ANDI study group

Advanced Non-Invasive Diagnostics in Inflammatory Bowel Disease

Feasibility of a non-invasive diagnostic algorithm in suspected Crohn's disease – a prospective comparison of pan-enteric capsule endoscopy *versus* ileocolonoscopy plus MR enterography or small-bowel capsule endoscopy

ANDI-3

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Background

Crohn's disease (CD) is a chronic inflammatory bowel disease (IBD) most often diagnosed in young adults. The etiology is unknown, but CD is thought to arise from a dysregulated interaction between the gut microbiome and the mucosal immune system in a genetically predisposed individual.[1] The incidence in Denmark continues to increase and is among the highest in the world. The current incidence is 9.1/100,000/year corresponding to approximately 500 patients diagnosed each year and up to 18,000 persons living with CD.[2]

Typical symptoms are chronic diarrhea, abdominal pain, and weight loss. A subgroup of patients experience extra-intestinal disease such as arthritis, uveitis, pyoderma gangrenosum, erythema nodosum, or primary sclerosing cholangitis. CD is characterized by recurrent disease activity and a strong tendency to relapse after remission with medical treatment (immunosuppressants) or surgical resection. A small proportion of patients experience continuous disease activity.[3]

Cardinal lesions are mucosal ulcerations ranging from small aphthous ulcerations to large ulcers and fissures. Histologically, the inflammation is transmural and often granulomatous. Typically, CD has a segmental distribution, and the entire gastrointestinal tract may be involved. The disease is often located in the terminal ileum and right colon (ileocecal CD). In approximately one third of patients, the disease is located in the small intestine, and one third has CD restricted to the colon.[4] At the time of diagnosis, the majority of patients have an inflammatory phenotype, i.e. mucosal ulcerations without stricture, fistula, or abscess.[5] In 10-30% of patients, however, strictures of varying degrees are present at debut; primarily in patients with CD in the small bowel.[5-7]

Current guidelines for diagnosing Crohn's disease

Most patients have CD located within reach of the colonoscope, and ileocolonoscopy (IC) with segmental biopsies is currently the first-line diagnostic procedure in patients with clinically suspected CD.[8] Regardless of findings at IC, however, an additional small bowel examination is recommended for evaluation of disease extension (e.g. MR enterography or small bowel capsule endoscopy). IC is invasive and reaching the terminal ileum is not always possible. Although significant adverse events such as bleeding and perforation are rare (< 0.1%),[9] up to one third of the patients experience minor adverse events (e.g. abdominal pain and bloating),[10] and patients prefer less invasive modalities.[11, 12]

Fecal calprotectin is an established clinical biomarker for IBD, and it is helpful in selecting patients for further diagnostic workup. Concentrations found in healthy individuals range between 10 and 50 mg/kg stool, and a fecal calprotectin concentration of ≤ 40 mg/kg confers a ≤ 1% probability of having IBD.[13] Several studies implicated that fecal calprotectin allowed differentiation between non-IBD and IBD at a cut-off between 100

and 200 mg/kg.[14] However, an exact cut-off value for the discrimination between IBD and functional bowel disease is not established.

Modalities for minimally invasive diagnosis

Technological advances have recently improved minimally invasive modalities for diagnosing and monitoring CD. The primary modalities are capsule endoscopy (CE), MR enterography and intestinal ultrasound (IUS). All modalities can visualize both the small intestine and colon in one procedure.

Visualizing the transmural component of CD (e.g., bowel wall thickening and post-contrast enhancement) is a key element of cross-sectional imaging.[8] However, patients with newly diagnosed CD most often have mucosal ulcerations, and over time, CD can progress to complicated disease involving the entire gut wall.[5] Hence, the diagnostic performance of different modalities differs between patient groups – from mucosal lesions at debut best visualized by endoscopy to transmural or penetrating lesions in longstanding disease. Correspondingly, recent studies have found an insufficient sensitivity of cross-sectional imaging for the initial diagnosis of CD, especially for CD located in the colon.[11, 15]

Pan-enteric capsule endoscopy

CE is a patient-friendly and minimally invasive procedure. Compared to cross-sectional imaging, CE allows direct and detailed evaluation of the gastrointestinal mucosa with detection of the earliest lesions of CD.[16]

Using CE to evaluate the small bowel and colon in a single examination is an attractive diagnostic approach. Pillcam colon capsule endoscopy (PCCE) was introduced in 2006 and a pan-enteric capsule endoscope is now available in clinical practice (PillCam™ Crohn's capsule, Medtronic, Dublin, Ireland).

Performing CE of the colon requires optimal cleansing, and the *European Society of Gastrointestinal Endoscopy* currently recommends a regimen consisting of polyethylene glycol (PEG) in two divided doses and a booster preparation for propulsion of the capsule through the gastrointestinal tract and maintenance of optimal bowel cleansing throughout the entire procedure.[17] The extensive bowel preparation required to achieve sufficient image quality is a significant limitation. In a recent study by our group, the volume of PEG was the main factor affecting the image quality.[18] Although few patients were able to ingest the recommended volume of PEG (2+2 L), the diagnostic yield for CD was not affected.

In a prospective study of patients with known CD, PCCE had a sensitivity of 86% for detection of ulcerations in the colon and terminal ileum, and lesions outside the reach of the colonoscope were detected in 15% of patients.[12] There was a moderate correlation between PCCE and IC for assessment of disease severity. *Leighton et al.* compared the diagnostic yield of pan-enteric CE with IC in 66 patients with known active CD.[19] The per-subject diagnostic yield for CD lesions was 83.3% for CE and 69.7% for IC (incremental yield 13.6%

(95% CI, 2.6-24.7%). CE detected a greater percentage of lesions in each evaluated segment than IC. The overall per-segment diagnostic yield was 40.6% and 32.7%, respectively. In a more recent study by *Bruining et al.,* the sensitivity and specificity of CE for active enteric inflammation was 94% and 74%, respectively.[20] The sensitivity of CE was superior to that of MRE for the proximal small bowel and similar for the terminal ileum. This study included patients with an established diagnosis of CD. A recent study by our group examined patients with clinically suspected CD going through their first diagnostic work-up. The sensitivity and specificity for diagnosing ileocolonic CD with MREC was 67.9% (CI 53.7–80.1) and 76.3% (CI 65.2–85.3) (terminal ileum 76.9% and 85.6%; colon 27% and 93%) compared to 87.5% (CI 73.2–95.8) and 87.8% (CI 78.2–94.3) with CE (terminal ileum 96.6% and 87.5%; colon 75.0% and 93.0%).[11] The sensitivity of CE was superior to that of MREC (P = 0.02). Furthermore, the level of patient discomfort was equal for CE and MREC and significantly less than for IC.

In a retrospective evaluation of histopathological findings, the additional information obtained from biopsies was limited after CE performed in patients with clinically suspected CD.[21] Biopsies added new diagnostic information in only 6.5%, and CE as a single diagnostic procedure was feasible in the majority of patients. Biopsies are warranted, however, in patients with an atypical endoscopic appearance or suspected malignancy.

Reading the capsule examination with computer assistance

Analysis of the CE videos is a time-consuming process. The use of artificial intelligence (AI) – especially deep learning techniques – has received much attention in recent years. Several clinical areas have been investigated, including the ability to analyze endoscopy images and assist in clinical decision making.[22-24] A recent meta-analysis showed a high sensitivity and specificity of deep learning techniques for ulcer detection in the small intestine.[23] In contrast, the ability of AI to diagnose CD in the large intestine has not been studied to the same extent. Therefore, our group have previously tested the ability of a deep-learning algorithm to detect CD lesions in single images of the small intestine or colon captured with CE, determine the localization of lesions and the ability to characterize lesions of different severity.[25] We obtained excellent agreement with the clinical standard, and diagnostic accuracy is equally high for the small intestine and colon. In a recent validation study, we examined the diagnostic accuracy of AI-assisted CE reading for the detection of inflammatory bowel disease in full-length CE examinations in 131 patients with suspected CD.[26] Videos were processed by an offline version of the deep learning solution AXARO® (Augmented Endoscopy, Paris, France). The AXARO® platform is based on: 1) a user-friendly human-machine interface that ensures efficient use of its modules; and 2) an AI core that ensures the different classification and detection tasks. The AI core of AXARO® was trained on annotated small bowel CE still frames from a multicenter database, CAD-CAP.[27] The

output of this AI solution is single images of interest, with and without marking the region of interest. The study revealed that the employment of AI assistance in CE reading significantly reduced review time while maintaining a high diagnostic accuracy for detection of CD.

Deep learning approaches have great potential to help clinicians detect, localize and determine the severity of CD with CE. Existing data are promising, and AI may have a central role in the future of non-invasive diagnosis of CD with CE, although significant development and testing of the technology is needed before clinical use.

MR enterography

Magnetic resonance imaging is characterized by the ability to visualize all manifestations of CD – luminal, mural and extraintestinal – with high tissue contrast and without ionizing radiation. MR enterography (MRE) is performed with oral and intravenous contrast. Typical manifestations of CD are ulcers, wall thickening, relative contrast enhancement, dilated vasa recta (Comb sign), enlarged mesenteric lymph nodes, stenosis, prestenotic dilatation, abscess, and fistula. MRE diagnoses CD in the small intestine with a moderate to high sensitivity, specificity and inter-observer agreement.[16, 28] In contrast, recent studies have demonstrated the significantly lower sensitivity of MRE (25-47 %) for diagnosing colonic CD manifestations compared to pan-enteric CE[11], IUS[15] and IC[11, 15]. The wall thickness, relative contrast enhancement and the presence of ulcers and edema are independent predictors for endoscopic disease severity.[29]

Ultrasound

IUS is an attractive imaging modality as it is non-invasive, associated with minimal to no patient discomfort and does not expose the patient to ionizing radiation. Typical findings in CD are wall thickening, loss of wall stratification, reduced peristalsis, stenosis, prestenotic dilatation, creeping fat, fistula, and abscess. IUS is able to diagnose CD in the terminal ileum and colon with a moderate to high sensitivity and a high specificity, although its diagnostic value is highly operator dependent.[30, 31] Visualization of the proximal small bowel as well as segments of the intestine located in the pelvis may be difficult[32] and the examination may be compromised by air-filled intestinal loops. The wall thickness and vascularization in affected bowel segments evaluated with Doppler IUS correlates with the endoscopic disease activity.[9]

Small bowel patency

In a recent meta-analysis by *Pasha et al.*, capsule retention occurred in 2.35% of patients examined for suspected CD,[33] and retention rates of 4-13% have been reported in patients with symptomatic CD.[34] Recent

data from centers with extensive experience in capsule endoscopy suggest even lower retention rates in patients with suspected CD of around 0,5 %.[35]

Different methods exist to determine small bowel patency before CE: 1) clinically, 2) a dissolvable test capsule or 3) cross-sectional imaging. Symptoms suggesting small bowel obstruction are abdominal pain (typically postprandial), distension, nausea, and vomiting.[36] If small bowel stenosis is not firmly excluded, the Pillcam patency capsule (Medtronic, Dublin, Ireland) can be used to confirm small bowel patency before performing CE. The patency capsule is a dissolvable capsule with the same size as the Pillcam SB3 capsule (26 x 11 mm). It is composed of a lactose body with barium added for radio opacity. In each end, the patency capsule has a timer plug designed to erode after 30 hours resulting in disintegration of the capsule, and it has been stated that all patency capsules are dissolved within 72 hours.[37] Capsule endoscopy is considered safe if the patency capsule is excreted before 30 hours, an intact capsule is excreted after 30 hours, or passage to the colon of an intact patency capsule is radiologically confirmed.

Herrerias et al. examined the Pillcam patency capsule in 106 patients with radiographic evidence of a small bowel stricture.[38] Small bowel patency was confirmed in 59, and none of these patients experienced capsule retention at a subsequent capsule endoscopy. No severe adverse events could be attributed to the patency capsule. Furthermore, *Yadav et al.* concluded that the Pillcam patency capsule and radiological examination were equally reliable for excluding small bowel obstruction or strictures.[39] Hence, available studies suggest that the Pillcam patency capsule is a safe method for testing small bowel patency before capsule endoscopy, even in patients with a radiologically verified stenosis.

In a study evaluating the accuracy of MRE for prediction of patency capsule retention in patients with established small bowel CD, the sensitivity and specificity was 92.3% and 59%, respectively.[40] If the decision to administer CE was based on imaging and not on patency capsule results, at least 40% of the patients would not have undergone CE. Hence, MRE is less accurate in the evaluation of functional small bowel patency, frequently overestimating the risk of obstruction.

Use of IUS in predicting capsule retention is less well studied, although a study of 50 patients with suspected small bowel stenosis found a sensitivity and specificity of 92.3% and 72,9%, respectively, for impassable stenosis at double-balloon enteroscopy.[41]

Future perspectives

Implementing pan-enteric CE as a first-line modality in patients with suspected CD could reduce the need for IC; changing IC from a first line procedure to a targeted procedure for obtaining biopsies or if CE is incomplete or contraindicated. Since pan-enteric CE visualizes the entire small bowel, this offers a potential single-examination strategy yielding the total disease distribution. This strategy might be feasible; especially in

young patients with low risk of neoplasia. The potential is a rapid and less invasive, better tolerated and possibly cost-effective diagnostic workup. Future research should develop new diagnostic algorithms using minimally invasive technology, examine the feasibility of CE as a first-line diagnostic procedure, reduce the time used for CE analysis (e.g., with AI), implementing pan-enteric activity scores, and optimize bowel preparation, which will add further potential to this modality. Cross sectional imaging should be reserved for more advanced stages of CD to harvest the full potential of this modality.

References

1. Torres J, Mehandru S, Colombel JF, et al. Crohn's disease. Lancet 2017;389:1741-1755.
2. Lophaven SN, Lynge E, Burisch J. The incidence of inflammatory bowel disease in Denmark 1980-2013: a nationwide cohort study. Aliment Pharmacol Ther 2017;45:961-972.
3. Binder V, Hendriksen C, Kreiner S. Prognosis in Crohn's disease--based on results from a regional patient group from the county of Copenhagen. Gut 1985;26:146-50.
4. Vind I, Riis L, Jess T, et al. Increasing incidences of inflammatory bowel disease and decreasing surgery rates in Copenhagen City and County, 2003-2005: a population-based study from the Danish Crohn colitis database. Am J Gastroenterol 2006;101:1274-1282.
5. Cosnes J, Cattan S, Blain A, et al. Long-term evolution of disease behavior of Crohn's disease. Inflamm Bowel Dis 2002;8:244-50.
6. Solberg IC, Vatn MH, Hoie O, et al. Clinical course in Crohn's disease: results of a Norwegian population-based ten-year follow-up study. Clin Gastroenterol Hepatol 2007;5:1430-8.
7. Chan WPW, Mourad F, Leong RW. Crohn's disease associated strictures. J Gastroenterol Hepatol 2018;33:998-1008.
8. Maaser C, Sturm A, Vavricka SR, et al. 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.
9. Benitez JM, Meuwis MA, Reenaers C, et al. Role of endoscopy, cross-sectional imaging and biomarkers in Crohn's disease monitoring. Gut 2013;62:1806-16.
10. Steffenssen MW, Al-Najami I, Baatrup G. Patient-reported minor adverse events after colonoscopy: a systematic review. Acta Oncol 2019;58:S22-S28.
11. Brodersen JB, Knudsen T, Kjeldsen J, et al. Diagnostic accuracy of pan-enteric capsule endoscopy and magnetic resonance enterocolonography in suspected Crohn's disease. United European Gastroenterol J 2022.

12. D'Haens G, Lowenberg M, Samaan MA, et al. Safety and Feasibility of Using the Second-Generation Pillcam Colon Capsule to Assess Active Colonic Crohn's Disease. Clin Gastroenterol Hepatol 2015;13:1480-6 e3.
13. Menees SB, Powell C, Kurlander J, et al. 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;110:444-54.
14. Jukic A, Bakiri L, Wagner EF, et al. Calprotectin: from biomarker to biological function. Gut 2021;70:1978-1988.
15. Taylor SA, Mallett S, Bhatnagar G, et al. Diagnostic accuracy of magnetic resonance enterography and small bowel ultrasound for the extent and activity of newly diagnosed and relapsed Crohn's disease (METRIC): a multicentre trial. Lancet Gastroenterol Hepatol 2018;3:548-558.
16. Jensen MD, Nathan T, Rafaelsen SR, et al. Diagnostic accuracy of capsule endoscopy for small bowel Crohn's disease is superior to that of MR enterography or CT enterography. Clin Gastroenterol Hepatol 2011;9:124-9.
17. Spada C, Hassan C, Galmiche JP, et al. Colon capsule endoscopy: European Society of Gastrointestinal Endoscopy (ESGE) Guideline. Endoscopy 2012;44:527-36.
18. Brodersen JB, Andersen KW, Jensen MD. Adherence to the bowel cleansing regimen for pan-enteric capsule endoscopy in patients with suspected Crohn's disease and factors affecting the image quality. Scand J Gastroenterol 2021:1-6.
19. Leighton JA, Helper DJ, Gralnek IM, et al. Comparing diagnostic yield of a novel pan-enteric video capsule endoscope with ileocolonoscopy in patients with active Crohn's disease: a feasibility study. Gastrointest Endosc 2016.
20. Bruining DH, Oliva S, Fleisher MR, et al. Panenteric capsule endoscopy versus ileocolonoscopy plus magnetic resonance enterography in Crohn's disease: a multicentre, prospective study. BMJ Open Gastroenterol 2020;7.
21. Thomsen SH, Zinolabedinbik P, Brodersen JB, et al. The additional information obtained from mucosal biopsies is limited after pan-enteric capsule endoscopy in patients with suspected Crohn's disease. Endosc Int Open 2023.
22. Ahmad OF, Soares AS, Mazomenos E, et al. Artificial intelligence and computer-aided diagnosis in colonoscopy: current evidence and future directions. Lancet Gastroenterol Hepatol 2019;4:71-80.
23. Soffer S, Klang E, Shimon O, et al. Deep learning for wireless capsule endoscopy: a systematic review and meta-analysis. Gastrointest Endosc 2020;92:831-839 e8.

24. Nadimi ES, Buijs MM, Herp J, et al. Application of deep learning for autonomous detection and localization of colorectal polyps in wireless colon capsule endoscopy. Computers & Electrical Engineering 2020;81:106531.
25. Majtner T, Brodersen JB, Herp J, et al. A deep learning framework for autonomous detection and classification of Crohn's disease lesions in the small bowel and colon with capsule endoscopy. Endosc Int Open 2021;9:E1361-E1370.
26. Brodersen JB, Jensen MD, Leenhardt R, et al. Artificial intelligence-assisted analysis of pan-enteric capsule endoscopy in patients with suspected Crohn's disease. A study on diagnostic performance. J Crohns Colitis 2023.
27. Leenhardt R, Li C, Le Mouel JP, et al. CAD-CAP: a 25,000-image database serving the development of artificial intelligence for capsule endoscopy. Endosc Int Open 2020;8:E415-E420.
28. Jensen MD, Ormstrup T, Vagn-Hansen C, et al. Interobserver and intermodality agreement for detection of small bowel Crohn's disease with MR enterography and CT enterography. Inflamm Bowel Dis 2011;17:1081-8.
29. Rimola J, Rodriguez S, Garcia-Bosch O, et al. Magnetic resonance for assessment of disease activity and severity in ileocolonic Crohn's disease. Gut 2009;58:1113-20.
30. Dong J, Wang H, Zhao J, et al. Ultrasound as a diagnostic tool in detecting active Crohn's disease: a meta-analysis of prospective studies. Eur Radiol 2014;24:26-33.
31. Panes J, Bouzas R, Chaparro M, et al. Systematic review: the use of ultrasonography, computed tomography and magnetic resonance imaging for the diagnosis, assessment of activity and abdominal complications of Crohn's disease. Aliment Pharmacol Ther 2011;34:125-45.
32. Parente F, Greco S, Molteni M, et al. Role of early ultrasound in detecting inflammatory intestinal disorders and identifying their anatomical location within the bowel. Aliment Pharmacol Ther 2003;18:1009-16.
33. Pasha SF, Pennazio M, Rondonotti E. Capsule retention in Crohn’s disease: a meta-analysis. Inflamm Bowel Dis 2020;26:33-42.
34. Cheifetz AS, Kornbluth AA, Legnani P, et al. The risk of retention of the capsule endoscope in patients with known or suspected Crohn's disease. Am J Gastroenterol 2006;101:2218-22.
35. Nemeth A, Wurm Johansson G, Nielsen J, et al. Capsule retention related to small bowel capsule endoscopy: a large European single-center 10-year clinical experience. United European Gastroenterology Journal 2017;5:677-686.
36. Karagiannis S, Faiss S, Mavrogiannis C. Capsule retention: a feared complication of wireless capsule endoscopy. Scand J Gastroenterol 2009;44:1158-65.

37. Lewis BS. Expanding role of capsule endoscopy in inflammatory bowel disease. World J Gastroenterol 2008;14:4137-41.
38. Herrerias JM, Leighton JA, Costamagna G, et al. Agile patency system eliminates risk of capsule retention in patients with known intestinal strictures who undergo capsule endoscopy. Gastrointest Endosc 2008;67:902-9.
39. Yadav A, Heigh RI, Hara AK, et al. Performance of the patency capsule compared with nonenteroclysis radiologic examinations in patients with known or suspected intestinal strictures. Gastrointest Endosc 2011;74:834-9.
40. Rozendorn N, Klang E, Lahat A, et al. Prediction of patency capsule retention in known Crohn's disease patients by using magnetic resonance imaging. Gastrointest Endosc 2016;83:182-7.
41. Nakano M, Oka S, Tanaka S, et al. Clinical usefulness of transabdominal ultrasonography prior to patency capsule for suspected small-bowel strictures. Scandinavian Journal of Gastroenterology 2016;51:281-287.
42. Hutchings HA, Cheung W-Y, Alrubaiy L, et al. Development and validation of the Gastrointestinal Endoscopy Satisfaction Questionnaire (GESQ). Endoscopy 2015;47:1137-1143.
43. Brodersen JB, Knudsen T, Kjeldsen J, et al. Diagnostic accuracy of pan-enteric capsule endoscopy and magnetic resonance enterocolonography in suspected Crohn's disease. United European Gastroenterol J 2022;10:973-982.
44. Vuik FER, Nieuwenburg SAV, Moen S, et al. Colon capsule endoscopy in colorectal cancer screening: a systematic review. Endoscopy 2021;53:815-824.
45. Pennazio M, Rondonotti E, Despott EJ, et al. Small-bowel capsule endoscopy and device-assisted enteroscopy for diagnosis and treatment of small-bowel disorders: European Society of Gastrointestinal Endoscopy (ESGE) Guideline - Update 2022. Endoscopy 2023;55:58-95.
46. International Committee of Medical Journal Editors. Recommendations for the Conduct, Reporting, Editing and Publication of Scholarly Work in Medical Journals. Volume 2024, 2024.
47. Eliakim R, Yablecovitch D, Lahat A, et al. A novel PillCam Crohn's capsule score (Eliakim score) for quantification of mucosal inflammation in Crohn's disease. United European Gastroenterol J 2020;8:544-551.
48. Magro F, Langner C, Driessen A, et al. European consensus on the histopathology of inflammatory bowel disease. J Crohns Colitis 2013;7:827-51.
49. Langner C, Magro F, Driessen A, et al. The histopathological approach to inflammatory bowel disease: a practice guide. Virchows Arch 2014;464:511-27.

50. Magro F, Sabino J, Rosini F, et al. ECCO Position on Harmonisation of Crohn's Disease Mucosal Histopathology. J Crohns Colitis 2022;16:876-883.

Hypothesis

Pan-enteric CE is a feasible, safe and patient friendly first-line diagnostic procedure reducing the need for IC and additional diagnostic procedures in patients examined for clinically suspected CD.

Aim

The aim of this study is to determine the feasibility, efficacy and safety of pan-enteric CE as the first-line diagnostic procedure compared to traditional diagnostic work-up with IC plus MRE or small bowel (SB)CE in patients with clinically suspected CD.

Inclusion criteria

- Clinical suspicion of CD*
- Age 18-40 years
- Signed informed consent

*A clinical suspicion of CD is based on the following definition: Diarrhea and/or abdominal pain for more than 1 month (or repeated episodes of diarrhea and/or abdominal pain) and *either* fecal calprotectin ≥ 200 mg/kg *or* fecal calprotectin ≥ 50 mg/kg plus one or more of the following findings: (1) C-reactive protein (CRP) > 5 mg/L, (2) thrombocytosis (> 400 x 10^9/L), (3) anemia (hemoglobin < 7.0 mmol/L for women and < 8.0 mmol/L for men *or* a decrease > 0.5 mmol/L compared to the usual level), (4) prolonged fever (> 37.5 °C for more than 2 weeks), (6) weight loss (≥ 3 kg or ≥ 5% compared to the normal body weight), (7) perianal abscess / fistula or (8) a family history of inflammatory bowel disease.

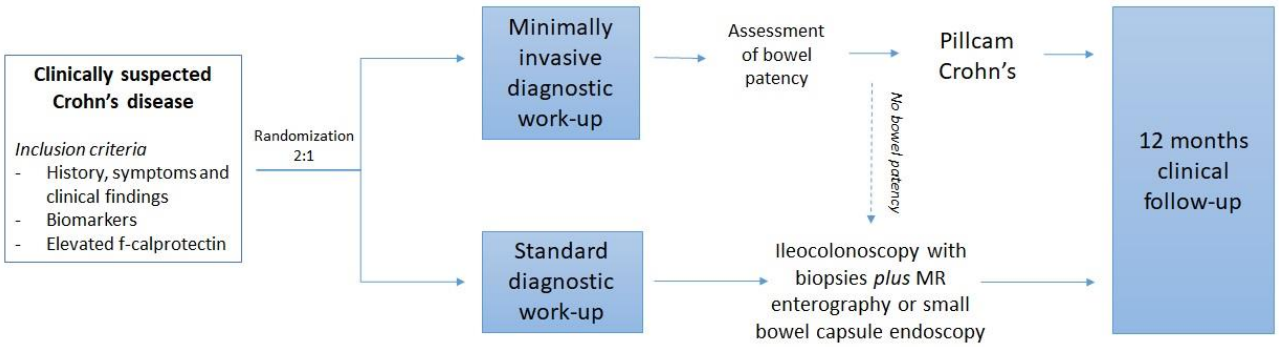
Exclusion criteria

- Previous intestinal resection
- Positive serologic markers for celiac disease
- Positive stool polymerase chain reaction for pathogenic bacteria
- Positive stool polymerase chain reaction for intestinal parasites

- Suspected or established acute bowel obstruction (ileus)
- Intake of NSAIDs or acetylsalicylic acid ≤ 4 weeks before inclusion, except low-dose, prophylactic acetylsalicylic acid (≤ 150 mg per day)
- Intake of opioid or opioid-like medication ≤ 1 week before inclusion
- Pregnancy or lactation
- Unable to comply with protocol requirements, e.g. for reasons including alcohol or recreational drug abuse
- Known gastrointestinal disorder other than functional gastrointestinal disorders
- Renal failure defined by a plasma-creatinine above the normal reference range

Study design

This is a pragmatic, prospective, randomized multicenter study comparing a new minimally invasive diagnostic algorithm with the traditional diagnostic work-up in patients with clinically suspected CD. Patients referred to medical gastroenterology units at public hospitals in the Region of Southern Denmark are screened for participation in the study at the time of referral from primary care or after the first diagnostic interview. Participation from centers outside the Region of Southern Denmark is possible if a physician responsible for the project can be appointed and centers are able to comply with the protocol requirements. Each patient will complete a standardized work-up including medical history, physical examination, blood samples and fecal calprotectin. Patients are randomized 2:1 stratified by participating center to a minimally invasive strategy with pan-enteric CE (Pillcam Crohn's) or IC plus MRE or SBCE. All examinations are reviewed and described in a standardized fashion.



Endpoints

Primary endpoint:

1. Diagnostic completeness, defined as the proportion of patients in each group achieving a complete gastrointestinal assessment and an unambiguous diagnosis after the first-line work-up strategy without need for supplementary examinations.

Secondary endpoints:

1. Feasibility of pan-enteric CE: Number of patients with suspected CD examined with pan-enteric CE and the number of ICs avoided
2. Additional examinations: Need for additional examinations in the two randomization arms
3. Safety: Number of severe adverse events, delayed or missed diagnoses
4. Time to diagnosis: Time from referral or first diagnostic procedure to a final diagnosis and treatment
5. Disease classification and medical treatments in the two randomization arms
6. Patient satisfaction: Difference in Gastrointestinal Endoscopy Satisfaction Questionnaire (GESQ) score[42]
7. Costs: Expenditure on diagnostic procedures, treatment and loss of productivity
8. Artificial intelligence: Diagnostic utility of AI algorithms in detection of gastrointestinal pathology using pan-enteric CE – sensitivity, specificity, severity, prediction and impact on clinical decision making

Participating centers

Patients are recruited from the following centers:

- Department of Internal Medicine, Esbjerg Hospital – University Hospital of Southern Denmark
- Department of Medical Gastroenterology, Odense University Hospital
- Department of Internal Medicine, Lillebaelt Hospital – University Hospital of Southern Denmark
- Department of Internal Medicine, Hospital Sønderjylland – University Hospital of Southern Denmark
- Department of Gastroenterology, Skåne University Hospital Malmö, Lund University, Sweden

Logistics

Subject identification and informed consent process

Subjects are identified either by physicians at trial sites when screening referrals to the trial sites on suspicion of inflammatory bowel disease or at the first interview with the treating physician, if the suspicion of inflammatory bowel disease is first raised here.

Blood samples, including serologic markers for celiac disease, and stool polymerase chain reaction for pathogenic bacteria and parasites are performed in accordance with the standard of care for newly referred patients at the site of inclusion. If fecal calprotectin is performed $\leq$ 4 weeks prior to enrollment in the study, a repeated test is not mandatory.

Regardless of how the subject is identified, the subject will be offered inclusion in the trial at the first interview with the treating physician, if the inclusion criteria and none of the exclusion criteria are met. Oral and written information is provided by the treating physician at the trial site, who has been delegated to do so by the principal investigator by written agreement.

Since oral and written information is provided at a scheduled interview with the treating physician in a gastroenterology outpatient clinic, the interview takes place undisturbed and the subject has the opportunity to bring an assistant to the interview. The subject will also be informed that there is an opportunity to request a cooling-off period or a new interview with a repetition of the oral information in the presence of an assistant. If the subject does not want a cooling-off period, consent is sought immediately, otherwise after at least 24 hours of cooling-off period. The declaration of consent is signed by the patient and the treating physician.

Baseline visit

Patients undergo a full medical history taking and physical examination by a physician. Patients are randomly allocated to a minimally invasive or standard diagnostic algorithm using block randomization in groups of two.

Minimally invasive diagnostic work-up

Pan-enteric CE is performed at the center from which the patient is included. Before CE, patients are evaluated for small bowel patency with a thorough clinical assessment, supplemented with the patency capsule system if deemed necessary. Assessment of small bowel patency can be supplemented with IUS prior to examination with the patency capsule in centers with experience in this procedure. If bowel patency is confirmed, pan-enteric CE is performed using standard bowel preparation as described below. If bowel patency is not confirmed, the patient will cross over to a standard diagnostic work-up with IC plus MRE. If the capsule fails to pass from the stomach to the duodenum during the examination, the procedure will be considered failed and the patient will cross over to a standard diagnostic work-up. Endoscopic delivery of the capsule to the duodenum is not permitted in this study.

CE is analyzed by central reading performed by an expert reader and lesions of interest are confirmed and countersigned by a second expert. In case of disagreement between the first and second expert on findings or clinical recommendation after the examination, an evaluation committee of several expert readers will provide a final decision. Results are reported standardized as described below, and the treating

gastroenterologist is provided with the result. Decisions regarding diagnosis, additional diagnostic work-up and treatment are made afterwards by the treating physician.

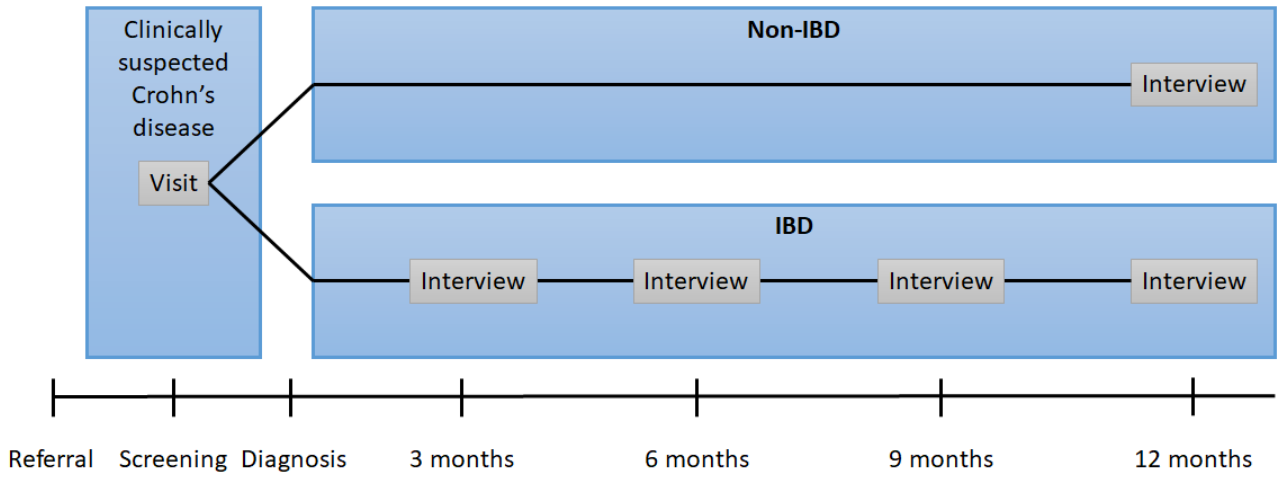
Standard diagnostic work-up

Patients go through a diagnostic work-up in accordance with international guidelines including IC with segmental biopsies plus a small bowel examination, either MRE or SBCE as selected by the investigating clinician. MRE is preferred in patients with suspected complications to CD (stenosis, abscess or fistula). CE is preferred in patients without disease complications. Patients are scheduled for IC at one of the participating centers using standard bowel preparation and sedation according to local preferences. MREs and SBCEs are performed locally at the participating centers. Results are reported in a standardized fashion. After completing all diagnostic procedures, the treating gastroenterologist is provided with the results of IC and MRE or SBCE, and decisions regarding diagnosis, additional diagnostic work-up and treatment are made.

Follow-up

Patients are followed clinically for 12 months according to the result of the initial diagnostic work-up:

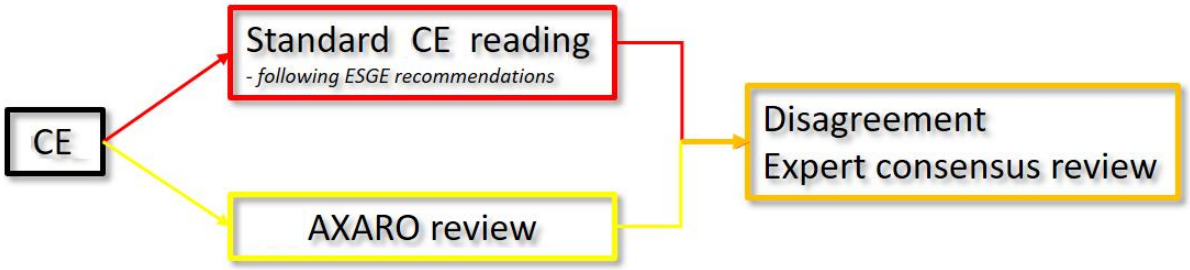
- **Non-IBD**: Patients are interviewed by the primary investigator or the study nurse after 12 months.
- **IBD**: Data are collected 3, 6, 9 and 12 months after diagnostic work-up.



Artificial intelligence

Parallel to the standard review of pan-enteric CEs, a secondary AI-supported review will be conducted. Full-length anonymized videos will be processed and reviewed in a cloud-based deep learning solution such as AXARO (Augmented Endoscopy, Paris, France). Results are reported in a standardized fashion and compared to the standard review. In cases with disagreement between standard review and AI-assisted review, findings

are presented to an IBD expert with experience in CE not involved in the standard or AI review for classification of lesions, diagnosis, severity, localization, and need for additional diagnostic work-up.



Treatment

After completing all bowel examinations, a final diagnosis is made. Patients are discharged (non-IBD) or followed in the gastroenterology outpatient clinics by the treating physician. Additional examinations, medical or surgical treatment are performed without restrictions.

Blood tests

Prior to inclusion in the study, the following blood tests are performed in accordance with the standard clinical praxis for newly referred patients: Hemoglobin, erythrocyte volume fraction, platelet count, total and differential leukocyte count, C-reactive protein, sodium, potassium, albumin, creatinine, alanine aminotransferase, alkaline phosphatase, bilirubin, thyrotropin (TSH), transglutaminase IgA, total IgA *or* deamidated gliadin IgG, ferritin, cobalamin and folate.

Stool samples

Stool samples are examined by polymerase chain reaction for pathogenic bacteria and intestinal parasites, and fecal calprotectin is measured as a part of routine clinical praxis.

Biobank

A biobank is not included in this study.

Number of patients

We aim to include 165 patients in the study.

Time perspective

Inclusion in the study begins 1st of September 2024 and ends 1st of April 2027. Clinical follow-up will continue until 1st of September 2027.

Statistical considerations

The diagnostic completeness of pan-enteric CE and conventional diagnostic work-up depends on the chosen inclusion criteria, severity of lesions and disease location. In two previous studies performed by our group with similar inclusion criteria, CD was diagnosed in 43% and 39% of patients, respectively.[16, 43] The following performance measures were derived:

- *Drop out:* Pan-enteric CE was not performed in 10% of patients because of suspected small bowel stricture, patient demands or unwillingness to complete the procedure.
- *Complete procedures:* A complete IC and pan-enteric CE was achieved in 86% and 82% of patients, respectively. MR-enterography was not completed in accordance with the protocol in 1-5% of patients.
- *Diagnostic performance:* The sensitivity of CE for diagnosing CD in the terminal ileum was significantly higher compared to MR (100% vs 81%). The diagnostic yield of CE for detection of CD in the proximal small bowel was also higher compared to MR (15-22% vs. 3%). The sensitivity of CE for diagnosing CD in the colon was 75% compared to IC.

Expected diagnostic completeness

Minimally invasive diagnostic work-up: With 10% of patients withdrawn from the procedure, 80% complete examinations and a diagnostic procedure in 90%, the expected diagnostic completeness of pan-enteric CE is 65%.

Standard diagnostic work-up: With 5% of patients withdrawn from at least one of the procedures, 90% complete examinations and diagnostic procedures in 90%, the expected diagnostic completeness of pan-enteric IC plus MR enterography or SBCE is 77%.

Sample size calculation

In a randomized controlled non-inferiority trial with a 2:1 ratio of patients examined with CE and standard diagnostic procedures (IC + MR enterography or SBCE), significance level 0.05, power 0.8, expected diagnostic completeness in samples 0.65, expected diagnostic completeness in controls 0.77 and a margin on risk difference scale 0.3, the following number of patients are required to show non-inferiority between two diagnostic strategies: 165 (110 in CE arm and 55 controls).

Data capture and randomization

Data are collected and stored in a secured REDCap database under OPEN (Open Patient data Explorative Network). REDCap also provides a tool for 2:1 randomization of patients for minimally invasive diagnosis or standard diagnostic work-up, respectively.

Risks, side effects and disadvantages for the participants

Modalities selected for this study are all – with the exception of IC – minimally invasive, patient friendly and without use of ionizing radiation. Patients with CD often develop small bowel strictures and in known CD, CE is associated with a 4-13% risk of capsule retention. However, this study includes patients with suspected CD undergoing their first diagnostic work-up, and the risk of capsule retention is significantly lower (approximately 2%). A thorough clinical assessment is performed prior to CE and supplemented with the patency capsule if a clinical suspicion of stenosis is raised, further minimizing the risk of capsule retention. CE is safe if small bowel stenosis is excluded with the patency capsule.

As IC is associated with discomfort from bowel cleansing and the investigation itself, the procedure is conducted using moderate conscious sedation or deep sedation with propofol. Serious side effects are rare with a risk of perforation < 1 per 1,000 colonoscopies. In accordance with international guidelines, IC is indicated as the first line diagnostic procedure if patients reject participation in this study.

Missed or delayed diagnosis of malignancy is a critical adverse event. All patients examined for CD in this study are young adults below 40 years of age, and malignancy is rare in this group of patients. In a previous study by our group, there were three cases of malignancy and one case of suspected malignancy in 153 patients with suspected CD. Pan-enteric CE was performed in 2 patients with malignancy, and both cases were detected. One patient, a 67-year old woman with a small bowel lymphoma, was misinterpreted as CD, but in retrospect, lesions were clearly abnormal and would prompt additional examinations. In a recent systematic review, the sensitivity of a complete CE for detection of colorectal cancer was 93%, which was comparable to IC.[44] CE was considered a safe and effective tool for the detection of colorectal cancer and polyps in a screening setting.

The additional AI-assisted review, will act as another layer of safety in CE – results of this review will never stand alone, but will be compared to the standard review. The cloud based software for AI-assisted review, are hosted on approved secure servers within the European Union and in compliance with current legislation for handling of personal data. Videos used in the analysis are created without identifiers and are deleted after review.

Hence, we believe no increased risk is associated with participation in this study. Participants are covered by *Patienterstatningen*.

Ethical considerations

This study is conducted in accordance with the guidelines for biomedical research involving human subjects outlined by the *Declaration of Helsinki* and after approval from the Regional Ethics Committee for Southern Denmark.

Patients are recruited from medical gastroenterology units at public hospitals in the Region of Southern Denmark. Patients are informed orally by the treating physician and in writing and offered time for reflection before signing the declaration of consent. The patient is offered another consultation if he or she needs a lay representative. Patients may at any time withdraw their consent to participate in the study without it impacting the treatment they otherwise receive in the gastroenterology outpatient clinics.

Imaging modalities selected for this study are all – except IC – minimally invasive, patient friendly and without use of ionizing radiation. IC is indicated as first line diagnostic procedure if patients reject participation in this study. We anticipate that rare cases of malignancy will be detected irrespective of the diagnostic modalities performed. We believe no increased risk is associated with participation in this study. We believe the additional AI-assisted review will pose no risk to the patients. On the contrary, previous studies have shown that AI systems find more pathology than standard analysis by an experienced physician, and any disagreement will be review by an expert. Our study examines whether a minimally invasive diagnostic strategy is non-inferior to traditional diagnosis using IC as first line procedure. Possibly, IC can be avoided in the future for the initial diagnosis of patients with suspected CD. In addition, only one diagnostic procedure will be required to visualize CD in both the colon and the small intestine compared to two or more examinations performed today.

At any time during the study, a patient can be withdrawn from the study by the treating gastroenterologist if indicated. Additional examinations and medical treatment can be performed without restrictions. Thus, neither diagnosis nor treatment of the patient will be compromised by participation in this study.

Current guidelines do not recommend routine use of a patency capsule prior to CE to prevent capsule retention in patients with suspected CD.[45] In the present study, pan-enteric CE is preceded by a thorough clinical assessment, supplemented with the patency capsule system if deemed necessary. This almost eliminates the risk of capsule retention. In patients examined with IUS or MRE, the radiologist has to inform the primary investigator if one or more of the following findings are identified:

- Small bowel stenosis
- Abscess or fistula

- Subileus or ileus
- Suspected malignancy
- Other intra-abdominal conditions requiring acute or subacute intervention

Approval

The study will be initiated after approval by the Regional Ethics Committee for Southern Denmark and listed on the trial register of the Region of Southern Denmark and the ClinicalTrials.gov database. All patients will give informed consent before participation, and the study is conducted within the requirements of the Danish law. Collaborations with national and foreign research institutions is conducted in agreement with the General Data Protection Regulation (GDPR).

Privacy

Patients will sign written informed consent before participation, and the study is conducted within the requirements of the Danish Data Protection Act (DDPA). Clinical data are prospectively collected after informed consent has been declared with the exceptions noted in the following section, and personal information will not be passed to persons without connection to the study. For collaborations with other research institutions, images / videos are anonymized. No personal data or person identifiable information will be shown (e.g. faces). For analysis in the AI based software, images are considered pseudo-anonymized data, and data processing agreements are made to ensure data safety, compliance with legislation and privacy of the participants. Apart from the anonymized images / videos, no clinical or person identifiable information is passed on to external partners, and data will not be stored externally after AI review. Only doctors involved in this project have access to these data. The primary investigator or sub-investigators at participating centers will obtain a medical history, perform a physical examination, and he is informed about the results of pan-enteric CE, IC, histopathology and MRE. These data will be stored at a secure server under OPEN SDU. Furthermore, digital copies of pan-enteric CEs and videos from the ICs will be sent to the primary investigator for subsequent analysis. MR images are saved digitally on the local and regional picture archiving and communications system (PACS), and images are accessible for central review by the participating radiologist at Department of Radiology, Lillebaelt Hospital. Results of pan-enteric CE, IC and MRE are reported in a standardized fashion and sent to the treating gastroenterologist.

Information from medical records

Transmission without consent

Before the patient has signed the declaration of consent, information including personal data from referrals to participating centers will be passed on to the investigators in order to determine eligibility for inclusion as per the in- and exclusion criteria mentioned above. Referrals marked with a diagnosis code listed in appendix 1 can be passed on to the investigators. Personal data passed on comprises name, Central Personal Register (CPR) number, and the referral text which may include symptoms, physical findings, medications, preexisting conditions, and results from previously performed biochemical and imaging examinations. We expect to screen 330 referrals during the inclusion period from September 1st 2024 to April 1st 2027.

Transmission with consent

The following data are collected by interview and review of the medical records:

- Demographic, socioeconomic and clinical characteristics
- Diagnosis and disease classification
- Patient satisfaction after diagnostic procedures
- Disease activity (Simple Clinical Colitis Activity Index and Harvey-Bradshaw index)
- Biochemistry including fecal calprotectin
- Endoscopic procedures
- Result of histology
- Imaging procedures
- Medical treatments
- Visits at the outpatient clinic, general practitioner or nurse including time for preparation for endoscopic procedures
- Hospital admissions
- Surgery
- Sick leave

Data regarding demographic, socioeconomic and clinical characteristics are necessary to evaluate the results of most endpoints and identify previously unrecognized differences in the study results across randomization arms. Diagnosis and disease classification, information on medical treatments as well as results from endoscopic procedures, histology, and imaging procedures are necessary to determine the main endpoint of the study, evaluate differences in disease classification and medical treatments between randomization arms and determine expenditures. Data on hospital admissions and sick leave are necessary to determine expenditures and loss of productivity.

By providing consent, the patient allows the investigators and regulatory authorities direct access to information in the patient's medical records, including electronic records, in order to view information about the patient's health status, which is necessary for the conduct of the research project and for control purposes, including self-inspection, quality control and monitoring, which they are obliged to carry out.

Steering committee responsible for the study

- Department of Internal Medicine, Section of Gastroenterology, Esbjerg Hospital – University Hospital of Southern Denmark
  - Frederik Drejer Thrane, MD
  - Michael Dam Jensen, Associate Professor, MD, PhD
  - Jacob Broder Brodersen, MD, PhD
  - Torben Knudsen, Professor, PhD, DMSc
- Department of Medical Gastroenterology, Odense University Hospital
  - Jens Kjeldsen, Professor, PhD
- Department of Radiology, Lillebaelt Hospital Vejle
  - Søren Rafael Rafaelsen, Professor, DMSc

Publications

Results will be presented at international conferences and published in international journals with an interest in CD, endoscopy and imaging. Positive as well as negative and inconclusive results will be published. Participating physicians are offered authorship based on each author's contributions to the work following the Vancouver recommendations[46]. Frederik Drejer Thrane is first author of the main study. Additional authorships, including the last author, as well as authorships for subsequent publications deriving from data collected according to this protocol are determined by the contribution of each author. Data are reported in accordance with the CONSORT guideline for non-inferiority and equivalence randomized trials.

Economy

This study was initiated by the principal investigator and physicians from the participating centers. None of the physicians in the steering committee have conflicts of interest in regard to this study. Physicians from the participating centers will declare their conflicts of interest. Granted financial support will be deposited on a research account at the Hospital of Southwest Jutland ("ANDI-3", account number SVS.41.8-11.17220) under public audit.

The project has received funding by a grant from Aage og Johanne Louis-Hansens Fond (DKR 1 275 000) and an unconditional grant from Tillotts Pharma AG (DKR 200 000).

Applications for grants from the PhD Fund of the Region of Southern Denmark (DKR 610 000) and the Region of Southern Denmark Independent and Strategic Research Fund (DKR 400 000) have been submitted. We will apply for a faculty scholarship from the Graduate School of Health Sciences at the University of Southern Denmark (DKR 400 000) when other funding has been secured.

BUDGET- OG FINANSIERINGSPLAN

Projekttitel: Feasibility of a non-invasive diagnostic algorithm in suspected Crohn's disease – a prospective comparison of pan-enteric capsule endoscopy versus ileocolonoscopy plus MR enterography or small-bowel capsule endoscopy

Budgetpost	Enhed	Udgift	Antal	Samlet beløb	Region Syddanmarks ph.d.-pulje	Syddansk Universitet - Institut for Regional Sundhedsforskning	Region Syddanmarks pulje for Fri- og Strategisk Forskning	Aage og Johanne Louis-Hansens Fond	Andre fonde
Aflønning									
Frederik Drejer Thrane, ph.d. årsværk inkl. studieafgift	År	623.333,33	3	1.870.000,00	610.000,00	400.000,00	0,00	650.000,00	210.000,00
Projektkordinator - deltidsansat sygeplejerske	År	200.000,00	2	400.000,00	0,00	0,00	400.000,00	0,00	0,00
Drift									
Pillcam Crohns (kamerapille)	Stk.	5.600,00	110	616.000,00	0,00	0,00	0,00	616.000,00	0,00
Pillcam Patency capsule (selvopløselig testkapsel)	Stk.	500,00	20	10.000,00	0,00	0,00	1.000,00	9.000,00	0,00
Bistand fra OPEN og statistiker				20.000,00	0,00	0,00	20.000,00	0,00	0,00
Kurser og kongresser				20.000,00	0,00	0,00	20.000,00	0,00	0,00
Besøg ved udenlandsk forskningsenhed				30.000,00	0,00	0,00	0,00	0,00	30.000
Udgifter til publikation				30.000,00	0,00	0,00	30.000,00	0,00	0,00
Andet									
Patientbefordring				50.000,00	0,00	0,00	50.000,00	0,00	0,00
I alt				**3.046.000,00**	**610.000,00**	**400.000,00**	**521.000,00**	**1.275.000,00**	**240.000**
Total budget									**kr 3.046.000,00**
Fondene markeret med grønt har bevilliget penge til projektet									

Diagnostic procedures and definitions

Diagnostic criterion for Crohn's disease

A single gold standard for the diagnosis of CD is not available. CD is a syndrome diagnosis based on a clinical evaluation and a combination of endoscopic, histological, radiological, and/or biochemical investigations. All patients included in this study have a clinical presentation suggesting CD, and findings consistent with CD with different modalities are outlined below.

Pan-enteric capsule endoscopy

CE is carried out with the Pillcam Crohn's capsule (Medtronic, Dublin, Ireland). The following bowel cleansing regimen is used:

Two days before CE:	Patients should avoid iron supplements and drink additional fluids (up to 2 L)
The day before CE:	Light breakfast followed by clear liquid diet throughout the day. 0,5 L Plenvu and 1 L clear noncarbonated nonalcoholic liquid 18.00-19.00.
The day of CE:	0,5 L Plenvu and either 240 mg Imogas (simethicone) or 200 mg Minifom (dimethicone) 45-75 min. before capsule ingestion. 30 minutes after 2 mg Resolor (prucalopride) is administered with 0,1 L water. The capsule is ingested with a cup of water and either 240 mg Imogas (simethicone) or 200 mg Minifom (dimethicone). In case the capsule has not reached the small bowel after 1 hour chewing gum is chewed for 15 min. x 2 and either 10 mg Metoclopramide or 20 mg Domperidone is administered. 1st boost (when the capsule reaches the small bowel): 1 sachet of Picoprep (sodium picosulphate, magnesium oxide, citric acid) in 150 mL water with either 240 mg Imogas (simethicone) or 200 mg Minifom (dimethicone). Drink additional 1 L of clear noncarbonated nonalcoholic liquid. 2nd boost (3 hours after 1st boost if capsule is still in the body): 1 sachet of Picoprep (sodium picosulphate, magnesium oxide, citric acid) in 150 mL water

with either 240 mg Imogas (simethicone) or 200 mg Minifom (dimethicone). Drink additional 1 L of clear noncarbonated nonalcoholic liquid.

3rd boost (2 hours after 2nd boost if capsule is still in the body): 20 mg Bisacodyl (Dulcolax) as suppository.

A light meal can be ingested 2 hours after the 3rd boost or after excretion of the capsule.

CEs are analyzed by the primary investigator or a specialist in medical gastroenterology with experience in capsule endoscopy. The PillCam Reader Software from Medtronic is used for the analysis. Findings are reported in a standardized fashion according to the *Capsule Endoscopy Minimal Standard Terminology* (CEMST). It is recorded whether the capsule reaches the colon and anus. The transit times through the stomach, small intestine and colon are determined. Pathological findings are localized according to the time interval after capsule ingestion and the usual landmarks. The small intestine is divided into thirds based on the passage time. The colon is divided into five segments: Cecum, ascending colon, transverse colon, descending/sigmoid colon and rectum. The right and left flexures are used as landmarks for this subdivision. Disease severity in both small bowel and colon is assessed with the SES-CD and Eliakim score[47], while disease severity in the small intestine is furthermore assessed with the Lewis score.

Findings at CE consistent with CD:

- Multiple (> 3) erosions or aphthous ulcers
- Irregular ulcers or fissures
- Cobblestone pattern
- Luminal narrowing because of inflammation and/or fibrous stenosis

CE report

A full report including photo documentation is prepared and disclosed to the treating physician. The description must state the following findings:

- Is the procedure complete?
- Image quality (cleanliness level)
- Lesions consistent with CD
- Localization and severity
- Other pathology
- Clinical recommendation:

1) A complete procedure with sufficient quality and an unambiguous diagnosis requiring no additional examinations
2) Additional examinations recommended because of an incomplete procedure, poor image quality, ambiguous lesions or suspected malignancy

Complete procedure

A capsule expelled from the rectum defines a complete CE procedure. An incomplete CE prompts additional examinations of the bowel segments not visualized.

Image quality

The colon cleansing is graded on a 4-point scale: Poor (1): Large amount of fecal residue precludes a complete examination. Fair (2): Enough feces or turbid fluid to prevent a reliable examination. Good (3): Small amount of feces or turbid fluid not interfering with examination. Excellent (4): No more than small bits of adherent feces. A poor image quality prompts additional examinations.

Ileocolonoscopy

Bowel cleansing and IC is performed according to standard clinical practice and local preferences. The following bowel cleansing regimen is an example used at several participating institutions:

Picoprep 10 mg + 3.5 g + 12 g (*or* Citrafleet 10 mg + 3.5g + 11g):

1 sachet ingested at 6 PM the day before IC followed by 1-2 liters of water

1 sachet ingested at 6 AM on the day of IC followed by 1-2 liters of water

A full colonoscopy is documented by identifying two of the following: Visualization of the appendicular orifice, tri-angular fold or intubation of the terminal ileum. Intubation of the terminal ileum is documented with a biopsy or a photo showing intestinal villi. The length of terminal ileum intubation is estimated and the reason for an unsuccessful intubation is recorded. The Simple Endoscopic Score for Crohn's Disease (SES-CD) assesses the disease severity. Photo- and video documentation of relevant findings is secured.

Findings at IC consistent with CD:

- Multiple (> 3) erosions or aphthous ulcers
- Irregular ulcers or fissures
- Cobblestone pattern
- Luminal narrowing because of inflammation and/or fibrous stenosis

Histopathology

The histological assessment is performed by pathologists at the participating centers. Biopsies are cut,

stained with hematoxylin and eosin and examined under a standard light microscope. The assessment is based on the following lesions:

1) Architectural and surface distortion: Ulceration/erosion, crypt irregularity, mucosal atrophy, mucin depletion.

2) Signs of chronic inflammation: Lamina propria chronic inflammation with lymphocytes and plasma cells, basal plasmocytosis, eosinophilic inflammation, epithelioid cell granulomas.

3) Signs of acute inflammation: Epithelial and lamina propria acute inflammation with neutrophil granulocytes, cryptitis, crypt abscesses and crypt destruction granulomas.

Findings at histopathology consistent with CD:

For surgical specimens, it has been suggested that CD is diagnosed when 3 features are present in the absence of granulomas or when granulomas are present with one 1 extra feature. Most experts agree that the same definition could be applied to endoscopic biopsies, i.e. epithelioid cell granulomas plus crypt irregularity and/or chronic inflammation is suggestive of CD.[48-50] The distribution of inflammatory lesions also supports a specific diagnosis – segmental inflammation in CD versus continuous inflammation in UC.

Small bowel capsule endoscopy

SBCE is performed with the Pillcam SB3 (Medtronic, Dublin, Ireland) according to standard clinical practice after fasting and, if preferred by the IBD center, with prior bowel preparation (polyethylene glycol). SBCEs are analyzed by a specialist in gastroenterology with capsule endoscopy experience. The PillCam Reader Software from Medtronic is used for the analysis. Findings are reported standardized according to the *Capsule Endoscopy Minimal Standard Terminology* (CEMST). It is recorded whether the capsule reaches the colon. The transit times through the stomach and small intestine are recorded. Pathological findings are localized according to the time interval after capsule ingestion and the usual landmarks. The small intestine is divided into thirds based on the passage time. Disease severity in the small bowel is assessed with the Lewis score.

Findings at SBCE consistent with CD:

- Multiple (> 3) erosions or aphthous ulcers
- Irregular ulcers or fissures
- Cobblestone pattern
- Luminal narrowing because of inflammation and/or fibrous stenosis

MR enterography

MRE with oral and intravenous contrast is performed as per local protocol at the participating centers. An example protocol is provided below:

Patients attend the Department of Radiology fasting and 1.5 hours before the examination. 1 L of Mannitol 7.5% solution is ingested 1.5 hours before the examination. 20 mg Buscopan (hyoscine butylbromide) is administered intravenously to reduce artifacts from bowel peristalsis. Images are recorded with coronal T2, B-FFE, T1, SPIR and axial T1w sequences. Gadolinium 0.1 mmol/kg is administered intravenously for post contrast assessment. In addition, a diffusion weighted sequence is performed. The patient is observed in the radiology department for 30 minutes after the procedure. Driving is prohibited for 4 hours because of accommodation disturbances secondary to Buscopan administration.

Radiologists analyze MREC at the participating centers. Radiologists are not blinded to the clinical information. Pathological findings are localized according to the estimated distance from the ileocecal valve or another fixed point. The small intestine is divided into thirds (proximal, middle and distal third) and the colon is divided into five segments: Cecum, ascending colon, transverse colon, descending/sigmoid colon and rectum. Findings are reported in a standardized fashion, and the treating gastroenterologist is provided with a report stating whether MREC is consistent with CD, the localization and severity, and the presence of disease complications. Images will be saved digitally on the local and regional picture archiving and communications system (PACS). The assessment is based on the following definitions:

Intestinal distension:

- Good distension (> 75% of the intestine is sufficiently distended)
- Adequate distension (50-75% of the intestine is sufficiently distended)
- Poor distension (< 50% of the intestine is sufficiently distended)

Image quality:

- Good (diagnostic images without artifact)
- Sufficient (diagnostic images with artifacts)
- Poor (non-diagnostic images)

Findings at MRE consistent with CD:

- Early or minimal disease
    - Superficial ulcerations

- Transmural disease
  - Deep ulcers
  - Cobblestone pattern
  - Post-contrast enhancement (the relative contrast enhancement (RCE) is recorded)
  - Wall thickening > 3 mm (the maximum wall thickness is recorded)
  - Stenosis (the relative change of the intestinal caliber (%), stricture grade and occurrence of prestenotic dilation is recorded)
    - *Definition of small bowel stenosis*: > 50% reduction of the intestinal lumen compared to the adjacent small intestine. *High-grade stenosis* is defined by the presence of prestenotic dilation > 2.5 cm and/or collapse of the distal segment.
    - *Definition of colonic stenosis*: > 20% reduction of the intestinal lumen compared to the adjacent colon. *High-grade stenosis* is defined by an intestinal lumen < 11 mm, prestenotic dilation > 2.5 cm and/or collapse of the distal segment.

- Extraintestinal disease:
  - Creeping fat
  - Dilated vasa recta (Comb sign)
  - Enlarged lymph nodes (> 5 mm)
  - Fistula
  - Abscess

- *Ileocolonic disease severity assessed with MaRIA:*
  - Ulcer healing < 11
  - Mucosal healing < 7

Patency capsule

The Pillcam Patency Capsule (Medtronic, Dublin, Ireland) is gold standard for securing small bowel patency before CE. The examination is performed according to standard clinical practice after overnight fasting. Approximately 24-30 hours after ingesting the patency capsule, the capsule is localized with a low dose CT-scan (or abdominal x-ray) unless the patency capsule has already been excreted.

Capsule endoscopy is considered safe if:

- The patency capsule is excreted before 30 hours

- An intact capsule is excreted after 30 hours
- Passage to the colon of an intact patency capsule is radiologically confirmed

Intestinal ultrasound

Assessment of small bowel patency can be supplemented with IUS prior to examination with the patency capsule in centers with experience in this procedure. The examination is performed by the primary investigator or a gastroenterologist with experience in IUS, and the examination is focused on detection of CD, localization, severity and stenosis precluding CE.

Findings at US consistent with CD:

- Wall thickening > 3 mm
- Loss of mural stratification
- Decreased peristalsis in a pathological bowel segment
- Stenosis (wall thickening, luminal narrowing, prestenotic dilatation, atypical hyperperistalsis or subileus)
- Reaction in the extraintestinal fat (hyperechoic and non-compressible mass)
- Fistula
- Abscess