TITLE: Comparison between Artificial Intelligence assisted Capsule Endoscopy and Standard reading to investigate Suspected Crohn Disease: the SCAI STUDY	
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PROMOTER OF THE STUDY:	**Fondazione Poliambulanza Istituto Ospedaliero, Brescia, Italy**
EXPECTED DURATION OF THE STUDY:	**36 Months**

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1. BACKGROUND E RAZIONALE

The diagnosis of Crohn's Disease (CD) is based on a combination of clinical, biochemical (serological and fecal), endoscopic, radiological, and histological investigations. In cases of suspected Crohn's disease, visualizing the small intestine plays a crucial role, as this area is affected in up to 83% of cases, with terminal ileal involvement in 90% of cases (1,2,3). In the absence of obstructive symptoms or known stenosis, European guidelines for inflammatory bowel diseases (ECCO guidelines) (3) and for digestive endoscopy (ESGE guidelines) (4) recommend to investigate the small intestine using Video Capsule Endoscopy (VCE). Clinical history and serum/fecal inflammatory markers are useful to select patients who may benefit from small bowel study (5,6). In particular, fecal calprotectin (FC) levels correlate with the endoscopic findings of VCE (7). An FC value of 100 µg/g appears to represent the best cutoff in terms of diagnostic accuracy (8), while an FC cutoff of 50 µg/g has the best negative predictive value of 91.8% (9). To perform VCE in symptomatic patients with increased FC may allow the diagnosis of CD in patients with negative ileocolonoscopy or with aspecific findings (10). Moreover, it lets safely exclude Crohn's disease thanks to a very high negative predictive value in the long term (11).

To reduce the reading time of VCE and increase the number of identified lesions during the examination, various artificial intelligence software/tools have been developed in recent decades. Recently, deep convolutional neural networks have demonstrated the ability to detect significant findings and reduce reading time without increasing the error rate (12,13). A CADe algorithm based on CNN, called SmartScan (OMOM, Chongqing Jinshan Science & Technology Group Co.), has been developed and evaluated for its ability to detect and classify lesions in the small intestine. In the validation phase, SmartScan-assisted reading (SSAR) achieved an overall higher detection rate and an overall higher sensitivity for all subtypes of findings compared to standard reading, with a mean reduction rate of the reading time of 89,3% (14).

To date, no prospective study in clinical practice has evaluated the role of AI-assisted reading of VCE in suspected CD. This study aims to be the first prospective multicentric real-life trial to evaluate AI-assisted VCE using SmartScan in identifying typical mucosal abnormalities of the small intestine in patients with suspected CD and its ability to reduce reading time while maintaining the same diagnostic yield and diagnostic accuracy of standard reading.

2. STUDY OBJECTIVE

The objective of the study is to evaluate the role of AI-assisted VCE using the OMOM SmartScan in detecting typical small bowel inflammatory lesions (i.e. erosions and ulcers) in patients with suspected CD, and comparing AI with standard reading.

3. STUDY DESIGN

This is an observational, prospective, multicentre study with repeated assessment of VCE (performed according to the standard of care, with a subsequent second reading AI-assisted for research purposes with no commercial intent).

The expected duration of the study is 36 months, with a proposed start date of 01/03/2025. A maximum enrolment period of 24 months is anticipated.

Details on the study design are discussed in the sections below.

4. STUDY POPULATION

Eligible patients for the study are those with clinical symptoms and laboratory results suggestive of CD who have previously undergone an ileocolonoscopy which excluded other organic pathology and/or resulted inconclusive for CD (aspecific terminal ileitis).

5. INCLUSION AND EXCLUSION CRITERIA

5.1 Inclusion criteria

- Age >= 18 and <= 75 years
- Clinical suspicion of Crohn's Disease (CD) with/without occlusive symptoms (see Table 1 below)
- Ileocolonoscopy: negative examination, aspecific inflammatory findings
- Signed informed consent form.

5.2 Exclusion criteria

- Known diagnosis of CD
- Endoscopic diagnosis of active diverticular disease, colorectal cancer, ulcerative colitis, or infectious colitis
- Positive stool tests for pathogenic bacteria, parasites, and C. difficile infection within 3 months before CE
- Known intestinal obstruction or unconfirmed small bowel patency
- Use of NSAIDs in the 4 weeks before ileocolonoscopy and before VCE
- Known gastrointestinal motility disorder
- Known or suspected delayed gastric emptying
- Swallowing disorders
- Allergy or other contraindications or intolerance to the medications/devices used in the study
- Endoscopic placement of the capsule
- Any condition that prevents adherence to the study
- Pregnancy
- Participation in another clinical trial involving experimental drugs or devices
- Concomitant life-threatening condition
- Chronic kidney disease
- Inability to sign the informed consent

6. AIMS AND ENDPOINTS

6.1 Primary Endpoint

- Non-inferiority of AI-assisted reading (AIR) compared to standard reading (SR) in detecting (diagnostic yield - DY) typical lesions of suspected CD (erosions and/or ulcers and/or stenosis).

6.2 Secondary Endpoint

- Overall diagnostic accuracy (sensitivity, specificity, PPV, NPV) of AIR and SR for detecting erosions and/or ulcers;
- Small bowel reading time of AIR and SR;
- Miss rate of AIR and SR for detecting erosions and/or ulcers;
- Correlation between VCE findings and clinical data.

7. METHODOLOGY AND OPERATIVE PROCEDURES

Screening

Patients with signs and symptoms of suspected CD AND negative/inconclusive ileocolonoscopy will be enrolled. Inconclusive ileocolonoscopy will be defined as the presence of aspecific inflammatory mucosal alterations in the ileum or colon, that do not allow a final diagnosis of CD.

At the Screening Visit, active or recent gastrointestinal infection will be ruled out. Patients who will present with sub-occlusive symptoms will undergo a patency capsule to exclude the presence of a stenosis. Only patients with a prompt patency transit (expulsion within 30-33 hours of the intact patency capsule or its absence on abdominal X-ray) will be enrolled.

Signs and symptoms of suspected CD will be defined according to the ECCO Guidelines and ICCE criteria. An ad-hoc protocol defined by the authors will be applied to define the patient with suspicion of CD, stratifying all factors as major or minor criteria (see **Table 1**): the presence of at least two major criteria or the combination of one major criteria with three minor criteria will be necessary for patient enrolment.

CE protocol

SBCE will be performed using the OMOM Capsule System (Chongqing Jinshan Science & Technology (Group) Co), equipped with a DNN based system called SmartScan (SC), which is able to automatically select suspected lesions thus creating a very short video constituted only by selected images.

The SC100 system tested in this study consists of:

1. **Ingestible microcamera SC1 OMOM HD:** the capsule is 25.4 x 11.4 mm in size, with a weight of 3.0 grams. It is embedded with a single camera with a 172° field of view; sampling rate varies between 4 and 35 frames per second, and the image resolution is 512 x 512 pixels. The depth of field is optimized between 0 and 50 mm. The Truecolor 24-bit model allows for high colour depth, displaying up to 16 million colours per pixel.
2. **Recorder and SC-RD1 belt:** antennas receive data from the OMOM video capsule
3. **Vue Smart Work Station:** SmartView reading software equipped with the CNN model. The CNN model analyses raw data during the download phase from the recorder and during video review. It supports the operator in reviewing and reporting through three functionalities:
    - **SmartScan**: Based on an AI algorithm developed and validated for reviewing capsule videos of the stomach and small intestine, it eliminates redundant images and identifies 16 different types of abnormalities found in the images.
    - **SmartView**: Allows the operator to quickly "navigate" through the entire video, showing only the images selected by SmartScan and highlighting the selected video portions on the timeline that can be viewed separately from the rest of the footage.
    - **SmartFinding**: Displays only the images selected by the operator, providing a description and characterization of the detected abnormalities.

VCE will be performed at each centre according to local regulations and requirements, and the study protocol will address the bowel preparation regimen as well as the reading methods and post-procedural analysis for each patient.

Pre-Procedural Patient Management

To achieve homogeneous results, a standard bowel preparation regimen will be adopted, involving the intake of Polyethylene glycol (PEG) in a split-dose manner, as recommended by ESGE guidelines (16).
The regimen includes:

- The day before VCE: the patient may have breakfast and consume a light meal until 3 PM, followed by fasting. At 7:00 PM, take dose 1 of the bowel preparation with a very low volume PEG solution (PlenVu, Norgine).

- The day of VCE: take dose 2 in the morning of the procedure so that it is completed 2 hours before capsule ingestion, fasting from liquids for 2 hours after ingestion, and fasting from solids for 4 hours after capsule ingestion. After this, the patient is allowed to drink clear liquids and have a light meal.

Post-Procedural Management

Patient follow-up will occur according to routine clinical practice, collecting any cases of retention or adverse events. Patients undergoing VCE will be instructed to check for the expulsion of the capsule and to report any relevant symptom that may suggest potential capsule retention. Patients who do not notice the expulsion of the capsule within 2 weeks of ingestion will undergo an abdominal X-ray to exclude capsule retention. Clinical and laboratory data of all patients enrolled will be collected at follow-up visits (at 6 and 12 months).

Video Capsule Reading

At the site of patient's enrolment, investigators will perform VCE by evaluating the video in standard mode according to the recommendations of the European Society of Gastrointestinal Endoscopy, at 10 frames per second in the small intestine, and 20 frames per second in the esophagus, stomach, and colon. Reference points (first gastric image, first duodenal image, first cecal image) will be manually selected by the reader. The cleanliness level will be assessed as adequate (excellent/good) or inadequate (fair/poor) according to the qualitative scale of Brotz. Inflammatory lesions will be described using the Nomenclature and semantic descriptions defined by Leenhardt et al. in the International Delphi consensus (17), specifically modified for this study to ensure inter-observer agreement in the description of lesions (see **Figure 1)**. Lesions will be reported specifying their time of appearance (h: min: s, timing of single frames). In case of multiple inflammatory lesions (>5 per tertile), time of appearance won't be specified and the reader will quantify the pathology burden for every tertile reported as 5-10 or >10 inflammatory lesions, specifying the predominant type of inflammatory lesion). At the end of the reading, readers will also calculate the Lewis score for each video. The Lewis score, used to score the known Crohn disease, split up the small bowel in three tertiles based on transit time, evaluating separately for each tertile the presence of villous edema, ulcerations, and stenosis. The assessment of these parameters is based on number, longitudinal extent and specific characteristics. The final score is the highest value among the

three tertiles (see **Figure 2** for details). A score between ≥ 135 and < 790 indicates mild inflammation; and a score of ≥ 790 signifies moderate-to-severe inflammation (18).

Investigators at the enrolment centre will anonymize the video which will be randomly reallocated to another centre for the second blind reading assisted by AI (i.e., the readers performing the capsule reading in AI mode will not be aware of the results of the first reading in standard mode). The same instructions specified earlier will be applied to the AI-assisted reading, except for the reading speed, limited to 2-5 frames per second.

To note, the first reading will always be performed at the centre where the patient is enrolled (not randomized). This choice is made to ensure that patients receive the standard level of care at the centre and have full access to clinical history and medical documents for the physician who ultimately diagnoses the condition.

Comparison and Shared Review

An external researcher will compare the results of standard and AI-assisted readings from all the centres to assess the agreement of the observations reported by both readers. For videos containing less than 5 inflammatory lesions per tertile, the correspondence of reading will be evaluated comparing the type and the timing of the lesions. For videos with diffuse disease and multiple lesions, the correspondence of readings will be evaluated considering the number of lesions category (5-10 or >10, classified for predominant type) reported in a specific tertile. In case of disagreement (for example, lesions missed by either reader in AIR or SR), an external expert reader (read more than 500 capsules) will review the discordant footage, blind to the source of the videos, open exclusively to the footage being reevaluated.

8. ANALYSIS AND STATISTICAL METHODS

8.1 Statistical Plan

Descriptive statistics will be provided in terms of mean ± standard deviation (SD) or median and interquartile range interval (IQR) for the continuous variables; and in terms of frequency and percentage (%) or rate for the categorical variables. Group comparisons will be assessed by Student t-test or non-

parametric Mann-Whitney test for continuous variables and Chi-squared test or test for proportion for categorical variables.

The accuracy performances will be evaluated by assessing diagnostic yield (DY), accuracy, sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV). Comparison of these metrics will be evaluated by test for proportions for independent samples or by McNemar test for paired samples. Analyses will be performed in both per-patient and per-lesion setting.

Further analyses to assess the predictors of diagnostic performance will involve the application of univariable and multivariable logistic regression models.

8.2 Sample Size

Sample size calculation is assessed at per-patient analysis based on previous evidence by Xie et al 2022 (14) in which the detection rate of erosions and ulcers (common lesions in suspected Crohn disease) in AI-assisted reading was 11.5%, compared to 9% in standard reading (i.e. a difference of the two proportion around D=2.5%). Considering a non-inferiority one side test for the difference between correlated proportions. with a non-inferiority margin M= 0.02, a type I error α of 0.05, a power 1-β of 80%, a difference of the two proportion D=0.025 and a plausible proportion of concordance on positive detection in both AIR and SR of 8%, the sample size needed to establish the non-inferiority of AI-reading with respect to Standard Reading is N=164 patients (i.e. 164 VCE). The size will be raised up to N=180 in order to take into account a potential dropout rate up to 10%. Details about the sample size computation can be found in Liu, J., et al. (19); and in PASS sample size software documentation at https://www.ncss.com/wp-content/themes/ncss/pdf/Procedures/PASS/Non-Inferiority_Tests_for_the_Difference_Between_Two_Correlated_Proportions.pdf).

9. PROJECT MANAGEMENT

The principal investigator will be responsible for the overall monitoring of data and the safety of study participants. The principal investigator will be assisted by other members involved in the study.

The investigators declare that they have no direct or indirect conflicts of interest.

10. POTENTIAL RISKS AND BENEFITS

There are no reasons to believe that enrolment in this study poses risks to the patient, as this is a prospective observational study involving the normal care activities of the patient, conducted according to GCP rules.

11. INSURANCE COVERAGE

Given the observational nature of the study and the absence of risks, no insurance coverage is provided.

12. ETHICAL ASPECTS

This study will be conducted in accordance with this protocol, the principles of good clinical practice, the ICH GCP regulations, and the requirements of the guidelines, following the principles of the Declaration of Helsinki (latest version: Tokyo, 2004 - Appendix I). The study protocol and all other necessary documents will be submitted to the Competent Authorities. The study will be submitted for approval to the relevant Territorial Ethics Committee. Amendments and new versions of the protocol will be promptly shared with the relevant Territorial Ethics Committee. This study will be conducted according to the protocol defined with the participating investigators. Participation in the study will be contingent upon obtaining informed consent.

13. PATIENT INFORMATION AND CONSENT

All patients will be invited to voluntarily participate in the study. They will be informed about the purpose of the study and the associated procedures. Patients will also have the opportunity to clarify any doubts or uncertainties by asking questions and receiving clear and satisfactory answers. After reviewing the study information, patients will have as much time as they need to decide whether to proceed with signing the informed consent form.

14. DATA MANAGEMENT AND STUDY DOCUMENT STORAGE

The data collected will be recorded, processed, managed, and stored in both paper and electronic formats exclusively for research purposes, in compliance with Legislative Decree No. 196 of June 30, 2003

(Code regarding the protection of personal data) and subsequent amendments, as well as in compliance with European Regulation No. 679 of 2016.

The Principal Investigator will be responsible for data management.

All information related to study participants, documentation regarding submission and approval by the relevant Ethics Committee, and regulatory documentation will be stored by the Research Manager, Dr. Stefania Piccirelli, at the archives of the Digestive Endoscopy Unit of the Fondazione Poliambulanza Istututo Ospedaliero in Brescia.

14.1. Data Confidentiality and Privacy

The privacy of the recruited subjects will be fully guaranteed, and the data will be processed confidentially in accordance with Italian law as outlined in Legislative Decree No. 196 of June 30, 2003, "Code regarding the protection of personal data" (Official Gazette No. 174 of July 29, 2003 – Ordinary Supplement No. 123) and in compliance with European Regulation No. 679 of 2016. Data collected during the study will be pseudonymized and processed solely for scientific purposes. Individual data will never be published but will be used exclusively, along with data from all other study patients, to produce descriptive and/or inferential analysis results. Each participating center must maintain adequate medical and research documentation for this trial and comply with regulatory/institutional requirements for the protection of study subjects' confidentiality. Data will be stored at the Digestive Endoscopy Unit of the Fondazione Poliambulanza Istututo Ospedaliero in Brescia and protected with specific security systems. Only specifically authorized personnel will have access.

14.2. Data Ownership

The ownership of the data related to the study, its execution, and its results belongs to the Fondazione Poliambulanza Istututo Ospedaliero (promoter and coordinator) (DL 30/11/2021).

15. POTENTIAL COSTS AND COVERAGE

No additional costs are expected beyond normal clinical practice. There is no funding provided for the study. The capsules used in the study will be supplied free of charge by the manufacturer. Due to the nature of the study, insurance coverage is not required.

16. DATA PUBLICATION

The results of the research will be made known to the public and to all interested parties through presentations at conferences and articles in scientific journals, preferably with international reach, without disclosing the identities of the patients.

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Tables and Figures

Table 1

Inclusion criteria: presence of <u>at least</u> 2 major criteria OR 1 major criteria + 2 minor criteria

Major criteria for suspected CD	Minor criteria for suspected CD
1. First-degree relative with confirmed IBD ***2.* Gastrointestinal manifestations** ○ Chronic diarrhoea (defined as more than 3 bowel movement per day and/or Bristol 6-7 stools for at least 3 months) ○ Chronic abdominal pain (at least 1 day/week in the last 3 months, typically not post-prandial) ○ Nocturnal symtoms ○ Blood and/or mucus in the stools ○ Non-healing or complex perianal fistula or abscess or perianal lesions (apart from haemorrhoids) **3. Systemic manifestations** ○ Weight loss (5% of usual body weight) in the last 3 months ○ Mild fever (TC>37.5°C) in the last 3 months **4. Laboratory findings** ○ Fecal calprotectin >100 µg/g ○ CRP > 5 mg/dL ○ Unexplained anemia (female Hb < 11 g/dL; male Hb < 13 g/dL) ○ Albumin < 4 g/dL ○ Iron deficiency (female ferritin < 20 ng/mL; male < 30 ng/mL) ○ B12 deficiency (< 150 pg/mL) ○ Folate deficiency (< 4 ng/mL)	**1. First-degree relative with autoimmune disease** **2. Extraintestinal manifestations** **1. Muscoloskeletal** ○ arthritis (colitic type, ankylosing spondylitis, isolated joint involvement) ○ hypertrophic osteoarthropathy (clubbing, periostitis) ○ miscellaneous manifestations (osteoporosis, aseptic necrosis, polymyositis) **2. Dermatologic and oral** ○ reactive lesions (erythema nodosum, pyoderma gangrenosum, aphthous ulcers, necrotizing vasculitis) ○ specific lesions (fissures, fistulas, oral Crohn's disease, drug rashes) ○ nutritional deficiencies (acrodermatitis enteropathica, purpura, glossitis, hair loss, brittle nails) ○ associated diseases (vitiligo, psoriasis, amyloidosis) **3. Hepatopancreatobiliary** ○ primary sclerosing cholangitis ○ bile-duct carcinoma ○ associated inflammation (autoimmune chronic active hepatitis, pericholangitis, portal fibrosis, cirrhosis, granulomatous disease) **4. Ocular** ○ uveitis/iritis, episcleritis, scleromalacia, corneal ulcers, retinal vascular disease **5. Renal** ○ Calcium oxalate stones **3. Systemic manifestations (malaise)** **4. Laboratory findings** ○ Vit.D deficiency (< 20 ng/mL)

Figure 1

Nomenclature and semantic descriptions of ulcerative and inflammatory lesions in Crohn's disease of the small bowel in VCE modified from the international Delphi consensus statement

Nomenclature	**Description**
Aphthoid erosion*	**Diminutive loss of epithelial layering (<5mm) with a whitish center and a red halo, surrounded by normal mucosa**
Ulceration*	**Mildly or frankly deep loss of tissue (>5mm) with a whitish base with or without edematous/swollen surrounding mucosa**
Stenosis*	**Narrowing of the intestinal lumen withholding or delaying the passing of the videocapsule**
Edema	Enlarged / swollen / engorged villi
Hyperemia	Area of reddish villi
Denudation	Reddish (but not whitish) mucosal area where villi are absent

*significant inflammatory lesions reported during CE reading and considered for the statistical analysis

Figure 2

Lewis Score

Rated for each tertile						
Parameters	**Number**		**Longitudinal extent**		**Descriptors**	
Villous appearance	Normal	0	Short segment	8	Single	1
	Edematous	1	Long segment	12	Patchy	14
			Whole tertile	20	Diffuse	17
Ulcer	None	0	Short segment	5	<1/4	9
	Single	3	Long segment	10	1/4–1/12	12
	Few	5	Whole tertile	15	>1/2	18
	Multiple	10				
Stenosis – rated for whole tertile						
	None	0	Ulcerated	24	Traversed	7
	Single	14	Non-ulcerated	2	Not traversed	10
	Multiple	20				

Lewis score: Score of the worst-affected tertile [(villous parameter × extent × descriptor) + (ulcer number × extent × size)] + stenosis score (number × ulcerated × traversed).