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Jin-Lai Wang, Director
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Baishideng Publishing Group Inc
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Capsule endoscopy: Current status and role in Crohn's disease

Loredana Goran, Ana Maria Negreanu, Ana Stemate, Lucian Negreanu

Loredana Goran, Ana Maria Negreanu, Ana Stemate, Lucian Negreanu, Internal Medicine 2-Gastroenterology Department, University Hospital, Carol Davila University, Bucharest 050098, Romania

ORCID number: Loredana Goran (0000-0002-5548-7392); Ana Maria Negreanu (0000-0003-1037-3014); Ana Stemate (0000-0003-2935-5406); Lucian Negreanu (0000-0003-3042-0754).

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Correspondence to: Lucian Negreanu, MD, PhD, Professor, Internal Medicine 2-Gastroenterology Department, University Hospital, Carol Davila University, 169, Splaiul Independentei Street, Sector 5, Bucharest 050098, Romania. lucian.negreanu@umfcd.ro
Telephone: +40-72-9439249

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Abstract

Capsule endoscopy (CE) has proved to be an important non-invasive tool for diagnosis and monitoring Crohn's disease patients. It has the advantage of excellent visualization of digestive tract mucosa, a good tolerability and safety in well-selected patients. The risk of retention can be diminished by good selection of patients using imaging techniques and by the use of patency capsule. The aim of a capsule examination is not only an early diagnosis but also a very good stratification of prognosis, thus directing the treatment strategy for either a step up or top-down approach and also permitting the optimization of the treatment depending on the findings. When symptoms and biomarkers point to a change in the disease's activity we can either adjust the treatment directly as recommended in CALM study or choose in selected patients to visualize the digestive mucosa through a CE and take a decision afterwards. The appearance of the new capsule from Medtronic-the Pillcam Crohn's might be an important step forward in diagnosis, evaluating disease extent, the severity of the disease, prognosis, management in a treat to target approach, with treatment modifications according to the data from CE examination. Serial examinations in the same patient can be compared and a more objective evaluation of the lesions modification from one exam to another can be performed. We present the latest developments and current status and evidence that in selected patients capsule can be a tool in a treat to target approach.

Key words: Capsule endoscopy; Crohn's disease; Treat to target; Optimise; Colon capsule

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Core tip: The target in inflammatory bowel disease has changed during the last years from controlling symptoms to achieving mucosal healing as the final goal

of treatment. C-reactive protein and fecal calprotectin have proved their efficacy in monitoring and guiding the treatment in Crohn's disease as shown by the pivotal CALM study. More and more evidence tends to support a role of iterative capsule endoscopy (CE) examinations. Evidence is based on small bowel and pillcam colon 2 capsule examinations. The appearance of the new capsule from Medtronic-Pillcam Crohn's might be an important step forward in diagnosis, evaluating disease extent, the severity of the disease, prognosis, management in a treat to target approach, with treatment modifications according to the data from CE examination.

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INTRODUCTION

Crohn's disease (CD) is a chronic inflammatory disease affecting the entire gastrointestinal tract but most frequently involving the small bowel (SB)^[1]. According to different studies, 70%-90% of CD patients have SB involvement^[2,3], and 30% of them have exclusive SB disease^[4]. SB disease, particularly jejunal disease, is considered to be a risk factor for strictures and is associated with a larger number of surgical procedures^[5]; thus, evaluation of the small bowel becomes of great interest in the diagnosis and management of CD patients. In the past, assessing the small bowel was limited due to an inability to visualize the mucosa through conventional methods. As new techniques emerged, the introduction of capsule endoscopy (CE) in 2000^[6] offered us the possibility of evaluating the small bowel.

CE is indicated in CD for diagnosis in patients with suspected disease, evaluation of mucosal healing and disease activity in established CD, confirmation of recurrence after surgery, evaluation of patients with overt or obscure gastrointestinal bleeding and evaluation of celiac disease patients with inexplicable symptoms regardless of treatment^[7].

CE imaging interpretation

When describing the images obtained by CE, findings suggestive of CD are erythema, mucosal edema, ulcerations or ulcers, strictures, fistulas and mucosal fissures^[8]. The reason why all clinical, biochemical and endoscopic findings must be put together when establishing a diagnosis is that CE findings are nonspecific, and up to 15% of normal individuals may have minor mucosal breaks^[9]. Another argument is that mucosal erosions are not pathognomonic for CD, being present in two thirds of patients with nonsteroidal anti-inflammatory (NSAID)-induced enteropathy^[10]. Although sometimes it is difficult to differentiate CD from NSAID lesions only

using CE findings, concentric diaphragmatic strictures are considered characteristic for mucosal injury after NSAID use^[11]. Other differential diagnoses based of CE mucosal findings are intestinal tuberculosis, ischemia, tumors, lymphoma, Behcet's disease or radiation enteritis^[9].

Scoring systems in CE

A limitation of CE is the lack of definitive diagnostic criteria for CD. Two scoring systems are currently used when assessing CE findings, the Lewis Score (LS) and more recently the Capsule Endoscopy Crohn's Disease Activity Index (CECDAI). The LS is an incorporated software algorithm that separates the small bowel into three parts and assigns points to different CD characteristic findings (strictures, ulcers, fistulas) in each of the segments. It takes into consideration the severity and the reproducibility of each lesion found^[12]. The most affected part of the small bowel with its accumulated number of points represents the final score. A score < 135 is clinically insignificant or normal; a score between 135 and 790 corresponds to mild inflammation and a score > 790 points to moderate-to-severe inflammation.

He *et al*^[13] studied the relationship between LS, clinical activity indices, level of C-reactive protein (CRP) and small bowel transit time (SBTT) in 150 pediatric and adult CD patients. For pediatric patients they used the abbreviated Pediatric Crohn's Disease Activity Index (aPCDAI), while for adult patients, the Harvey-Bradshaw Index (HBI) was used. A strong correlation between the clinical activity indices and CRP was found in all patients, while the correlation between the CRP and the LS was moderate. The correlation between the LS and clinical activity indices was moderate in pediatric patients but weak in adult patients. The LS in pediatric patients was reduced after treatment, but in adult patients there was no difference that was statistically significant^[13]. Similar results were obtained by Yang *et al*^[14] on 58 patients with established or suspected CD^[14]. It seems that the LS correlates better than the CECDAI score with fecal calprotectin levels, mainly when the level is less than 100 µg/g^[15].

The CECDAI splits the small bowel into proximal and distal segments and evaluates the inflammation, presence of strictures and extent of disease in each segment. A segmental score is calculated by multiplying the inflammation with the extent of the disease and then adding the presence of strictures if they exist. The final score is obtained by adding the two results^[16]. The CECDAI score was validated in patients with small bowel CD showing a good correlation between endoscopists from different centers^[17]. The correlation between the two scoring systems is very strong, but no significant correlation with CRP and HBI was obtained.

CE INDICATIONS IN CD

CE in suspected CD

The diagnosis of CD is based on clinical symptoms, endoscopic and radiologic findings and it is confirmed

by histology results. The range of symptoms and laboratory findings that can support the diagnosis in a patient with suspected CD is wide, and it includes chronic diarrhea, abdominal pain, anemia, changes in CRP, erythrocyte sedimentation rate (ESR), elevated fecal calprotectin level, hypoalbuminemia and extraintestinal manifestations^[17]. Further, the next step is a total ileocolonoscopy, with biopsies and radiologic exams if needed. Classical radiology has a very limited place in diagnosis; computed tomography enterography (CTE) or magnetic resonance enterography (MRE) are the preferred imaging modalities.

Approximately 27% of CD patients have disease limited to the ileum; thus, a normal ileocolonoscopy does not exclude a CD diagnosis^[18]. On the other hand, there are cases when the ileum cannot be visualized properly, or the ileocolonoscopy and the radiologic investigations are inconclusive. For these situations, a CE is indicated in establishing a diagnosis rather than a double-balloon endoscopy (DBE), which is more invasive^[7].

Since there is no gold standard for the diagnosis of CD, the studies made until now evaluate the diagnostic yield and not the diagnostic accuracy of CE. Based on these studies, there was an obviously superior diagnostic yield with small bowel CE compared with SB radiography, ileocolonoscopy, CTE, but not MRE^[19]. In a South Korean study, the diagnostic yield of CE in the suspected CD group was 59.7%, and the therapeutic management was changed in 70.2% of these patients^[20]. Jensen *et al.*^[21] found similar sensibility and specificity for CE and MRE in CD patients.

CE vs other investigations: When compared to other means of investigating CD patients, CE has proved its efficiency. In a recent meta-analysis made by Choi *et al.*^[22], in patients with suspected CD, CE had a superior diagnostic yield compared to small bowel follow-through and enteroclysis (EC) and is comparable to CTE and MRE. In patients with established CD, the diagnostic yield of CE compared to EC was greater, and CE identified significantly more lesions in the terminal ileum compared with ileoscopy^[22].

In another meta-analysis, for suspected CD cases, CE was superior to SBR, CTE and ileocolonoscopy, and in established CD cases, CE also proved superiority over CTE, PE and SBR. There were similar results between CE and MRE^[19]. Other studies evaluated the diagnostic yield of CE compared with other forms of investigation. Albert *et al.*^[23] compared CE with MRE and fluoroscopic enteroclysis in a prospective study of 52 suspected or established CD patients. CE detected small bowel lesions in 93% of patients, whereas MRI was effective in 78% of patients and fluoroscopy in 33% of cases. They concluded that CE and MRI are complementary in the diagnosis of CD; CE identified small bowel lesions that MRI might fail to spot, but MRI was able to detect extraluminal complications and transmural inflammation^[23]. Similar results were also obtained in the pediatric population, with CE and MRI having comparable

specificity and sensibility^[24]. In patients with small bowel disease, CE had a lower diagnostic yield (57.6%) than that of single-balloon enteroscopy (SBE) (69.7%)^[25].

CE in unclassified IBD: Nearly 15% of patients with colonic inflammatory disease have unclassified/undetermined colitis at the time of diagnosis^[26], with 30% of them being reclassified as CD later on during the course of disease^[27]. In a study of 120 patients with UC and unclassified inflammatory bowel disease (IBD), 15.8% had capsule endoscopic findings characteristic of CD. Almost all of these patients had a small-bowel follow-through (SBFT) before CE, and in only one of them were CD findings described^[28]. In the pediatric population, a study conducted with 28 patients revealed that 4 out of 5 patients with UC were reclassified as CD after CE examination. At the same time, the patients with CD had more extensive bowel disease at CE, and the majority had newly diagnosed jejunal disease^[29]. Nevertheless, although CE is useful in establishing a diagnosis in patients with IBDU, a negative examination does not exclude a further CD diagnosis^[30].

CE in established CD

During the last decade, the treatment dogma in IBD has changed from having clinical control of the symptoms to reversing inflammation and obtaining mucosal healing, thus limiting progression and bowel damage^[31]. The definition of mucosal healing includes the absence of visible endoscopic inflammation that is associated with fewer complications on long-term evolution, and the gold-standard evaluation method is ileocolonoscopy^[32]. A CE diagnostic yield of 85.7% was found in patients with established disease, and findings may lead to management changes in 64% of patients^[33].

Deep remission is now the endpoint in IBD patient treatment, and it is defined by clinical, biochemical and endoscopic remission. Mucosal healing in the small bowel was achieved in only 15.4% of patients in clinical remission in a study made by Kopylov *et al.*^[34]. They also proved that CRP and fecal calprotectin have a poor correlation with active SB inflammation^[35]; therefore, the evaluation of mucosal healing might be a new indication for CE.

Hall *et al.*^[36] evaluated 43 symptomatic CD patients by clinical active disease indices, looking at CRP, fecal calprotectin and CECDAI score at the beginning of treatment and again after 52 wk. The study showed that biochemical response was correlated with endoscopic remission in 42% of patients^[36]. In another study, it was confirmed that mucosal healing does not correlate with clinical remission^[37].

In the Canadian Capsule Endoscopy Guidelines, CE is indicated in CD patients with clinical symptoms and signs which are not explained by an ileocolonoscopy or other imaging modalities^[7] and for possible lesions that are inaccessible with conventional investigations^[38]. In a retrospective study of small bowel CE made by

Dussault *et al*^[39] on CD patients for unexplained anemia, inconsistency between symptoms and ileocolonoscopy aspect, a full evaluation of disease extent and assessment of mucosal healing showed that 38 out of 71 patients had suffered a change in their management due to a severe lesion found on CE^[39]; similar results were shown by Kim *et al*^[20].

Another study showed similar results, with 62% of patients having their treatment changed and 40% of patients initiating a new treatment, with Budesonide being the most frequent treatment introduced in their therapy^[40]. Regarding the pediatric IBD patients, abnormal CE findings in 86% of patients led to treatment step-up in 75% of them, with the important decision to add an anti-TNF agent in the majority of cases. Evaluation after one year showed significant improvement in clinical and biological status. In the same study, the CE findings excluded IBD in 94% of patients in the suspected CD group^[41]. Based on these studies, a change in therapeutic management in established CD patients can be correctly made based on CE findings. Another indication for CE in the case of an established diagnosis is for patients with suspected CD recurrence after surgery^[7]. Postsurgical recurrence of CD has a high rate^[42] after one year of ileocolonic resection, and frequently the recurrence is proximal to the surgical anastomosis, with the recommendation that an ileocolonoscopy be performed within 6 mo to one year after surgery^[43]. The endoscopic recurrence precedes the apparition of clinical symptoms, and a severe endoscopic aspect offers a poor prognosis^[44]. CE can play a role in identifying patients with recurrences after surgery, being a non-invasive method and likely offering us a better visualization of the neoterminal ileum. Bourreille *et al*^[45] evaluated 31 CD patients by CE and ileocolonoscopy within 6 mo after surgery, and recurrence was defined by a Rutgeerts score ≥ 1 ^[44]. In 68% of patients who had suffered recurrence, the sensitivity of CE in detecting the lesions of the neoterminal ileum was lower than that of ileocolonoscopy. On the other hand, more than two-thirds of patients had lesions outside the reach of ileocolonoscopy^[45]. Moreover, another study found different conclusions - that CE is more effective than ileocolonoscopy in detecting recurrences - after CE identified 68% of patients with disease relapses compared to 25% identified by ileocolonoscopy^[46]. Postsurgical anatomy may play a role in the inability of the colonoscope to reach the neoterminal ileum.

In other words, current evidence supports CE as a reasonable choice for evaluating a patient after surgery when ileocolonoscopy is contraindicated or the neoterminal ileum cannot be intubated or when the patients refuses an endoscopic evaluation^[47].

CE IN COLON EVALUATION

Colonic capsule has been designed and mostly used for colorectal cancer screening, reaching a sensitivity of 88% in detecting polyps compared to standard colonoscopy^[48]. Most of the data that we have now about CE in CD

are gained using the small bowel capsule endoscopy (SBCE), but the Pillcam Colon 2 has proved useful in the evaluation of the entire gastrointestinal mucosa, showing great accuracy in detecting mucosal changes. When comparing the Pillcam Colon 2 with ileocolonoscopy, MRE, and small intestine contrast sonography, the colon capsule endoscopy (CCE) had better results for small bowel lesions than the other techniques in detecting colonic inflammation, with sensitivity, specificity, and positive and negative predictive values that were 89% and 100%, 100% and 91% in a study with a pediatric population^[49]. The CE also showed better tolerability than ileocolonoscopy.

D'Haens *et al*^[50] used the second-generation Pillcam Colon Capsule Endoscope (PCCE-2) in order to assess its safety and feasibility compared to colonoscopy in 40 patients with active colonic CD. The results showed that the colon capsule findings underestimated severity, the total ulcerated area and disease activity score, with a rate of missing ulcers of 14%. PCCE-2 had an ulcer recognition sensitivity of 86%, but a specificity of only 40%^[50]. Overall, the colon capsule was safe to use and well tolerated and no adverse event was reported. In a small study from our team that included 6 patients with suspected or established CD who refused colonoscopy or had incomplete examinations, the colonic capsule was safe to use and played an important role in patient's therapeutic management^[51].

PILLCAM CROHN'S® CAPSULE

The use by many clinicians of the Pillcam Colon 2 as a tool for an endoscopy of the entire digestive tract in CD lead to the appearance of the new capsule from Medtronic - Pillcam Crohn's®. This might be an important step forward in the diagnosis and evaluation of disease extent, severity, prognosis, and management in a treat-to-target approach, with treatment modifications based on data from CE examinations since it is specially designed to detect CD lesions.

Pillcam Crohn's is similar to PillCam C2 and allows complete examination of the gastrointestinal tract. It comes with the new IBD-dedicated software (Rapid 9), in which the small bowel is divided into three segments, and the colon is divided into two parts (right and left). Two new descriptors are introduced: The most severe lesion (MSL) and the most common lesion (MCL) and the extent of involvement in the specific segment are analyzed; these are also shown visually in a GI tract map which allows fast comparison with previous examinations. The LS for the small bowel is still available for use.

With this software, serial examinations in the same patient can be compared, and a more objective evaluation of the lesion modification from one exam to another can be performed. Leighton *et al*^[52] compared the diagnostic yield of the new capsule with ileocolonoscopy, showing at least as good as, if not even better than ileocolonoscopy results, with a diagnostic yield of 83% compared with 70% for ileocolonoscopy.

In Italy, 18 patients with suspected or known CD were assessed by CE with the new Crohn's PillCam capsule^[53]. In the suspected CD group, approximately one-half of patients had major inflammatory lesions, most of them being in the third tertile. In 75% of these patients, the diagnosis was confirmed. In the established CD group, 90% of patients had important lesions in the terminal and neoterminal ileum. No adverse events were reported.

Another study made in Israel included 49 patients who were examined by the new capsule in order to assess the system's capacity to visualize and examine the small bowel and the colon^[54]. From 71% of patients who had established CD, 31% of them had proximal inflammatory lesions. All recordings were of good quality, and no retention of the capsule was reported.

Studies with Crohn's capsule are ongoing in the pediatric population, based on encouraging results in 48 children with CD who underwent pan-enteric capsule endoscopy (PCE) with Pillcam Colon 2. In this study, treatment was adapted according to the PCE findings, and the results were compared afterward^[55]. At week 52, 28 patients who had mucosal healing at the PCE evaluation had fewer disease relapses, reduced hospitalization rates and decreased treatment escalation. The diagnostic yield of PCE in this study was 54% compared to 37% of MRE. Regarding costs, Saunders *et al*^[56] found that using VCE compared to other investigations would notably reduce costs and, at the same time, improve quality of life for CD patients, especially in those after surgical intervention or with considerable symptoms.

CE IN A "TREAT-TO-TARGET" CONCEPT

The target in IBD has changed during the last years from controlling symptoms to achieving mucosal healing as the final goal of treatment. The Selecting Therapeutic Targets in Inflammatory Bowel Disease (STRIDE) initiative group published a guideline to define the targets in IBD patient treatment^[57]. In CD, the endpoints are composite according to this guide. Clinical remission, endoscopic remission, resolution of inflammation signs on cross-sectional imaging and decline of CRP and calprotectin, which is with histological remission as the final goal are the targets to be pursued. Patients that reach the targets are less likely to suffer surgeries, hospitalizations and their quality of life is better. The biomarkers CRP and fecal calprotectin have proved their efficacy in monitoring and guiding the treatment in CD, as shown by the pivotal CALM study^[58]. In this study, optimizing biologic therapy based only on clinical symptoms resulted in worse outcomes than when combining biomarkers with symptoms in a proactive monitoring setting since there is a discordance between symptoms and mucosal healing.

In the study of Lazarev *et al*^[5], with 2015 patients analyzed, 14% had proximal involvement, and notably, jejunal involvement was associated with patterns of stenosis, which predict more hospitalizations and further surgery. Due to these CE findings, the author proposed revising the Montreal Classification, as jejunal

involvement should be considered a separate phenotype due to the prognostic implications of this location^[5]. Lesions with proximal location at CE examination have a poor prognostic value, similar to the ileal location that most frequently develops a stenotic pattern. Maybe these patients may need to be treated earlier and more aggressively with a more rapid step up or in a top-down approach based on capsule findings to prevent the ulterior complications.

A prospective study from Israel in 89 patients who underwent biomarker evaluation, MRE exams, patency capsule tests and then VCE every 6 mo concluded that CE predicts short-term and long-term disease relapses compared to calprotectin, which is a good predictor of exacerbation in the short term^[59]. The authors also suggest that an worst-segment LS under 350 might be the target with clinical impact for mucosal healing. Similarly, after surgery where the majority of patients will relapse, CE could identify the lesions earlier since it is more accepted than colonoscopy and treatment would be initiated promptly.

CONTRAINDICATIONS AND RISKS

When we talk about risks in performing a CE examination, the biggest concern is capsule retention, which is defined as the failure to excrete the capsule in 2 wk or more, which prompts the need of medical, endoscopic or surgical intervention^[60]. Thereby, patients with known stenotic disease or with a history of bowel obstruction have an increased risk of capsule retention. In patients with suspected obstruction, imaging investigations should be done before CE, but they do not completely exclude capsule retention totally^[61]. Usually, patients with capsule retention are asymptomatic^[62], but they may experience symptoms of a complete bowel obstruction. Depending of the nature of the stricture, the patient may excrete the capsule after corticosteroid treatment if the stricture is an inflammatory one or with endoscopic or surgical intervention.

The risk of capsule retention varies according to different studies and ranges from 1.4%^[20] to 2.6%^[63] in patients with suspected disease and up to 13% in patients already diagnosed^[64]. In patients with suspected CD, the risk of capsule retention is similar to that of other indications, being higher in patients with established CD. Capsule retention in patients with diagnosed strictures reaches 21%^[65].

To avoid capsule retention, the patency capsule was developed, which is identical in shape and dimensions to the renal capsule. The advantage of the patency capsule is that its components enable it to dissolve after ingestion, and the barium it contains helps us to identify its location through radiologic exams. If not excreted, it can be localized by radiography or computed tomography^[66]. Currently a second generation patency capsule is used-the Agile® capsule, which with two timer plugs, one at each end, dissolves faster (30 h compared to 80 h)^[67].

Patients with suspected strictures who have a

successful passage of the patency capsule also should have a high chance of a successful passage of the CEE. However, cases of patency capsule retention requiring surgery and also few cases of capsule impaction after successful patency examination were reported^[67].

Some clinicians see capsule retention as a good indicator of lesions, allowing a change in management of the patient-device assisted endoscopy with capsule removal and dilation, surgery, modification of treatment. The Canadian guideline and the European Society of Gastrointestinal Endoscopy (ESGE) Technical Review regarding small bowel CE recommend that, in case of suspected strictures or symptoms of obstruction, imaging exams should be performed on the first intention, and if there is a high risk of retention, a patency capsule should be administered before CE^[7,68]. The ESGE Technical Review recommends observation in cases of asymptomatic capsule retention and treatment with steroids if indicated^[68]. When capsule retrieval is indicated, device-assisted enteroscopy is the recommended method^[68].

CONCLUSION

CE has proved to be an important noninvasive tool for the diagnosis and monitoring of CD patients. It has the advantage of excellent visualization of digestive tract mucosa, a good tolerability and safety in well-selected patients. The risk of retention can be diminished with careful selection of patients using imaging techniques and by the use of a patency capsule.

The aim of a capsule examination is not only to produce an early diagnosis but also to provide a very good stratification of prognosis, thus directing the treatment strategy for either a step-up or top-down approach and permitting the optimization of the treatment, depending on the findings. In patients with a high suspicion of CD, since the negative predictive value of CE examination is more than 96%, perhaps in the future, the pan-enteric CE could be used as a screening tool even before ileocolonoscopy. In established CD, it is very important to assess the extent and the severity of the disease dynamically in order to make the best decision about the treatment and its optimization. For the best assessment of the bowel damage, both mucosal and extramucosal, an ideal approach will include both CE and MRE. A similar approach can be used when monitoring patients with suspected post-surgery CD recurrence, where acceptance of capsule examination is higher. Based on CE findings, treatment can be optimized in order to avoid recurrence and a new surgical intervention.

When symptoms and biomarkers point to a change in the disease's activity, we can either adjust the treatment directly, as recommended in CALM study, or choose to visualize the digestive mucosa in selected patients through a CE and make a decision afterward. We believe that increasing evidence tends to support a role of iterative CE examinations in treat to target approach, the only issues being related to costs and potential impaction risks, which are not negligible. The new Crohn's Capsule

is promising, and perhaps we are not that far away from using such capsule technologies for drug delivery and tissue sampling in CD patients^[69].

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