

Silent Inflammatory Bowel Disease

Matthew D. Coates, MD, PhD*[†],^{ID} and David G. Binion, MD*[†],^{ID}

*Department of Medicine, Division of Gastroenterology & Hepatology, Penn State College of Medicine, Hershey, Pennsylvania, USA

[†]Department of Pharmacology, Penn State College of Medicine, Hershey, Pennsylvania, USA

[‡]Department of Medicine, Division of Gastroenterology, Hepatology & Nutrition, University of Pittsburgh Medical Center, Pittsburgh, Pennsylvania, USA

Address correspondence to: Matthew D. Coates, MD, PhD, Division of Gastroenterology & Hepatology, Penn State College of Medicine, Hershey, PA 17033, USA (mcoates@pennstatehealth.psu.edu).

Inflammatory bowel disease (IBD) is frequently associated with a variety of problematic symptoms, including abdominal pain and bowel habit changes, which are associated with poor patient quality of life and significant healthcare expenditure. Interestingly, silent IBD, a condition where patients demonstrate reduced perception and/or reporting of symptoms in the setting of active inflammation, may be as clinically consequential. This condition has been associated with serious complications leading to more costly interventions. It is by its nature an under-recognized phenomenon that affects substantial portions of patients with either Crohn's disease or ulcerative colitis. At the present time, although there are a variety of theories relating to the underlying causes and contributors, little is known about why this phenomenon occurs. As a result, there is a lack of cost-effective, reliable diagnostic methods to identify and manage "at-risk" patients. However, it is significantly likely that further study and an improved understanding of this condition will lead to improved approaches for the diagnosis and treatment of patients with silent IBD as well as other gastrointestinal disorders associated with alterations in symptomatic perception. In this article, we critically review studies that have investigated silent IBD. Specifically, we discuss the following: (1) the methods for defining silent IBD, (2) the known epidemiology of silent IBD, (3) potential causes of and contributors to this clinical entity, (4) current diagnostic modalities available to identify it, and (5) gaps in our understanding as well as potential novel diagnostic and therapeutic applications that could be developed with further study of this condition.

Lay Summary

Silent inflammatory bowel disease is a poorly understood and impactful condition where patients with active disease exhibit minimal symptoms. Here, we review prior relevant studies and explore how more careful research could refine our understanding of this phenomenon.

Key Words: silent inflammatory bowel disease, Crohn's disease, ulcerative colitis, asymptomatic active disease, visceral hypoaesthesia

Introduction

Crohn's disease (CD) and ulcerative colitis (UC) are forms of inflammatory bowel disease (IBD), and are characterized as chronic, lifelong, incurable disorders associated with relapsing episodes of inflammation involving the gastrointestinal (GI) tract. IBD may affect more than 3 million Americans, most of whom were diagnosed at an early age.¹ At the onset of disease or during periods of increased disease activity or "flares," patients frequently report experiencing significant abdominal pain and/or changes in their bowel habits (including development of looser stools often associated with fecal urgency and frequency). Abdominal pain and bowel habit changes are both commonly reported during active phases of IBD (exhibited in >70% of patients in these circumstances) and are a major reason that individuals with IBD seek medical attention.^{2,3} As a result, these symptoms are also significant drivers of healthcare resource utilization, lost work hours and reduction in quality of life, even during the periods of relative disease quiescence.^{2,4,5}

Importantly, though, the lack of symptoms in IBD can also pose significant challenges. Individuals with so-called "silent IBD" have grossly evident intestinal inflammatory changes or complications of inflammation (eg, strictures, fistulae, abscesses) that either do not produce identifiable symptoms (including abdominal pain and bowel habit changes) and/or produce symptoms that are minimized by the patient. In fact, it has been

increasingly recognized that symptom-based assessment tools can be relatively insensitive for accurately assessing IBD activity.⁶ Various estimates have suggested that a third or more of IBD patients with active disease may be asymptomatic.^{7–10} This is important considering that individuals with "silent IBD" are less likely to seek appropriate medical attention and may be more likely to develop certain serious complications (including strictures, fistulae, and abscesses) that ultimately incur major healthcare costs, including hospitalization.^{8,9,11}

This review was written to describe what is known about the clinical entity known as silent IBD and to discuss the necessary steps to improve our understanding about this condition in order to effectively identify and manage it. In the process, we describe how silent IBD is currently defined, review what is known about its epidemiology and identify potential causes and contributors, while also discussing current gaps of knowledge in our understanding of this condition. Finally, we discuss the potential scientific and clinical applications that could be developed with further study of this enigmatic condition.

Defining Silent IBD

Silent diseases are generally defined as medical conditions without overt or obvious signs or symptoms. What constitutes an overt or obvious symptom may be debatable for any

Received for publications: March 26, 2021. Editorial Decision: August 7, 2021

© The Author(s) 2021. Published by Oxford University Press on behalf of Crohn's & Colitis Foundation.

This is an Open Access article distributed under the terms of the Creative Commons Attribution-Non-Commercial License (<https://creativecommons.org/licenses/by-nc/4.0/>), which permits non-commercial re-use, distribution, and reproduction in any medium, provided the original work is properly cited. For commercial re-use, please contact journals.permissions@oup.com

particular condition and/or patient and may be influenced by a wide variety of factors. For example, silent diseases may be relatively mild in severity during portions of their existence, allowing them to be insidious in their inception and/or during part of their course, such as is often the case with hypertension,¹² diabetes mellitus,¹³ ischemic heart disease,¹⁴ and fatty liver disease.¹⁵ They may affect anatomical regions (including a variety of malignancies, such as breast,¹⁶ kidney,¹⁷ pancreatic,¹⁸ and prostate¹⁹ cancer), and/or physiological functions (eg, impaired renal function in chronic kidney disease²⁰) that are less likely to impart problems that are easily observed by patients or their caregivers, particularly during early or indolent periods of the disease. Even in cases where a disease process leads to dysfunction and outward indicators of poor health, if the symptoms are subtle or not intuitively related to a particular bodily function, individuals may still not perceive them effectively and/or may simply ignore them. In fact, all diseases are associated with a potential clinical profile of signs and symptoms, each of which have the capability of exhibiting a spectrum of severity. In some cases, detection of an otherwise “silent” disorder could be a matter of evaluating for specific findings, in an appropriate location at the right time.

As with the disorders described above, silent IBD could be described as existing when patients with established or undiagnosed versions of these disorders fail to exhibit and/or recognize signs or symptoms during active phases of the disease. Technically, however, there is no single, universally accepted definition of silent IBD, or set of diagnostic criteria to conclusively identify individuals with this condition. In fact, the terminology used to describe these individuals can vary a great deal. This inconsistency in terminology is likely due to the wide range of potential contributors associated with this condition. For example, some individuals have been labeled as having “asymptomatic” IBD. Interestingly, previous studies using this descriptor have demonstrated that many of these individuals actually did harbor previously unrecognized GI or other related symptoms.^{10,21}

Accordingly, early in the course and/or during seemingly quiescent phases of the disease, patients with silent IBD may be labeled as having “unrecognized,” “undetected,” “undiagnosed,” or “prodromal” disease,^{22,23} particularly if they have not been formally labeled as having CD or UC. This is relevant as patients and providers often report that it can take years after the onset of symptoms to apply the formal diagnosis of IBD, due to underappreciated clinical manifestations of the disease and/or overlap with different conditions (eg, celiac disease, irritable bowel syndrome, acute and chronic GI infections, other autoimmune enterocolitides, neuroendocrine disorders of the gut) that have similar symptomatic profiles.²² This is made all the more likely given the great number of clinical conditions that mimic symptoms classically associated with IBD.

Silent IBD patients are also often described as “under-feelers,” “under-sensers,” or “under-reporters,”^{9,24} demonstrating the frequent reliance that patients and their caregivers have on using abdominal pain as an indicator of the presence and/or activity of IBD. Importantly, in these cases, other symptoms (including diarrhea, hematochezia, and fecal urgency) may frequently still be concurrently present.⁹

In spite of the myriad approaches investigators and healthcare providers have described and studied silent IBD, it is important to note that most scientific publications relating

to this clinical entity are focused on individuals with established diagnosis of CD, UC, or undifferentiated IBD-associated colitis. Thus, unless specifically indicated otherwise, the following studies evaluated patients with known diagnoses of IBD.

Evaluating for Silent IBD

One of the primary challenges that silent IBD poses is the reliable identification of active inflammation and/or related complications. While a variety of approaches can be employed, there is significant debate about the optimal method(s) for screening and identifying this clinical entity. Studies attempting to evaluate for silent IBD have utilized a wide range of measures to address this challenge. Regardless of their sensitivity in calling attention to active IBD, a careful accounting of each patient’s symptomatic experience is essential. In order to obtain an accurate sense of the symptomatic experience, investigators have relied upon a variety of approaches, including use of the physician global assessment, direct inquiry of the patient and/or several validated clinical scores for IBD, including the Crohn’s disease activity index (CDAI) and Harvey–Bradshaw Index (HBI) for CD,^{25,26} and the Truelove and Witt’s Severity Index, Clinical Activity Index (CAI), and Simple Clinical Colitis Activity Index (SCCAI) for UC.^{27,28} In some studies, measures of quality of life, such as the Short Inflammatory Bowel Disease Quotient (SIBDQ),²⁹ have been included to provide additional information about patient status, though silent IBD patients have not been shown to be significantly impacted using this measure.^{8,9,24} Of note, there has been significant variation in how studies of silent IBD have determined whether a patient has clinically meaningful symptoms. Additionally, the choices of cutoff scores for each index to define a patient as “asymptomatic” or “silent” also vary among studies (even when employing the same assessment). This has made the comparison and interpretation of results among different studies difficult.

Incidental findings during patient examinations may also prove helpful in this regard. Several coincident examination findings and/or medical conditions have been identified at the time of or just before the incidental diagnosis of asymptomatic IBD. A variety of phenomena that would classically be considered extraintestinal manifestations of IBD, including ankylosing spondylitis/spondyloarthritis,^{30,31} primary sclerosing cholangitis,³² anemia, and venous thromboembolism³³ have been associated with previously unrecognized IBD. There are also a number of atypical conditions that may foretell the presence of IBD, including splenic abscesses,³⁴ Takayasu’s arteritis,³⁵ and vertebral subluxation.³⁶ Some rare conditions that may manifest in the absence of overt GI symptoms also appear to be uniquely associated with IBD, including pyostomatitis vegetans, a perioral condition reported almost exclusively in the setting of CD or UC.^{37–39}

As previous studies have proven, though, historical and physical examination-based patient assessments frequently fail to identify individuals with active inflammation.^{7,40} Thus, it is standard practice to pair these approaches with objective measures of disease activity. There are a variety of evidence-based objective assessment tools that can be used in this setting and have been used in studies of silent IBD, including serological measures of inflammatory activity (eg, C-reactive protein [CRP], sedimentation rate [ESR]), stool tests (eg,

fecal calprotectin), radiological imaging (eg, small bowel follow through, ultrasound, computed tomography [CT] scan, magnetic resonance imaging), and endoscopic evaluation (eg, colonoscopy ± esophagogastroduodenoscopy, capsule enteroscopy).^{41–43} Some measures, such as the Mayo Clinic (UC) Disease Activity Index (DAI), incorporate both symptoms and objective testing (eg, activity assessed during endoscopic evaluation).²⁸

It is not currently known if one or more of these assessments is better at revealing the presence of IBD-associated inflammation and/or complications. Direct endoscopic evaluation of the GI tract with mucosal biopsy (using an ileocolonoscopy with or without an upper endoscopic examination) has been the preferred method for diagnosing and monitoring IBD for decades,^{43–45} but there is evidence that these tests can miss a significant number of active cases, particularly when cases involve deep small bowel CD. Sorrentino and Nguyen demonstrated in a small retrospective series of CD patients with unexplained GI symptoms (eg, abdominal pain, diarrhea, etc.), that contemporary endoscopic evaluation had missed approximately half of the active cases that capsule endoscopy, cross-sectional abdominal imaging (eg, abdominal CT scan) and/or serological inflammatory markers identified.⁴⁶ Capsule endoscopy has proven to be relatively sensitive for detecting and helping to localize small bowel CD when compared to cross-sectional imaging tests,^{47,48} but it may miss extraluminal inflammatory disease or complications, and its use can be limited in the setting of known or suspected stricturing disease.⁴⁹ Fecal (calprotectin) and serological markers (CRP, ESR) of inflammatory activity can be sensitive for the presence of IBD-related activity, especially that related to IBD-associated colitis,^{50–52} but are nonspecific and, in the case of fecal calprotectin, have less utility in the setting of small bowel disease.⁵³ While each of these tests is frequently employed individually and collectively in CD and UC, none of them have been compared in the setting of silent IBD.

Epidemiology and Clinical Characteristics of Silent IBD

Estimates for the prevalence of silent IBD vary widely depending on the diagnostic criteria and testing utilized. Of the studies that have attempted to directly assess this, values have ranged between 19% and 57% of all IBD patients.^{8–10,24,54–56} Notably, in the investigations utilizing endoscopic evaluation of disease activity, estimates of silent IBD were relatively higher. For example, in a Japanese study of 2829 individuals who had positive fecal occult blood tests, abnormal barium enemas and who underwent colonoscopy, 21 individuals were newly identified as having IBD (19 UC, 2 CD). Of these 21 individuals, 12 (57%) were described as having asymptomatic or minimally symptomatic IBD.¹⁰ Baars et al evaluated IBD patients in clinical remission (defined by physician global assessment and lack of patient reports of abdominal pain, diarrhea, blood loss, and/or weight loss) for at least 1 month who underwent colonoscopy, and found that 49% still had some degree of grossly evident inflammation.⁵⁵ In the SONIC trial (a multicenter, randomized, active controlled trial comparing infliximab to azathioprine and infliximab with azathioprine in CD patients who were naive to these therapies), clinical remission was defined as a CDAI score <150 but disease activity was further evaluated using ileocolonoscopy evaluation

and CRP (obtained at the beginning of the study period as well as at 6 months).⁷ The SONIC investigators found that, after 6 months of follow-up, 64 of 136 patients (47%) with CDAI <150 had endoscopic and/or laboratory evidence of inflammation. In our own study of hypoalgesic IBD patients (ie, individuals with moderate–severe inflammation observed on endoscopic examination with little to no reported abdominal pain), we found that approximately 26% of CD patients and 31% of UC patients qualified for this condition.⁹

Of note, both CD (19%–47%)^{7–9,24} and UC (31%–57%)^{9,10} have been associated with silent IBD. No study to date has demonstrated that silent IBD is more common in 1 particular subtype of IBD.^{7–11,21,24} While Sakata et al demonstrated that most of their silent IBD cohort had colonic disease,¹⁰ no other study has determined that silent IBD is associated with active disease in a particular region of the GI tract, even when considering subtypes of CD and/or UC based upon the Montreal location classification.^{9,11,24,57} Several studies suggest that silent IBD patients are more likely to be male,^{9,10} while others demonstrate no significant difference in sex/gender distribution.^{8,11,24} In regard to age, at least 1 study demonstrated that silent IBD patients are older than their symptom perceptive counterparts,⁹ while most investigations have shown no significant difference in this regard in the context of silent IBD.

Few studies have assessed other clinical and demographic characteristics in silent IBD but there are some notable findings from those that have. Click et al revealed a lower incidence of prior IBD-related surgery in the setting of silent CD,⁸ while Coates et al found no significant difference in likelihood of prior surgery when hypoalgesic IBD patients were compared to other IBD patients.⁹ Click et al also demonstrated that diabetes mellitus was more common in silent CD.⁸ There are discrepancies in association with assessment of comorbid psychiatric conditions, as Click et al demonstrated an increased incidence of psychiatric conditions (eg, depression and anxiety),⁸ while Coates et al found that symptoms of anxiety and/or depression and antidepressant/anxiolytic use were less likely in hypoalgesic IBD patients.⁹ Coates et al also demonstrated that hypoalgesic IBD is less frequently associated with opiate use as well as use of other pain medications (including acetaminophen, antispasmodics, and nonsteroidal anti-inflammatory drugs [NSAIDs]).⁹

Consequences of Silent IBD

It has been difficult to determine the exact impact of this condition, but patients with silent IBD appear to be at risk for several consequential outcomes. Bhattacharya et al demonstrated that CD patients considered to be in remission (in this case having a HBI score of ≤4) with abnormal elevations in their inflammatory marker (CRP) levels are at increased risk for worsening Lemann index scores (suggesting the development of progressive bowel damage).^{24,58} In 2 separate studies, we demonstrated that patients who deny having abdominal pain despite having concomitant endoscopically proven moderate–severe active IBD are significantly more likely to have intra-abdominal fistulae.^{9,11} Other observational studies have indicated that individuals with silent IBD are also at risk for many of the same complications as those with associated active disease, including nutritional deficiency (eg, iron),⁵⁹ anemia,⁵⁹ osteoporosis,⁶⁰ venous thromboembolism,³³ and precancerous changes in the intestinal tract.⁵⁵ Additionally,

several case reports or case series have tied more devastating outcomes with the revelation of unrecognized or silent IBD, including intestinal obstruction,^{61,62} intra-abdominal and/or enterocutaneous fistulae,^{63–65} intestinal perforation,⁶⁶ and colon or small bowel cancer.^{61,67–69}

In addition to the health-related impacts, there are cost and healthcare resource related impacts of silent IBD. For example, Click et al evaluated a large cohort of asymptomatic CD patients with elevated CRP values and found that these individuals were at increased risk of future hospitalization.⁸ Oh et al demonstrated that CD patients in symptomatically defined “clinical remission” (as defined by a CDAI of <150) with concomitant CRP elevations were at increased risk of hospitalization and bowel surgery.⁵⁶ If patients are feeling relatively well and/or do not perceive their IBD to be problematic or dangerous, they may be less likely to take their medications, follow up for important tests or clinic visits or undergo otherwise appropriate procedures.^{70–72} Similarly, if healthcare providers perceive that their patients are in remission due to a lack of reported or recognized symptoms, or due to miscommunication, they may be less likely to pursue further testing to objectively evaluate IBD activity.^{54,73,74} These issues are all known to be important determinants of longer term healthcare costs in the setting of IBD.^{71,75}

Potential Etiology of Silent IBD

What leads to the development of silent IBD and contributes to its manifestation remains unclear. There are a variety of potential contributors that may influence the development of this condition either individually or simultaneously (Figure 1). One theory suggests that at least some of these individuals are “stoic” patients.⁵⁴ In other words, some individuals may experience pain and/or other problematic symptoms, but they either ignore or minimize them because they do not believe they are meaningful, do not want the symptoms to adversely impact their life, and/or do not want to trouble others with these issues.⁷⁶

Another potential contributor relates to the fact that IBD-associated inflammation and complications in some forms of IBD may develop very slowly, allowing for certain patients to “acclimate” to the changes occurring in their gut without experiencing acute changes more apt to lead to symptoms

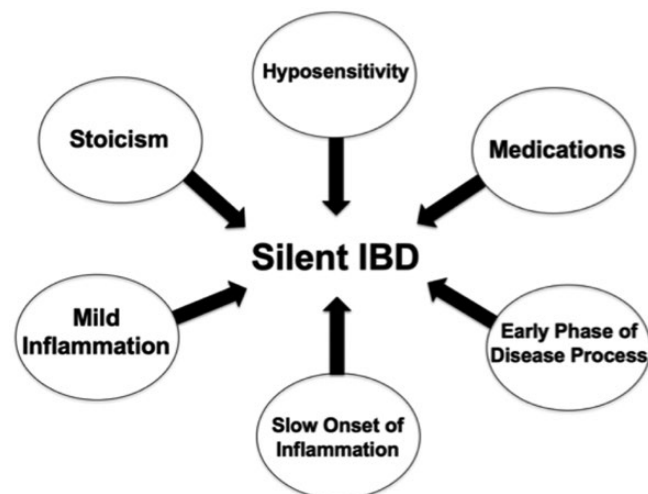


Figure 1. Potential contributors to silent inflammatory bowel disease.

such as pain or bowel habit changes. This may be particularly true in the beginning stages of some forms of IBD, when patients are not necessarily monitoring for specific symptoms. Evidence for this phenomenon is supported by observational and natural history studies of individuals with established or eventually diagnosed IBD.^{77–79} First-degree relatives of IBD patients are known to more frequently demonstrate intestinal inflammation,⁸⁰ and these individuals may serve as a more easily identifiable study population to help model the natural history of at least certain types of IBD. For example, in a study of 38 individuals undergoing colonoscopy who were “completely asymptomatic regarding digestive symptoms” who had first-degree relatives with established diagnoses of CD, Sorrentino et al found that 13 individuals harbored at least moderate inflammation on histological examination and 4 of these study participants had histological findings that were consistent with CD.⁴⁰ Even in cases of established IBD diagnoses, progression of disease activity can be insidious enough to escape symptomatic detection, particularly in the earlier stages of disease development. For example, it may take years for enteric CD patients to report symptoms after undergoing ileal resection, even when disease-related inflammatory changes are present.^{81,82}

Certain therapies and behaviors also have the potential to diminish symptoms. Recreational drug (including cannabis and opioids) and prescription medication use, including analgesics (acetaminophen, antispasmodics, tricyclic antidepressants, NSAIDs, and opioids) and antidiarrheal agents, could also dull the development or perception of certain symptoms.^{83–85} Dietary modification, in particular the reduction of the consumption of poorly absorbed short chain carbohydrates (FODMAPs) has been associated with improved GI symptoms in the setting of IBD.^{86,87} Additionally, some studies have demonstrated that regular cardiovascular and/or strengthening exercise has been associated with reduced pain, fatigue, and other symptoms from the viscera.⁸⁸ The presence of stress can exacerbate psychiatric and other symptoms associated with visceral disorders,⁸⁹ including in the setting of CD and UC.⁹⁰ Thus, interventions designed to reduce stress, including developing coping strategies and maintaining good sleep hygiene, may also help minimize IBD-associated symptoms.

Beyond these explanations, there is evidence that some individuals appear to have altered perception of symptoms. For example, we demonstrated that patients with active IBD who described little to no abdominal pain (“hypoalgesic IBD”) were more likely to be homozygous for a mutation (rs6795970) in the voltage-gated sodium channel (VGSC) gene SCN10A.¹¹ We also found that homozygotes for this polymorphism exhibited diminished abdominal pain scores following sigmoidectomy.⁹¹ This gene encodes for Na_v1.8, a sodium channel that has previously been shown to be critical for appropriate perception of noxious signals from the viscera.⁹² Prior studies have suggested that this mutation can lead to increased tolerance to somatosensory pain stimulation.⁹³ Given the role of Na_v1.8 in visceral pain, it is likely that genetic polymorphisms such as the one described above can significantly impact patient pain perception from the gut, even during periods of significant inflammation, potentially contributing to the likelihood of harboring silent IBD.

Other theoretical contributors to silent IBD include interruption of visceral sensory nerves and/or anatomical modifications related to surgery, coincidence of demyelinating and/

or neuropathic diseases affecting visceral sensory nerves or possible decompression of bowel secondary to the development of a fistula to another segment of bowel, though clear and convincing evidence for these types of associations are currently lacking.

Future Considerations and Directions

The studies reviewed here demonstrate that, while we still have a great deal to learn about silent IBD, it is clear that it is a relatively common and consequential entity that has multiple potential contributors. As indicated above, although silent IBD patients have fewer, if any symptoms, their condition may increase their risk for complications necessitating expensive and more complicated testing and therapeutic interventions. These findings highlight the importance of regularly evaluating IBD patients using a multimodal approach that includes physical examination, serological and stool testing, imaging studies, and endoscopic evaluations. Although many cases of silent IBD may be identified using the test modalities described above, there is a clear need to identify novel, easier methods for recognizing when patients are at risk. Newer test options have offered further promise in this regard. Enhanced endoscopic tools such as dye-based and/or optical chromoendoscopy and confocal laser endomicroscopy may provide a more sensitive assessment of disease status in the setting of IBD.^{94–96} Additionally, inclusion of genomic and proteomic techniques to the standard and evolving diagnostic testing modalities described above might help to predict disease recurrence (in the case of established diagnoses of IBD) or occurrence (in those in whom a diagnosis has not yet been made).^{97–99} With the advent and application of advanced statistical and computational approaches, such as machine learning, we may be on the precipice of major improvements in our ability to screen for and predict silent IBD cases.^{98,100}

However, we are still in the early stages of properly understanding this condition. In order to better understand silent IBD, we first need to reach a clearer consensus regarding several relevant questions and unresolved issues. For example, what is considered significant disease-related inflammation? In other words, is mild disease significant enough? Does it need to be manifest on gross examination and/or is histological assessment adequate? Is this inflammation restricted to the layers of the bowel itself or does it include active strictures, fistulae, abscesses? What are the most reliable methods to make this determination? Is there a particular test that, if employed, is reliable enough to rule in or rule out significant disease activity (eg, capsule endoscopy)? If not, are there a particular battery of tests that are necessary for this assessment? Additionally, how do we determine if someone is truly asymptomatic? Which symptoms are essential for making this assessment? Do we focus only on gastrointestinal issues such as abdominal pain, diarrhea, and rectal bleeding and/or we need to include systemic (eg, fatigue) and/or extraintestinal manifestations of IBD (eg, anxiety, depression, arthralgias, dermatopathies, etc.)? Whatever the key symptoms are, do they need to be completely absent or is it still relevant to include individuals who experience any of the essential symptoms only very rarely and, if so, to a mild degree? Which symptom assessment tools are most effective to make these determinations? The answers to these questions

are all essential if we are to come to a consensus definition of silent IBD and develop meaningful criteria for identification of people who have it. If agreements can be reached in regard to each of these questions, we will be able to move forward with larger, more carefully designed studies of silent IBD. This would allow us to more effectively investigate the true prevalence, natural history, pathophysiology, and clinical consequences of this condition.

Further study of silent IBD also has significant potential to provide insights into the development of better methods and strategies to manage symptoms associated with IBD and other related conditions (eg, irritable bowel syndrome). For example, there is a great deal that silent IBD could reveal about human abdominal pain perception. Many silent IBD patients simply do not perceive nociceptive (or pain-inducing) stimulation like most other people do. Why this is the case is still unclear, though. Unlocking this mystery, though, could be particularly important because, as previously mentioned, abdominal pain is a major driver of cost and reduced quality of life in IBD^{2–5} and other digestive diseases.¹⁰¹ Unfortunately, the most frequently utilized analgesic options (including opioids and NSAIDs) are frequently ineffective and/or toxic.^{102,103} There are also currently a paucity of tests that can objectively assess patient abdominal pain experience and so providers must rely on inconsistent and/or inaccurate means for assessing patient pain intensity and medication requirements.^{2,84} A clearer understanding of what keeps silent IBD patients from perceiving abdominal pain could lead to better targeted, safer and more effective visceral analgesic therapies as well as more objective methods for assessing patient pain experience. Similarly, examination of other impactful symptoms inexplicably missing in the setting of silent IBD, including bowel habit changes, arthralgias, and even fatigue, could lead to a variety of other significant insights and breakthroughs in IBD and digestive disease management.

Considering the findings of this review, and in the interest of providing a framework for future discussions and research, we recommend utilizing the following criteria to diagnose silent IBD. In individuals with established diagnoses of CD, UC, or IBD-associated colitis (as determined by at least 1 healthcare provider, with expertise in the identification and management of these conditions, using standard symptomatic, endoscopic, histologic, radiologic, and/or laboratory-based characteristics), they will be determined to have silent IBD if they: (1) exhibit moderate-to-severe IBD-associated inflammation of the bowel, based upon direct gross (eg, surgical), endoscopic and/or histologic assessment(s), and (2) are found to be in clinical remission based upon simultaneous, IBD-symptom assessment surveys. Assessments of GI inflammation and symptoms should be based upon scores derived from established, standardized and (preferably) validated tools that are appropriate for the underlying subtype of IBD being evaluated. As described above, and recognizing that these criteria have their limitations, we believe that establishing a standardized approach to the diagnosis of silent IBD is critical to better understanding this condition.

In summary, silent IBD is an important condition that has significant implications for the patients it affects. There is still a great deal to be learned about this clinical entity but, with more thoughtful and targeted study and careful consideration for its causes and consequences, there is the potential to learn a great deal about IBD and its associated symptomatology.

Funding

This research was supported by a grant from the NIH NIDDK (R01 DK122364), the Peter and Marsha Carlino Early Career Professorship in Inflammatory Bowel Disease, and the Margot E. Walrath Career Development Professorship in Gastroenterology (MDC).

Conflicts of Interest

None declared.

Data Availability

No original data were reported in this manuscript.

References

- Dahlhamer JM, Zammitti EP, Ward BW, Wheaton AG, Croft JB. Prevalence of inflammatory bowel disease among adults aged ≥ 18 years—United States, 2015. *mmwr Morb Mortal Wkly Rep*. 2016;65:1166–1169.
- Bielefeldt K, Davis B, Binion DG. Pain and inflammatory bowel disease. *Inflamm Bowel Dis*. 2009;15:778–788.
- Farrell D, McCarthy G, Savage E. Self-reported symptom burden in individuals with inflammatory bowel disease. *J Crohns Colitis*. 2016;10:315–322.
- Allegretti JR, Borges L, Lucci M, et al. Risk factors for rehospitalization within 90 days in patients with inflammatory bowel disease. *Inflamm Bowel Dis*. 2015;21:2583–2589.
- Barnes EL, Kochar B, Long MD, et al. Modifiable risk factors for hospital readmission among patients with inflammatory bowel disease in a nationwide database. *Inflamm Bowel Dis*. 2017;23:875–881.
- af Björkesten CG, Nieminen U, Turunen U, Arkkila P, Sipponen T, Farkkila M. Surrogate markers and clinical indices, alone or combined, as indicators for endoscopic remission in anti-TNF-treated luminal Crohn's disease. *Scand J Gastroenterol*. 2012;47:528–537.
- Peyrin-Biroulet L, Reinisch W, Colombel JF, et al. Clinical disease activity, C-reactive protein normalisation and mucosal healing in Crohn's disease in the SONIC trial. *Gut*. 2014;63:88–95.
- Click B, Vargas EJ, Anderson AM, et al. Silent Crohn's disease: asymptomatic patients with elevated C-reactive protein are at risk for subsequent hospitalization. *Inflamm Bowel Dis*. 2015;21:2254–2261.
- Coates MD, Soriano C, Dalessio S, et al. Gastrointestinal hypoalgesia in inflammatory bowel disease. *Ann Gastroenterol*. 2020;33:45–52.
- Sakata T, Niwa Y, Goto H, et al. Asymptomatic inflammatory bowel disease with special reference to ulcerative colitis in apparently healthy persons. *Am J Gastroenterol*. 2001;96:735–739.
- Gonzalez-Lopez E, Imamura Kawasawa Y, Walter V, et al. Homozygosity for the SCN10A polymorphism rs6795970 is associated with hypoalgesic inflammatory bowel disease phenotype. *Front Med (Lausanne)*. 2018;5:324.
- Kalehoff JP, Oparil S. The story of the silent killer: a history of hypertension: its discovery, diagnosis, treatment, and debates. *Curr Hypertens Rep*. 2020;22:72.
- Kraft JR, Wehrmacher WH. Diabetes—a silent disorder. *Compr Ther*. 2009;35:155–159.
- Ahmed AH, Shankar K, Eftekhari H, et al. Silent myocardial ischemia: current perspectives and future directions. *Exp Clin Cardiol*. 2007;12:189–196.
- Sivell C. Nonalcoholic fatty liver disease: a silent epidemic. *Gastroenterol Nurs*. 2019;42:428–434.
- Sidiropoulou Z, Vasconcelos AP, Couceiro C, et al. Prevalence of silent breast cancer in autopsy specimens, as studied by the disease being held by image-guided biopsies: the pilot study and literature review. *Mol Clin Oncol*. 2017;7:193–199.
- Shaw G. The silent disease. *Nature*. 2016;537:S98–S99.
- Vincent A, Herman J, Schulick R, Hruban RH, Goggins M. Pancreatic cancer. *Lancet*. 2011;378:607–620.
- Estebanez J, Teyrouz A, Gutierrez MA, et al. Natural history of prostate cancer. *Arch Esp Urol*. 2014;67:383–387.
- Kopyt NP. Chronic kidney disease: the new silent killer. *J Am Osteopath Assoc*. 2006;106:133–136.
- Galbraith SS, Drolet BA, Kugathasan S, Paller AS, Esterly NB. Asymptomatic inflammatory bowel disease presenting with mucocutaneous findings. *Pediatrics*. 2005;116:e439–e444.
- Barratt SM, Leeds JS, Robinson K, Lobo AJ, McAlindon ME, Sanders DS. Prodromal irritable bowel syndrome may be responsible for delays in diagnosis in patients presenting with unrecognized Crohn's disease and celiac disease, but not ulcerative colitis. *Dig Dis Sci*. 2011;56:3270–3275.
- Howarth GF, Robinson MH, Jenkins D, Hardcastle JD, Logan RF. High prevalence of undetected ulcerative colitis: data from the Nottingham fecal occult blood screening trial. *Am J Gastroenterol*. 2002;97:690–694.
- Bhattacharya A, Rao BB, Koutroubakis IE, et al. Silent Crohn's disease predicts increased bowel damage during multiyear follow-up: the consequences of under-reporting active inflammation. *Inflamm Bowel Dis*. 2016;22:2665–2671.
- Best WR. Predicting the Crohn's disease activity index from the Harvey-Bradshaw index. *Inflamm Bowel Dis*. 2006;12:304–310.
- Best WR, Beckett JM, Singleton JW, Kern F Jr. Development of a Crohn's disease activity index. National Cooperative Crohn's disease study. *Gastroenterology*. 1976;70:439–444.
- Walmsley RS, Ayres RC, Pounder RE, Allan RN. A simple clinical colitis activity index. *Gut*. 1998;43:29–32.
- D'Haens G, Sandborn WJ, Feagan BG, et al. A review of activity indices and efficacy end points for clinical trials of medical therapy in adults with ulcerative colitis. *Gastroenterology*. 2007;132:763–786.
- Irvine EJ, Zhou Q, Thompson AK. The short inflammatory bowel disease questionnaire: a quality of life instrument for community physicians managing inflammatory bowel disease. CCRPT Investigators. Canadian Crohn's Relapse Prevention Trial. *Am J Gastroenterol*. 1996;91:1571–1578.
- Haraoui B, Krelbaum M. Emergence of Crohn's disease during treatment with the anti-tumor necrosis factor agent etanercept for ankylosing spondylitis: possible mechanisms of action. *Semin Arthritis Rheum*. 2009;39:176–181.
- Cooper J, Flückiger B, Traichl B, Diener PA, Otto P, von Kempis J. Abdominal pain in a patient with ankylosing spondylitis under treatment with infliximab. *J Clin Rheumatol*. 2009;15:244–246.
- Åberg F, Abdulle A, Mäkelä A, Nissinen M. Asymptomatic de novo inflammatory bowel disease late after liver transplantation for primary sclerosing cholangitis: a case report. *Transplant Proc*. 2015;47:2775–2777.
- Di Fabio F, Lykoudis P, Gordon PH. Thromboembolism in inflammatory bowel disease: an insidious association requiring a high degree of vigilance. *Semin Thromb Hemost*. 2011;37:220–225.
- Bavaro DF, Ingravallo G, Signorile F, et al. Splenic abscesses as a first manifestation of Crohn's disease: a case report. *bmc Gastroenterol*. 2019;19:144.
- Yilmaz N, Can M, Alibaz-Oner F, Direskeneli H. Clinically silent Crohn's disease in a patient with Takayasu's arteritis unresponsive to conventional therapies. *Rheumatol Int*. 2013;33:3091–3093.
- Jordan JM, Obeid LM, Allen NB. Isolated atlantoaxial subluxation as the presenting manifestation of inflammatory bowel disease. *Am J Med*. 1986;80:517–520.
- Atarbashi-Moghadam S, Lotfi A, Atarbashi-Moghadam F. Pyostomatitis vegetans: a clue for diagnosis of silent Crohn's disease. *J Clin Diagn Res*. 2016;10:ZD12–ZD13.

38. Tursi A. Concomitant hidradenitis suppurativa and pyostomatitis vegetans in silent ulcerative colitis successfully treated with golimumab. *Dig Liver Dis.* 2016;48:1511–1512.
39. Markiewicz M, Suresh L, Margarone J III, Aguirre A, Brass C. Pyostomatitis vegetans: a clinical marker of silent ulcerative colitis. *J Oral Maxillofac Surg.* 2007;65:346–348.
40. Sorrentino D, Avellini C, Geraci M, et al. Tissue studies in screened first-degree relatives reveal a distinct Crohn's disease phenotype. *Inflamm Bowel Dis.* 2014;20:1049–1056.
41. Peyrin-Biroulet L, Panes J, Sandborn WJ, et al. Defining disease severity in inflammatory bowel diseases: current and future directions. *Clin Gastroenterol Hepatol.* 2016;14:348–354.e317.
42. Allocca M, Danese S, Laurent V, Peyrin-Biroulet L. Use of cross-sectional imaging for tight monitoring of inflammatory bowel diseases. *Clin Gastroenterol Hepatol.* 2020;18:1309–1323.e1304.
43. Lichtenstein GR, Loftus EV, Isaacs KL, Regueiro MD, Gerson LB, Sands BE. ACG clinical guideline: management of Crohn's disease in adults. *Am J Gastroenterol.* 2018;113:481–517.
44. Pera A, Bellando P, Caldera D, et al. Colonoscopy in inflammatory bowel disease. Diagnostic accuracy and proposal of an endoscopic score. *Gastroenterology.* 1987;92:181–185.
45. Maaser C, Sturm A, Vavricka SR, et al.; European Crohn's and Colitis Organisation [ECCO] and the European Society of Gastrointestinal and Abdominal Radiology [ESGAR]. ECCO-ESGAR guideline for diagnostic assessment in IBD part 1: initial diagnosis, monitoring of known IBD, detection of complications. *J Crohns Colitis.* 2019;13:144–164.
46. Sorrentino D, Nguyen VQ. Clinically significant small bowel Crohn's disease might only be detected by capsule endoscopy. *Inflamm Bowel Dis.* 2018;24:1566–1574.
47. Albert JG, Martiny F, Krummenerl A, et al. Diagnosis of small bowel Crohn's disease: a prospective comparison of capsule endoscopy with magnetic resonance imaging and fluoroscopic enteroclysis. *Gut.* 2005;54:1721–1727.
48. González-Suárez B, Rodríguez S, Ricart E, et al. Comparison of capsule endoscopy and magnetic resonance enterography for the assessment of small bowel lesions in Crohn's disease. *Inflamm Bowel Dis.* 2018;24:775–780.
49. Bruining DH, Zimmermann EM, Loftus EV Jr, Sandborn WJ, Sauer CG, Strong SA; Society of Abdominal Radiology Crohn's Disease-Focused Panel. Consensus recommendations for evaluation, interpretation, and utilization of computed tomography and magnetic resonance enterography in patients with small bowel Crohn's disease. *Gastroenterology.* 2018;154:1172–1194.
50. Bjarnason I. The use of fecal calprotectin in inflammatory bowel disease. *Gastroenterol Hepatol (n y).* 2017;13:53–56.
51. Langhorst J, Elsenbruch S, Koelzer J, Rueffer A, Michalsen A, Dobos GJ. Noninvasive markers in the assessment of intestinal inflammation in inflammatory bowel diseases: performance of fecal lactoferrin, calprotectin, and PMN-elasticase, CRP, and clinical indices. *Am J Gastroenterol.* 2008;103:162–169.
52. Zittan E, Kelly OB, Kirsch R, et al. Low fecal calprotectin correlates with histological remission and mucosal healing in ulcerative colitis and colonic Crohn's disease. *Inflamm Bowel Dis.* 2016;22:623–630.
53. Zittan E, Kelly OB, Gralnek IM, Silverberg MS, Hillary Steinhart A. Fecal calprotectin correlates with active colonic inflammatory bowel disease but not with small intestinal Crohn's disease activity. *Jgh Open.* 2018;2:201–206.
54. Binion DG. Silent Crohn's disease. *Gastroenterol Hepatol (n y).* 2014;10:510–512.
55. Baars JE, Nuij VJ, Oldenburg B, Kuipers EJ, van der Woude CJ. Majority of patients with inflammatory bowel disease in clinical remission have mucosal inflammation. *Inflamm Bowel Dis.* 2012;18:1634–1640.
56. Oh K, Oh EH, Baek S, et al. Elevated C-reactive protein level during clinical remission can predict poor outcomes in patients with Crohn's disease. *PLoS One.* 2017;12:e0179266.
57. Clark LG, Tolkachjov SN, Bridges AG, Camilleri MJ. Pyostomatitis vegetans (PSV)-pyodermitis vegetans (PDV): a clinicopathologic study of 7 cases at a tertiary referral center. *J Am Acad Dermatol.* 2016;75:578–584.
58. Pariente B, Mary JY, Danese S, et al. Development of the Lémann index to assess digestive tract damage in patients with Crohn's disease. *Gastroenterology.* 2015;148:52–63.e53.
59. Bou-Fakhredin R, Halawi R, Roumi J, Taher A. Insights into the diagnosis and management of iron deficiency in inflammatory bowel disease. *Expert Rev Hematol.* 2017;10:801–808.
60. Targownik LE, Bernstein CN, Leslie WD. Risk factors and management of osteoporosis in inflammatory bowel disease. *Curr Opin Gastroenterol.* 2014;30:168–174.
61. Eitan B, Zisman I, Qarawany M, Grishkan A, Mazor A. Crohn's disease of small bowel manifested by obstructive carcinoma. *Harefuah.* 1993;125:209–211, 256.
62. Slim R, Chemaly M, Yaghi C, Honein K, Moucari R, Sayegh R. Silent disease revealed by a fruit—ileal obstruction. *Gut.* 2006;55:181, 190.
63. Asghar JI, Crosby J, Beilman GJ. Enterocutaneous fistula as early presentation of Crohn's disease in an adult woman. *BMJ Case Rep.* 2012;2012.
64. Tsukui H, Koinuma K, Morimoto M, et al. Crohn's disease presenting as a ceco-urachal fistula. *Clin j Gastroenterol.* 2017;10:32–36.
65. Sankararaman S, Sabe R, Sferra TJ, Khalili AS. Enterourachal fistula as an initial presentation in Crohn disease. *Pediatr Gastroenterol Hepatol Nutr.* 2019;22:90–97.
66. Greenstein AJ, Barth JA, Sachar DB, Aufses AH Jr. Free colonic perforation without dilatation in ulcerative colitis. *Am j Surg.* 1986;152:272–275.
67. Craft CF, Mendelsohn G, Cooper HS, Yardley JH. Colonic "precancer" in Crohn's disease. *Gastroenterology.* 1981;80:578–584.
68. Katsanos KH, Christodoulou D, Siozopoulou V, et al. Silent ulcerative colitis adjacent to a regular sigmoid adenocarcinoma. *Eur j Gastroenterol Hepatol.* 2011;23:957–960.
69. Magro F, Correia M, Moreira G, et al. Adenocarcinoma of the cecum as the first manifestation of ulcerative colitis complicated by primary sclerosing cholangitis and endomyocardial fibrosis. *Inflamm Bowel Dis.* 2002;8:287–290.
70. Kim SB, Kim KO, Jang BI, et al.; Daegu-Gyeongbuk Gastrointestinal Study Group (DGSG). Patients' beliefs and attitudes about their treatment for inflammatory bowel disease in Korea. *J Gastroenterol Hepatol.* 2016;31:575–580.
71. Selinger CP, Robinson A, Leong RW. Clinical impact and drivers of non-adherence to maintenance medication for inflammatory bowel disease. *Expert Opin Drug Saf.* 2011;10:863–870.
72. Noiseux I, Veilleux S, Bitton A, et al. Inflammatory bowel disease patient perceptions of diagnostic and monitoring tests and procedures. *bmc Gastroenterol.* 2019;19:30.
73. Papay P, Ignjatovic A, Karmiris K, et al. Optimising monitoring in the management of Crohn's disease: a physician's perspective. *J Crohns Colitis.* 2013;7:653–669.
74. Schreiber S, Panés J, Louis E, Holley D, Buch M, Paridaens K. Perception gaps between patients with ulcerative colitis and healthcare professionals: an online survey. *bmc Gastroenterol.* 2012;12:108.
75. Mehta F. Report: economic implications of inflammatory bowel disease and its management. *Am j Manag Care.* 2016;22:s51–s60.
76. Taft TH, Keefer L. A systematic review of disease-related stigmatization in patients living with inflammatory bowel disease. *Clin Exp Gastroenterol.* 2016;9:49–58.
77. Cosnes J, Gower-Rousseau C, Seksik P, Cortot A. Epidemiology and natural history of inflammatory bowel diseases. *Gastroenterology.* 2011;140:1785–1794.
78. Burisch J, Kiudelis G, Kupcinskis L, et al.; Epi-IBD Group. Natural disease course of Crohn's disease during the first 5 years after diagnosis in a European population-based inception cohort: an Epi-IBD study. *Gut.* 2019;68:423–433.

79. Fumery M, Singh S, Dulai PS, Gower-Rousseau C, Peyrin-Biroulet L, Sandborn WJ. Natural history of adult ulcerative colitis in population-based cohorts: a systematic review. *Clin Gastroenterol Hepatol*. 2018;16:343–356.e343.
80. Thjodleifsson B, Sigthorsson G, Cariglia N, et al. Subclinical intestinal inflammation: an inherited abnormality in Crohn's disease relatives? *Gastroenterology*. 2003;124:1728–1737.
81. Olaison G, Smedh K, Sjö Dahl R. Natural course of Crohn's disease after ileocolic resection: endoscopically visualised ileal ulcers preceding symptoms. *Gut*. 1992;33:331–335.
82. Rutgeerts P, Geboes K, Vantrappen G, Beyls J, Kerremans R, Hiele M. Predictability of the postoperative course of Crohn's disease. *Gastroenterology*. 1990;99:956–963.
83. Ahmed W, Katz S. Therapeutic use of cannabis in inflammatory bowel disease. *Gastroenterol Hepatol (n y)*. 2016;12:668–679.
84. Docherty MJ, Jones RC III, Wallace MS. Managing pain in inflammatory bowel disease. *Gastroenterol Hepatol (n y)*. 2011;7:592–601.
85. Shah SB, Hanauer SB. Treatment of diarrhea in patients with inflammatory bowel disease: concepts and cautions. *Rev Gastroenterol Disord*. 2007;7(suppl 3):S3–S10.
86. Garry RB, Irving PM, Barrett JS, Nathan DM, Shepherd SJ, Gibson PR. Reduction of dietary poorly absorbed short-chain carbohydrates (FODMAPs) improves abdominal symptoms in patients with inflammatory bowel disease—a pilot study. *J Crohns Colitis*. 2009;3:8–14.
87. Cox SR, Lindsay JO, Fromentin S, et al. Effects of low FODMAP diet on symptoms, fecal microbiome, and markers of inflammation in patients with quiescent inflammatory bowel disease in a randomized trial. *Gastroenterology*. 2020;158:176–188.e177.
88. Engels M, Cross RK, Long MD. Exercise in patients with inflammatory bowel diseases: current perspectives. *Clin Exp Gastroenterol*. 2018;11:1–11.
89. Mayer EA. Gut feelings: the emerging biology of gut-brain communication. *Nat Rev Neurosci*. 2011;12:453–466.
90. Sun Y, Li L, Xie R, Wang B, Jiang K, Cao H. Stress triggers flare of inflammatory bowel disease in children and adults. *Front Pediatr*. 2019;7:432.
91. Coates MD, Kim JS, Carkaci-Salli N, et al. Impact of the NaV1.8 variant, A1073V, on post-sigmoidectomy pain and electrophysiological function in rat sympathetic neurons. *J Neurophysiol*. 2019;122:2591–2600.
92. Coates MD, Vrana KE, Ruiz-Velasco V. The influence of voltage-gated sodium channels on human gastrointestinal nociception. *Neurogastroenterol Motil*. 2019;31:e13460.
93. Duan G, Han C, Wang Q, et al. A SCN10A SNP biases human pain sensitivity. *Mol Pain*. 2016;12:1–16.
94. Salvatori F, Siciliano S, Maione F, et al. Confocal laser endomicroscopy in the study of colonic mucosa in IBD patients: a review. *Gastroenterol Res Pract*. 2012;2012:525098.
95. Klenske E, Atreya R, Hartmann A, et al. Magnification endoscopy with optical chromoendoscopy shows strong correlation with histologic inflammation in patients with inflammatory bowel disease. *Endosc Int Open*. 2019;7:E1018–E1026.
96. De Palma GD, Rispo A. Confocal laser endomicroscopy in inflammatory bowel diseases: dream or reality? *World J Gastroenterol*. 2013;19:5593–5597.
97. van Schaik FD, Oldenburg B, Hart AR, et al. Serological markers predict inflammatory bowel disease years before the diagnosis. *Gut*. 2013;62:683–688.
98. Taylor KM, Hanscombe KB, Prescott NJ, et al. Genetic and inflammatory biomarkers classify small intestine inflammation in asymptomatic first-degree relatives of patients with Crohn's disease. *Clin Gastroenterol Hepatol*. 2020;18:908–916.e913.
99. Choung RS, Princen F, Stockfisch TP, et al.; PREDICTS Study Team. Serologic microbial associated markers can predict Crohn's disease behaviour years before disease diagnosis. *Aliment Pharmacol Ther*. 2016;43:1300–1310.
100. Torres J. Prediction of inflammatory bowel disease: a step closer? *Gastroenterology*. 2020;158:278–279.
101. Peery AF, Crockett SD, Murphy CC, et al. Burden and cost of gastrointestinal, liver, and pancreatic diseases in the United States: update 2018. *Gastroenterology*. 2019;156:254–272.e211.
102. Coates MD, Seth N, Clarke K, et al. Opioid analgesics do not improve abdominal pain or quality of life in Crohn's disease. *Dig Dis Sci*. 2020;65:2379–2387.
103. Long MD, Kappelman MD, Martin CF, Chen W, Anton K, Sandler RS. Role of nonsteroidal anti-inflammatory drugs in exacerbations of inflammatory bowel disease. *J Clin Gastroenterol*. 2016;50:152–156.