for endoscopic biomarkers for FGIDs, many studies have focused on the presence of intestinal low-grade inflammation. Some studies have found that patients with FGIDs have increased inflammatory cells (eg, eosinophils in the duodenum for FD and mast cells in the ileum or colon for IBS).⁹⁵⁻⁹⁸ However, those evaluations are currently limited to research purposes because their detection in a clinical setting would rarely influence patients' management. A study by Friesen and colleagues showed that montelukast, a leukotriene receptor antagonist, improved FD symptoms in some children regardless of endoscopic findings.⁹⁹ Studies in adults have used different anti-inflammatory medications, such as corticosteroids¹⁰⁰ and aminosalicylates (mesalazine)^{101,102} without any significant difference on IBS symptoms when compared with placebo.

A common justification for performing endoscopies is to reassure parents by demonstrating a normal study. However, these procedures are not exempt from risks that include pain, bleeding, infection, and/or perforation. Attard and colleagues reported a complication rate of 0.6% in a cohort of 217,817 children undergoing diagnostic endoscopic procedures.¹⁰³ Bonilla and colleagues reported that normal endoscopies do not impact

positively the outcomes of children with FGIDs (Rome II criteria).¹⁰⁴ Symptoms persisted in 61% and 64% of patients with and without endoscopies, respectively ($P=.76$).¹⁰⁴ These findings contrast results from studies in adults that suggested that normal endoscopies had potential positive impacts on treatment and patient reassurance.¹⁰⁵⁻¹⁰⁷ Furthermore, an adult study demonstrated that repeat EGD within 1 year after an initial normal EGD is not recommended in patients with FD.¹⁰⁸

In summary, most studies in children with FAPDs looking for abnormalities in endoscopy have been limited by small sample size, selection and sample bias, variability of findings, lack of standardization, and questionable specificity and generalizability. In line with the AAP/NASPGHAN recommendations,²¹ there is limited evidence to recommend the use of endoscopy and biopsy in the absence of alarm signs and normal FC. Based on these data, we recommend a thoughtful and conservative approach to the use of endoscopies. The decision should be tailored to each case, keeping in mind that children who had stable symptoms for several years in the setting of good general health and the absence of red flags are unlikely to have clinically significant endoscopic findings. Similarly, children who had negative endoscopies without change in chronic symptoms are unlikely to have abnormal findings in repeat testing.

Video Capsule Endoscopy

The efficacy of video capsule endoscopy (VCE) has been evaluated in adults with CAP, and findings have ranged from 23% to 48%.¹⁰⁹⁻¹¹¹ CAP alone as an indication for VCE has had significantly lower abnormal findings than VCE performed for other indications.^{110,111} In the presence of alarm signs, the possibility of abnormal findings in VCE increases from 18% to 42%.^{112,113} In general, the use of VCE is not recommended for CAP and/or FAPD.^{110,111}

Evaluation and Care Costs of Functional Abdominal Pain Disorders

Direct and indirect expenses related to IBS in adults account for over \$20 billion annually, as those patients use 50% more health care resources compared to patients without IBS.¹¹⁴ In 2014, annual outpatient health costs for patients with CAP in the Netherlands were approximately \$690 million, and 53.6% (approximately \$370 million) was related to FGIDs.¹¹⁵ For Dutch children with IBS or FAP, health care total annual costs were estimated to be approximately \$2800 per patient. Considering this individual cost per patient, the Dutch health care system could be spending over \$550 million in children age 8 to 18 years with FAPDs.¹¹⁶ In the United States, a

study estimated a mean cost of \$11,787 in adolescents (age 10-17 years) with chronic pain, extrapolated as an annual cost of \$19.5 billion to the US health care system.¹¹⁷

The inpatient economic burden has increased over the years in pediatric patients with FGIDs, as described by Park and colleagues.¹¹⁸ From 1997 to 2009, there was a significant increase in the total mean cost per discharge from \$6115 to \$18,058, despite a relatively stable length of stay. Abdominal pain as the primary discharge diagnosis had the greatest rise in average cost per hospital stay, with an increase from \$3558 to \$13,331. Dyspepsia was the most expensive treated condition, having increased costs from \$12,674 to \$35,898, a 183.2% rise in mean total charges.¹¹⁸

A retrospective descriptive study in a US tertiary care center calculated the cost-effectiveness of diagnostic studies in pain-predominant FGIDs. The average cost of diagnostic evaluation per patient was \$6104.30. All of the children included in the study underwent some type of diagnostic workup that included laboratory, radiologic, and endoscopic tests with a low diagnostic yield. The authors mentioned that their results likely underestimated costs because costs prior to the visit were not calculated.¹⁶ The study was conducted in the 2000s, so costs to the health care system have likely increased even further. A study in adult patients with functional bowel disorders reported that laboratory and radiologic tests accounted for 10% to 17% of outpatient costs.¹¹⁹ Research on adult patients has reported low clinical yield and low cost-effectiveness of gastric and duodenal biopsies for EGDs to evaluate abdominal pain,¹²⁰ although these results cannot be extrapolated to children.

As previously mentioned, the use of FC has increased due to its usefulness in GI disorders. A cost-effectiveness analysis of FC screening prior to endoscopic confirmation for suspected IBD saved \$300 per child and \$417 per adult. Direct endoscopic evaluation added a cost of \$6250 per child and \$18,955 per adult. Lower pretest probability for IBD enhanced the cost-effectiveness of the FC screening strategy, which also applies to patients with FAPDs.¹²¹ Although a systematic review in adults concluded that the utility of screening for CD in adults with IBS was unclear,⁶⁶ Mohseninejad and colleagues reported that in adult Dutch patients with an IBS-diarrhea or IBS-mixed phenotype, CD screening is most likely cost-effective.¹²² There are no studies addressing the cost-effectiveness for CD screening or other routine testing in children with FAPDs. Even though it is an added cost, as with FC, noninvasive testing could help with risk stratification of children with CAP, and is likely cost-effective. Invasive testing could be 7 to 300 times more expensive depending on the test used.¹⁶

Conclusion

This article shows that there is limited evidence to perform tests in children with FAPDs in the absence of alarm features. Pediatric patients with FAPDs and FGIDs usually undergo various evaluations ordered by either a general pediatrician or pediatric gastroenterologist due to clinical suspicion of a potential organic condition, but also for parental reassurance. Even though it has been almost 15 years since the publication of the AAP/NASPGHAN technical report on CAP, the current evidence still does not justify the need for routine diagnostic testing, especially in the absence of alarm signs. Many of the available studies were published prior to the generalization of the use of FC, which has shown to be a useful tool. If future studies show accuracy and reproducibility, another potential approach could involve an assessment algorithm with risk factors. Unnecessary testing usually carries into more patient and parental anxiety, affects the patient-physician relationship, and increases health care costs with very low yield in the end. The key intervention is to provide a diagnosis of FAPD with confidence and reassurance using a biopsychosocial approach.

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References

- van Tilburg MA, Hyman PE, Walker L, et al. Prevalence of functional gastrointestinal disorders in infants and toddlers. *J Pediatr*. 2015;166(3):684-689.
- Lewis ML, Palsson OS, Whitehead WE, van Tilburg MAL. Prevalence of functional gastrointestinal disorders in children and adolescents. *J Pediatr*. 2016;177:39-43.e3.
- van den Berg MM, Benninga MA, Di Lorenzo C. Epidemiology of childhood constipation: a systematic review. *Am J Gastroenterol*. 2006;101(10):2401-2409.
- Vandenplas Y, Abkari A, Bellaiche M, et al. Prevalence and health outcomes of functional gastrointestinal symptoms in infants from birth to 12 months of age. *J Pediatr Gastroenterol Nutr*. 2015;61(5):531-537.
- Chogle A, Velasco-Benitez CA, Koppen IJ, Moreno JE, Ramirez Hernandez CR, Saps M. A population-based study on the epidemiology of functional gastrointestinal disorders in young children. *J Pediatr*. 2016;179:139-143.e1.
- Rouster AS, Karpinski AC, Silver D, Monagas J, Hyman PE. Functional gastrointestinal disorders dominate pediatric gastroenterology outpatient practice. *J Pediatr Gastroenterol Nutr*. 2016;62(6):847-851.
- Koppen IJ, Nurko S, Saps M, Di Lorenzo C, Benninga MA. The pediatric Rome IV criteria: what's new? *Expert Rev Gastroenterol Hepatol*. 2017;11(3):193-201.
- Drossman DA. Functional gastrointestinal disorders: history, pathophysiology, clinical features and Rome IV. *Gastroenterology*. 2016;150(6):1262-1279.e2.
- Van Oudenhove L, Crowell MD, Drossman DA, et al. Biopsychosocial aspects of functional gastrointestinal disorders. *Gastroenterology*. 2016;150(6):1355-1367.e2.
- Rasquin-Weber A, Hyman PE, Cucchiara S, et al. Childhood functional gastrointestinal disorders. *Gut*. 1999;45(suppl 2):II60-II68.
- Hyams JS, Di Lorenzo C, Saps M, Shulman RJ, Staiano A, van Tilburg M. Functional disorders: children and adolescents. *Gastroenterology*. 2016;150(6):1456-1468.e2.
- Robin SG, Keller C, Zwiener R, et al. Prevalence of pediatric functional gastrointestinal disorders utilizing the Rome IV criteria. *J Pediatr*. 2018;195:134-139.
- Saps M, Velasco-Benitez CA, Langshaw AH, Ramirez-Hernández CR. Prevalence of functional gastrointestinal disorders in children and adolescents: comparison between Rome III and Rome IV criteria. *J Pediatr*. 2018;199:212-216.
- Saps M, Di Lorenzo C. Interobserver and intraobserver reliability of the Rome II criteria in children. *Am J Gastroenterol*. 2005;100(9):2079-2082.
- Chogle A, Dhroove G, Sztainberg M, Di Lorenzo C, Saps M. How reliable are the Rome III criteria for the assessment of functional gastrointestinal disorders in children? *Am J Gastroenterol*. 2010;105(12):2697-2701.
- Dhroove G, Chogle A, Saps M. A million-dollar work-up for abdominal pain: is it worth it? *J Pediatr Gastroenterol Nutr*. 2010;51(5):579-583.
- Ben-Menachem T, Decker GA, Early DS, et al; ASGE Standards of Practice Committee. Adverse events of upper GI endoscopy. *Gastrointest Endosc*. 2012;76(4):707-718.
- Fisher DA, Maple JT, Ben-Menachem T, et al; ASGE Standards of Practice Committee. Complications of colonoscopy. *Gastrointest Endosc*. 2011;74(4):745-752.
- Heinsch ML, Nightingale S. Functional gastrointestinal disorders in children and adolescents: knowledge, practice and attitudes of Australian paediatricians [published online January 9, 2019]. *J Paediatr Child Health*. doi:10.1111/jpc.14342.
- Sood MR, Matta SR. Approach to a child with functional abdominal pain. *Indian J Pediatr*. 2016;83(12-13):1452-1458.
- Di Lorenzo C, Colletti RB, Lehmann HP, et al; AAP Subcommittee; NASPGHAN Committee on Chronic Abdominal Pain. Chronic abdominal pain in children: a technical report of the American Academy of Pediatrics and the North American Society for Pediatric Gastroenterology, Hepatology and Nutrition. *J Pediatr Gastroenterol Nutr*. 2005;40(3):249-261.
- Gijsbers CF, Benninga MA, Schweizer JJ, Kneepkens CM, Vergouwe Y, Büller HA. Validation of the Rome III criteria and alarm symptoms for recurrent abdominal pain in children. *J Pediatr Gastroenterol Nutr*. 2014;58(6):779-785.
- GI Genius Interactive Clinical Decision Toolkit. Rome Foundation. <https://romeonline.org/product/rome-iv-interactive-clinical-decision-toolkit-logicnets/>. Accessed May 1, 2019.
- Devanarayana NM, Rajindrajith S. Irritable bowel syndrome in children: current knowledge, challenges and opportunities. *World J Gastroenterol*. 2018;24(21):2211-2235.
- Fishbein M, Bernard B, Ehrlich C. The primary care physician's approach to functional abdominal pain in childhood. *J Clin Gastroenterol*. 2006;40(6):497-503.
- van der Meer SB, Forget PP, Arends JW, Kuijten RH, van Engelshoven JM. Diagnostic value of ultrasound in children with recurrent abdominal pain. *Pediatr Radiol*. 1990;20(7):501-503.
- Wewer V, Strandberg C, Paerregaard A, Krasilnikoff PA. Abdominal ultrasonography in the diagnostic work-up in children with recurrent abdominal pain. *Eur J Pediatr*. 1997;156(10):787-788.
- Wallis EM, Fiks AG. Nonspecific abdominal pain in pediatric primary care: evaluation and outcomes. *Acad Pediatr*. 2015;15(3):333-339.
- Younas M, Shah S, Talaat A. Frequency of Giardia lamblia infection in children with recurrent abdominal pain. *J Pak Med Assoc*. 2008;58(4):171-174.
- Skorochodzki J, Ołdak E, Taraszkiewicz F, et al. Frequency of giardiasis in children with chronic abdominal pain coming from North-East Poland [in Polish]. *Przegl Epidemiol*. 1998;52(3):309-315.
- Zeyrek D, Zeyrek F, Cakmak A, Cekin A. Association of Helicobacter pylori and giardiasis in children with recurrent abdominal pain. *Turkiye Parazitoloj Derg*. 2008;32(1):4-7.
- Omrak EK, Mohammad AN. Intestinal parasites in patients with chronic abdominal pain. *J Egypt Soc Parasitol*. 2015;45(2):389-396.
- Gökben B, Appak YC, Girginkardeşler N, Ecemiş T, Kasirga E. Coexistence of Helicobacter pylori and intestinal parasitosis in children with chronic abdominal pain. *Turkiye Parazitoloj Derg*. 2016;40(1):32-36.
- de Jong MJ, Kortterink JJ, Benninga MA, Hillbink M, Widdershoven J, Deckers-Kocken JM. Dientamoeba fragilis and chronic abdominal pain in children: a case-control study. *Arch Dis Child*. 2014;99(12):1109-1113.
- Soon GS, Saunders N, Ipp M, Sherman PM, Macarthur C. Community-based case-control study of childhood chronic abdominal pain: role of selected laboratory investigations. *J Pediatr Gastroenterol Nutr*. 2007;44(4):524-526.
- John B, Fagerhol MK, Lyberg T, et al. Functional and clinical aspects of the myelomonocyte protein calprotectin. *Mol Pathol*. 1997;50(3):113-123.
- Dale I, Brandtzaeg P, Fagerhol MK, Scott H. Distribution of a new myelomonocytic antigen (L1) in human peripheral blood leukocytes. Immunofluorescence and immunoperoxidase staining features in comparison with lysozyme and lactoferrin. *Am J Clin Pathol*. 1985;84(1):24-34.
- Røseth AG, Fagerhol MK, Aadland E, Schjønby H. Assessment of the neu-

- trophil dominating protein calprotectin in feces. A methodologic study. *Scand J Gastroenterol.* 1992;27(9):793-798.
39. Roseth AG, Aadland E, Jahnsen J, Raknerud N. Assessment of disease activity in ulcerative colitis by faecal calprotectin, a novel granulocyte marker protein. *Digestion.* 1997;58(2):176-180.
40. Olafsdottir E, Aksnes L, Fluge G, Berstad A. Faecal calprotectin levels in infants with infantile colic, healthy infants, children with inflammatory bowel disease, children with recurrent abdominal pain and healthy children. *Acta Paediatr.* 2002;91(1):45-50.
41. Flagstad G, Helgeland H, Markestad T. Faecal calprotectin concentrations in children with functional gastrointestinal disorders diagnosed according to the pediatric Rome III criteria. *Acta Paediatr.* 2010;99(5):734-737.
42. Carroccio A, Iacono G, Cottone M, et al. Diagnostic accuracy of fecal calprotectin assay in distinguishing organic causes of chronic diarrhea from irritable bowel syndrome: a prospective study in adults and children. *Clin Chem.* 2003;49(6 pt 1):861-867.
43. Henderson P, Anderson NH, Wilson DC. The diagnostic accuracy of fecal calprotectin during the investigation of suspected pediatric inflammatory bowel disease: a systematic review and meta-analysis. *Am J Gastroenterol.* 2014;109(5):637-645.
44. Menees SB, Powell C, Kurlander J, Goel A, Chey WD. A meta-analysis of the utility of C-reactive protein, erythrocyte sedimentation rate, fecal calprotectin, and fecal lactoferrin to exclude inflammatory bowel disease in adults with IBS. *Am J Gastroenterol.* 2015;110(3):444-454.
45. Holtman GA, Lisman-van Leeuwen Y, Day AS, et al. Use of laboratory markers in addition to symptoms for diagnosis of inflammatory bowel disease in children: a meta-analysis of individual patient data. *JAMA Pediatr.* 2017;171(10):984-991.
46. Davidson F, Lock RJ. Paediatric reference ranges for faecal calprotectin: a UK study. *Ann Clin Biochem.* 2017;54(2):214-218.
47. Garg M, Leach ST, Coffey MJ, et al. Age-dependent variation of fecal calprotectin in cystic fibrosis and healthy children. *J Cyst Fibros.* 2017;16(5):631-636.
48. Guerrant RL, Araujo V, Soares E, et al. Measurement of fecal lactoferrin as a marker of fecal leukocytes. *J Clin Microbiol.* 1992;30(5):1238-1242.
49. Kane SV, Sandborn WJ, Rufo PA, et al. Fecal lactoferrin is a sensitive and specific marker in identifying intestinal inflammation. *Am J Gastroenterol.* 2003;98(6):1309-1314.
50. Mosli MH, Zou G, Garg SK, et al. C-reactive protein, fecal calprotectin, and stool lactoferrin for detection of endoscopic activity in symptomatic inflammatory bowel disease patients: a systematic review and meta-analysis. *Am J Gastroenterol.* 2015;110(6):802-819.
51. Dai C, Jiang M, Sun MJ, Cao Q. Fecal lactoferrin for assessment of inflammatory bowel disease activity: a systematic review and meta-analysis [published online April 15, 2019]. *J Clin Gastroenterol.* doi:10.1097/MCG.0000000000001212.
52. Holtman GA, Lisman-van Leeuwen Y, van Rheenen PF, et al. Evaluation of point-of-care test calprotectin and lactoferrin for inflammatory bowel disease among children with chronic gastrointestinal symptoms. *Fam Pract.* 2017;34(4):400-406.
53. Zhou XL, Xu W, Tang XX, et al. Fecal lactoferrin in discriminating inflammatory bowel disease from irritable bowel syndrome: a diagnostic meta-analysis. *BMC Gastroenterol.* 2014;14:121.
54. Silberer H, Küppers B, Mickisch O, et al. Fecal leukocyte proteins in inflammatory bowel disease and irritable bowel syndrome. *Clin Lab.* 2005;51(3-4):117-126.
55. Leonard MM, Sapone A, Catassi C, Fasano A. Celiac disease and nonceliac gluten sensitivity: a review. *JAMA.* 2017;318(7):647-656.
56. Ludvigsson JF, Leffler DA, Bai JC, et al. The Oslo definitions for celiac disease and related terms. *Gut.* 2013;62(1):43-52.
57. Verdu EF, Armstrong D, Murray JA. Between celiac disease and irritable bowel syndrome: the "no man's land" of gluten sensitivity. *Am J Gastroenterol.* 2009;104(6):1587-1594.
58. Llanos-Chea A, Fasano A. Gluten and functional abdominal pain disorders in children. *Nutrients.* 2018;10(10).
59. Ford AC, Chey WD, Talley NJ, Malhotra A, Spiegel BM, Moayyedi P. Yield of diagnostic tests for celiac disease in individuals with symptoms suggestive of irritable bowel syndrome: systematic review and meta-analysis. *Arch Intern Med.* 2009;169(7):651-658.
60. Sanders DS, Carter MJ, Hurlstone DP, et al. Association of adult coeliac disease with irritable bowel syndrome: a case-control study in patients fulfilling ROME II criteria referred to secondary care. *Lancet.* 2001;358(9292):1504-1508.
61. Sainsbury A, Sanders DS, Ford AC. Prevalence of irritable bowel syndrome-type symptoms in patients with celiac disease: a meta-analysis. *Clin Gastroenterol Hepatol.* 2013;11(4):359-365.e1.
62. Fitzpatrick KP, Sherman PM, Ipp M, Saunders N, Macarthur C. Screening for celiac disease in children with recurrent abdominal pain. *J Pediatr Gastroenterol Nutr.* 2001;33(3):250-252.
63. Hyams JS, Treem WR, Justinich CJ, Davis P, Shoup M, Burke G. Characterization of symptoms in children with recurrent abdominal pain: resemblance to irritable bowel syndrome. *J Pediatr Gastroenterol Nutr.* 1995;20(2):209-214.
64. Turco R, Boccia G, Miele E, et al. The association of coeliac disease in childhood with functional gastrointestinal disorders: a prospective study in patients fulfilling Rome III criteria. *Aliment Pharmacol Ther.* 2011;34(7):783-789.
65. Cristofori F, Fontana C, Magistà A, et al. Increased prevalence of celiac disease among pediatric patients with irritable bowel syndrome: a 6-year prospective cohort study. *JAMA Pediatr.* 2014;168(6):555-560.
66. Irvine AJ, Chey WD, Ford AC. Screening for celiac disease in irritable bowel syndrome: an updated systematic review and meta-analysis. *Am J Gastroenterol.* 2017;112(1):65-76.
67. Sanders DS, Patel D, Stephenson TJ, et al. A primary care cross-sectional study of undiagnosed adult coeliac disease. *Eur J Gastroenterol Hepatol.* 2003;15(4):407-413.
68. Choung RS, Rubio-Tapia A, Lahr BD, et al. Evidence against routine testing of patients with functional gastrointestinal disorders for celiac disease: a population-based study. *Clin Gastroenterol Hepatol.* 2015;13(11):1937-1943.
69. Kansu A, Kuloglu Z, Demir A, Yaman A; Turkish Celiac Study Group. Yield of coeliac screening in abdominal pain-associated functional gastrointestinal system disorders. *J Paediatr Child Health.* 2015;51(11):1066-1070.
70. Pulido O, Zarkadas M, Dubois S, et al. Clinical features and symptom recovery on a gluten-free diet in Canadian adults with celiac disease. *Can J Gastroenterol.* 2013;27(8):449-453.
71. Sansotta N, Amirikian K, Guandalini S, Jericho H. Celiac disease symptom resolution: effectiveness of the gluten-free diet. *J Pediatr Gastroenterol Nutr.* 2018;66(1):48-52.
72. Saps M, Adams P, Bonilla S, Nichols-Vinueza D. Abdominal pain and functional gastrointestinal disorders in children with celiac disease. *J Pediatr.* 2013;162(3):505-509.
73. Saps M, Sansotta N, Bingham S, et al. Abdominal pain-associated functional gastrointestinal disorder prevalence in children and adolescents with celiac disease on gluten-free diet: a multinational study. *J Pediatr.* 2017;182:150-154.
74. Thakkar K, Chen L, Tessier ME, Gilger MA. Outcomes of children after esophagogastroduodenoscopy for chronic abdominal pain. *Clin Gastroenterol Hepatol.* 2014;12(6):963-969.
75. Bourke B. Outcomes of children after esophagogastroduodenoscopy for chronic abdominal pain. *Clin Gastroenterol Hepatol.* 2015;13(2):409.
76. Mones RL. Outcomes of children after esophagogastroduodenoscopy for chronic abdominal pain. *Clin Gastroenterol Hepatol.* 2015;13(2):408-409.
77. Rosen R, Vandenplas Y, Singendonk M, et al. Pediatric gastroesophageal reflux clinical practice guidelines: joint recommendations of the North American Society for Pediatric Gastroenterology, Hepatology, and Nutrition and the European Society for Pediatric Gastroenterology, Hepatology, and Nutrition. *J Pediatr Gastroenterol Nutr.* 2018;66(3):516-554.
78. Jones NL, Koletzko S, Goodman K, et al; ESPGHAN, NASPGHAN. Joint ESPGHAN/NASPGHAN guidelines for the management of *Helicobacter pylori* in children and adolescents (update 2016). *J Pediatr Gastroenterol Nutr.* 2017;64(6):991-1003.
79. Sýkora J, Huml M, Siala K, et al. Paediatric Rome III criteria-related abdominal pain is associated with *Helicobacter pylori* and not with calprotectin. *J Pediatr Gastroenterol Nutr.* 2016;63(4):417-422.
80. Akbulut UE, Emeksiz HC, Kocak FG, Livaoglu A. Diagnostic yield of esophagogastroduodenoscopy in children with chronic abdominal pain. *Arch Med Sci.* 2018;14(1):74-80.
81. Spee LA, Madderom MB, Pijpers M, van Leeuwen Y, Berger MY. Association between *Helicobacter pylori* and gastrointestinal symptoms in children. *Pediatrics.* 2010;125(3):e651-e669.
82. Soon IS, Butzner JD, Kaplan GG, deBruyn JC. Incidence and prevalence of eosinophilic esophagitis in children. *J Pediatr Gastroenterol Nutr.* 2013;57(1):72-80.
83. Kapel RC, Miller JK, Torres C, Aksoy S, Lash R, Katzka DA. Eosinophilic esophagitis: a prevalent disease in the United States that affects all age groups. *Gastroenterology.* 2008;134(5):1316-1321.
84. Thakkar K, Chen L, Tatevian N, et al. Diagnostic yield of oesophagogastroduodenoscopy in children with abdominal pain. *Aliment Pharmacol Ther.* 2009;30(6):662-669.
85. Sheiko MA, Feinstein JA, Capocelli KE, Kramer RE. Diagnostic yield of EGD in children: a retrospective single-center study of 1000 cases. *Gastrointest Endosc.*

- 2013;78(1):47-54.e1.
86. Liacouras CA, Furuta GT, Hirano I, et al. Eosinophilic esophagitis: updated consensus recommendations for children and adults. *J Allergy Clin Immunol*. 2011;128(1):3-20.e6; quiz 21-22.
 87. Lucendo AJ, Molina-Infante J, Arias Á, et al. Guidelines on eosinophilic esophagitis: evidence-based statements and recommendations for diagnosis and management in children and adults. *United European Gastroenterol J*. 2017;5(3):335-358.
 88. Dellon ES, Liacouras CA, Molina-Infante J, et al. Updated international consensus diagnostic criteria for eosinophilic esophagitis: proceedings of the AGREE conference. *Gastroenterology*. 2018;155(4):1022-1033.e10.
 89. Gunasekaran TS, Chu C, Ronquillo N Jr, et al. Detailed histologic evaluation of eosinophilic esophagitis in pediatric patients presenting with dysphagia or abdominal pain and comparison of the histology between the two groups. *Can J Gastroenterol Hepatol*. 2017;2017:3709254.
 90. El-Chammas K, Majeskie A, Simpson P, Sood M, Miranda A. Red flags in children with chronic abdominal pain and Crohn's disease—a single center experience. *J Pediatr*. 2013;162(4):783-787.
 91. Kawada PS, O'Loughlin EV, Stormon MO, Dutt S, Lee CH, Gaskin KJ. Are we overdoing pediatric lower gastrointestinal endoscopy? *J Pediatr Gastroenterol Nutr*. 2017;64(6):898-902.
 92. Singh HK, Ee LC. Recurrent abdominal pain in children: is colonoscopy indicated? *J Pediatr Gastroenterol Nutr*. 2019;68(2):214-217.
 93. Thomson M, Tringali A, Dumonceau JM, et al. Paediatric gastrointestinal endoscopy: European Society for Paediatric Gastroenterology Hepatology and Nutrition and European Society of Gastrointestinal Endoscopy guidelines. *J Pediatr Gastroenterol Nutr*. 2017;64(1):133-153.
 94. Mark JA, Campbell K, Gao D, Kramer RE. Algorithm to predict which children with chronic abdominal pain are low suspicion for significant endoscopic findings. *Clin Pediatr (Phila)*. 2019;58(1):79-87.
 95. Lee E, Schiller LR, Fordtran JS. Quantification of colonic lamina propria cells by means of a morphometric point-counting method. *Gastroenterology*. 1988;94(2):409-418.
 96. Salzmann JL, Peltier-Koch F, Bloch F, Petite JP, Camilleri JP. Morphometric study of colonic biopsies: a new method of estimating inflammatory diseases. *Lab Invest*. 1989;60(6):847-851.
 97. Friesen CA, Andre L, Garola R, Hodge C, Roberts C. Activated duodenal mucosal eosinophils in children with dyspepsia: a pilot transmission electron microscopic study. *J Pediatr Gastroenterol Nutr*. 2002;35(3):329-333.
 98. Talley NJ, Walker MM, Aro P, et al. Non-ulcer dyspepsia and duodenal eosinophilia: an adult endoscopic population-based case-control study. *Clin Gastroenterol Hepatol*. 2007;5(10):1175-1183.
 99. Friesen CA, Kearns GL, Andre L, Neustrom M, Roberts CC, Abdel-Rahman SM. Clinical efficacy and pharmacokinetics of montelukast in dyspeptic children with duodenal eosinophilia. *J Pediatr Gastroenterol Nutr*. 2004;38(3):343-351.
 100. Dunlop SP, Jenkins D, Neal KR, et al. Randomized, double-blind, placebo-controlled trial of prednisolone in post-infectious irritable bowel syndrome. *Aliment Pharmacol Ther*. 2003;18(1):77-84.
 101. Lam C, Tan W, Leighton M, et al. Efficacy and mode of action of mesalazine in the treatment of diarrhoea-predominant irritable bowel syndrome (IBS-D): a multicentre, parallel-group, randomised placebo-controlled trial. In: *Efficacy and Mechanism Evaluation, No. 2.2*. Southampton, UK, NIHR Journals Library; 2015. <https://www.ncbi.nlm.nih.gov/books/NBK280103/>.
 102. Barbara G, Cremon C, Annesse V, et al. Randomised controlled trial of mesalazine in IBS. *Gut*. 2016;65(1):82-90.
 103. Attard TM, Miller M, Lee B, Champion TW, Thomson M. Pediatric elective diagnostic procedure complications: a multicenter cohort analysis. *J Gastroenterol Hepatol*. 2019;34(1):147-153.
 104. Bonilla S, Wang D, Saps M. The prognostic value of obtaining a negative endoscopy in children with functional gastrointestinal disorders. *Clin Pediatr (Phila)*. 2011;50(5):396-401.
 105. Drossman DA, Whitehead WE, Camilleri M. Irritable bowel syndrome: a technical review for practice guideline development. *Gastroenterology*. 1997;112(6):2120-2137.
 106. Rabeneck L, Wristers K, Soucek J, Ambriz E. Impact of upper endoscopy on satisfaction in patients with previously uninvestigated dyspepsia. *Gastrointest Endosc*. 2003;57(3):295-299.
 107. Chey WD, Nojkov B, Rubenstein JH, Dobhan RR, Greenson JK, Cash BD. The yield of colonoscopy in patients with non-constipated irritable bowel syndrome: results from a prospective, controlled US trial. *Am J Gastroenterol*. 2010;105(4):859-865.
 108. Guo JF, Bai Y, Li ZS. Diagnostic yield of repeat upper gastrointestinal endoscopy for patients with functional dyspepsia. *J Dig Dis*. 2013;14(11):574-578.
 109. Yang L, Chen Y, Zhang B, et al. Increased diagnostic yield of capsule endoscopy in patients with chronic abdominal pain. *PLoS One*. 2014;9(1):e87396.
 110. Egnatios J, Kaushal K, Kalmaz D, Zarrinpar A. Video capsule endoscopy in patients with chronic abdominal pain with or without associated symptoms: a retrospective study. *PLoS One*. 2015;10(4):e0126509.
 111. Valero M, Bravo-Velez G, Oleas R, et al. Capsule endoscopy in refractory diarrhoea-predominant irritable bowel syndrome and functional abdominal pain. *Clin Endosc*. 2018;51(6):570-575.
 112. Kalla R, McAlindon ME, Sanders DS, Sidhu R. Subtle mucosal changes at capsule endoscopy in diarrhoea predominant irritable bowel syndrome. *Med Hypotheses*. 2012;79(3):423.
 113. Xue M, Chen X, Shi L, Si J, Wang L, Chen S. Small-bowel capsule endoscopy in patients with unexplained chronic abdominal pain: a systematic review. *Gastrointest Endosc*. 2015;81(1):186-193.
 114. Brandt LJ, Chey WD, Foxx-Orenstein AE, et al; American College of Gastroenterology Task Force on Irritable Bowel Syndrome. An evidence-based position statement on the management of irritable bowel syndrome. *Am J Gastroenterol*. 2009;104(suppl 1):S1-S35.
 115. Jansen LA, Knauff EA, Tan SS, Löwenberg M. Estimated hospital health costs of chronic abdominal pain in the Netherlands. *Neth J Med*. 2014;72(2):102-106.
 116. Hoekman DR, Rutten JM, Vlieger AM, Benninga MA, Dijkgraaf MG. Annual costs of care for pediatric irritable bowel syndrome, functional abdominal pain, and functional abdominal pain syndrome. *J Pediatr*. 2015;167(5):1103-1108.e2.
 117. Groenewald CB, Essner BS, Wright D, Fesinmeyer MD, Palermo TM. The economic costs of chronic pain among a cohort of treatment-seeking adolescents in the United States. *J Pain*. 2014;15(9):925-933.
 118. Park R, Mikami S, LeClair J, et al. Inpatient burden of childhood functional GI disorders in the USA: an analysis of national trends in the USA from 1997 to 2009. *Neurogastroenterol Motil*. 2015;27(5):684-692.
 119. Nyrop KA, Palsson OS, Levy RL, et al. Costs of health care for irritable bowel syndrome, chronic constipation, functional diarrhoea and functional abdominal pain. *Aliment Pharmacol Ther*. 2007;26(2):237-248.
 120. Nelsen EM, Lochmann-Bailkey A, Grimes IC, Benson ME, Gopal DV, Pfau PR. Low yield and high cost of gastric and duodenal biopsies for investigation of symptoms of abdominal pain during routine esophagogastroduodenoscopy. *Dig Dis Sci*. 2017;62(2):418-423.
 121. Yang Z, Clark N, Park KT. Effectiveness and cost-effectiveness of measuring fecal calprotectin in diagnosis of inflammatory bowel disease in adults and children. *Clin Gastroenterol Hepatol*. 2014;12(2):253-262.e2.
 122. Mohseninejad L, Feenstra T, van der Horst HE, Woutersen-Koch H, Buskens E. Targeted screening for coeliac disease among irritable bowel syndrome patients: analysis of cost-effectiveness and value of information. *Eur J Health Econ*. 2013;14(6):947-957.