DanCap

Camera Capsule Endoscopy in the Routine Diagnostic Pathway for Colorectal Diseases

Administrative Information

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Trial registration

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Short summary

The Department of Surgery at Odense University Hospital (OUH) carries out approximately 10,000 colonoscopies each year, and this number is continuously increasing. Since 2014, the screening for colorectal cancer (CRC) has resulted in a significant increase in the colonoscopy workload. Conventional optical colonoscopy (OC) is a hospital-based procedure that can require sedation or analgesics and is often considered uncomfortable, intimidating, or even painful. The diagnostic yield of OC can be as low as 3-5% in some patient groups, which means that an endoscopist may need to perform 20 to 30 colonoscopies to identify one case requiring treatment. Physical or cultural barriers can also deter patients from attending appointments, leading to missed cancers or precancerous lesions. To address these challenges, an alternative pathway is needed to reduce the colonoscopy burden on the healthcare system while ensuring fewer findings are missed.

One solution is to use Colon Capsule Endoscopy (CCE) as a triage tool. This procedure can be performed in outpatient healthcare centers and requires less equipment than an OC. However, CCE offers no therapeutic capability, and individuals with clinically significant findings will still require an OC. A low reinvestigation rate (<25%-30%) is desirable for patient preference and the economy.

Therefore, **DanCap** will introduce a new pathway that relies on CCE for routine colorectal examinations of symptomatic patients who are expected to have a low rate of positive findings and, consequently, a low reinvestigation rate, and asses the cost of this new pathway.

Background

As the sensitivity of OC and CCE is constantly increasing (1) and progressively smaller-size pathologies are detected, the association between detected lesions and patients' short- and long-term outcomes is becoming more uncertain (2). In some cases, such as with the resection of diminutive polyps, the number needed to treat to save one person (approx. 8.000) is very close to the number needed to cause one procedure-related death (10.000) (3, 4). Therefore, there is an increasing need to filter OC candidates and define a realistic threshold for treating or ignoring lesions. The **DanCap** study fulfils this need by introducing a renewed approach to the diagnostic pathways using CCE. This approach offers out-of-hospital, accurate bowel diagnostics that allow for the decongestion of endoscopic services, as seen in the UK. It has an upscaling potential for national and international redesign of bowel diagnostics (5-7).

The foundation of the CCE, the PillCam® Colon Capsule2, was introduced approximately 15 years ago (8). Several clinical trials have demonstrated the strengths and weaknesses of CCE as compared to OC (9, 10). The Scottish and English Services have shown the feasibility of routine use of CCE (to date, collectively delivered 15.000 capsules). (11) Additionally, results from the large-scale CareForColon2015 trial, investigating the application of CCE in CRC screening, will soon be published (12). The UK CCE-based services confirmed already known data with real-world equivalents regarding CCE's safety and high diagnostic quality (13).

However, there are remaining concerns, primarily due to the high (45-60%) re-investigation rate, which makes the patient experience and cost-efficiency of CCE-based services inferior to that of the conventional OC counterpart (14). Based on these recent findings, setting up a routine diagnostic pathway for further evaluation of CCE in the clinical routine of patients with a low frequency of positive findings, including cost-efficiency assessment, is highly relevant. Here, introducing methods to predict a patient's findings may be extra relevant in the future. Currently, studies suggest that the use of faecal haemoglobin concentration or the microbiome composition may be useful biomarkers for colorectal cancer or precursor lesions (15-20). The predictive potential of these biomarkers in a diagnostic pathway has yet to be sufficiently tested, and more evidence is needed before clinical application is possible.

Aim & hypothesis

Our study aims to investigate the DanCap pathway as a viable solution for CCE-based diagnostics in symptomatic patients, considered to have a high need for endoscopic evaluation due to the symptoms compatible with neoplastic disease, as referred from general practice (GP). This approach is expected to be cost-effective and maintain high clinical quality while relieving the burden on endoscopy wards in a Danish setting.
The study will provide data for pathway cost analysis of the CCE-based pathway compared to the traditional colonoscopy pathway based on a realistic medicine outcomes assessment.

The secondary aims are to:

1) Compare the polyp detection rate (PDR) and CRC detection rates in both groups
2) Investigate the role of FIT-testing and microbiome analyses in CCE-based diagnostics for predictive purposes

Methods

Study Design

DanCap is a two-armed prospective clustered case-crossover randomized controlled trial investigating the use of CCE in routine clinical practice in symptomatic patients referred for colonic examination, which is usually done by OC in current practice. The project is planned to start September 1st, 2024, and finish August 31st, 2025.

All patients referred for a 2-week diagnostic lower gastrointestinal (GI) procedure (symptoms compatible with neoplastic disease) will be considered for inclusion. Participants will either be investigated by CCE at home or by colonoscopy at OUH. Patients will be included in parallel groups and be allocated 1:1. 800 consecutive patients referred from GPs will be randomized in clusters determined by the GP clinic provider number. At the start of the project, odd provider numbers will be referred to OC, and even provider numbers will be referred to CCE. After the inclusion of the first 200 consecutive CCE patients, the two arms will be swapped, i.e., patients from clinics with even provider numbers are referred for OC, and odd provider numbers are referred for CCE. A complete list of all GP clinics can be seen in Appendix B. The project inclusion is expected to last one year. Ten patients in total can be included per week in the CCE arm at the beginning of the study. Depending on capacity, this capacity can potentially be increased when the study has been initiated. The number of polyps and cancers detected in the two diagnostic pathways will be measured.

Study Population

All participants with symptoms from the lower GI tract who are referred to OUH by GPs located in Funen, Denmark, for a colonic assessment will be invited to the study. After invitation, the patients will be included and excluded based on the following criteria.

Inclusion Criteria

Patients must meet the following criteria for inclusion in the study (**Table 1**).

Table 1: Inclusion criteria

	Criteria
1.	Older than 18 years
2.	Symptomatic patient referred for colonoscopy assessment
3.	Able to provide oral and written informed consent

Exclusion Criteria

Patients will be excluded from CCE based on the criteria in **Table 2**; and from investigation with OC based on the standard protocols in effect. The project secretary will ensure the absence of any exclusion criteria when contacting the patients to confirm study participation. Any uncertainties will be discussed with and handled by a project doctor at the research unit. Any participants excluded from the study will be treated as per routine clinical procedures outside of the project.

Table 2: Exclusion criteria

	Criteria
1.	Require hospital admission for inpatient colonoscopy
2.	Previous OC with poor bowel preparation within the last 5 years
3.	Patient is unable to provide oral and written informed consent
4.	History of stenosis of the gastrointestinal tract
5.	Previous major surgery of the gastrointestinal tract*
6.	Patient has a pacemaker/defibrillator
7.	Patient is pregnant or breastfeeding
8.	Known allergies to the bowel preparation regimen
9.	Have severe kidney disease
10.	Known chronic constipation

*excluding appendectomy, gallbladder removal, partial colectomy

Patient flow

The following steps outline the patient flow for participants in both the CCE and colonoscopy arms. The first three steps are represented by the current clinical routine for symptomatic patients (symptoms compatible with neoplastic disease) referred for endoscopic investigation.

1. Patients are referred to the endoscopic unit by a GP.
2. The referral is received, and a secretary forwards the referral for triage by a specialist doctor.
3. A list of referrals is inspected by a specialist doctor who is on duty in the Nyborg department from approximately 07:45 to 09:00 on weekdays. Any referral that meets the criteria for a colonoscopy procedure is a candidate for this study.

3.1. In the current clinical routine setting, after these steps, patients get information, the date for the scheduled colonoscopy and the bowel preparation kit sent by mail according to the date for the colonoscopy. A few days before the scheduled colonoscopy, the patients receive a call from the endoscopy nurses, who confirm the appointment date and answer any patient questions regarding the procedure, bowel preparation, diet, etc. We are adding a recruitment letter and a phone call by one of the secretaries to this clinical routine. This setup is necessary because the current time limits for our diagnostic processes for cancer are established by legal decree, and traditional approaches to inclusion (i.e. written material as the initial point of contact) are not applicable if we are to meet the established guarantees

(kræftpakkeforløb). The referrals are assigned for examination by the triaging doctor, who will perform the preliminary exclusion based on the inclusion and exclusion criteria.

4. Following triage, the patient will receive an electronic recruitment letter informing them about the DanCap study and about an upcoming informative phone call from a secretary scheduled for the following day.
5. The next day, the secretary calls the study candidates, informs them about the project and asks the patients if they prefer getting more information at this call or in a physical/virtual meeting. Either way, the patients who manifest interest will receive information about the study by mail.

5.1. If patients prefer to be informed **over the phone**, the secretaries will continue explaining all the relevant information about the study. If the patients want to participate or manifest interest, they will receive an information letter with the study invitation (Appendix E), an initial questionnaire (Appendix F), and a consent form (Appendix H) through mail. After 24 hours of contemplation, the secretaries will contact the patients who had uncertainties and ask if they have any further questions, if they want more details at a physical meeting where they can also come accompanied or if they have decided already. If the patient has decided, they will be allocated to either the intervention or control arm based on their previous randomization by GP clinic provider number and receive a date and place for the colonic examination in their mail.

5.2. If patients prefer to be informed in **a physical meeting**, it will be scheduled at one of the Odense University Hospital (OUH) regional outpatient clinics (Nyborg, Odense or Svendborg) after a maximum of 2 work days. The patients are informed that they have the right to be accompanied by a person of his/her choice if they want to. Here, the discussion will be conducted by one of our clinical researchers and will take place in a location we are establishing exclusively for private talks so that we can ensure that the discussion will be undisturbed.

6. After acceptance to participate in the study, the individual is informed that he/she has a 24-hour consideration period before any further steps will be set in motion (bowel preparation and FIT test delivery). If they wish to withdraw from the study at any time, they can call the secretary.
7. If a participant cannot attend the scheduled CCE for any reason (other than intolerance of bowel preparation), he/she can call and make another appointment.
8. Written consent will be given before any trial-related procedures are initiated. This is marked by the patient's arrival at the clinic where he/she is scheduled for his/her colonic investigation.
9. Patients follow their designated pathway and complete the related procedures.
10. The final investigation report is handled by the assigned doctor at the Department of Surgery.

Patients who reject participation in the study will return to the standard diagnostic pathway (they will receive a date and time for a colonoscopy and be sent the bowel preparation regimen).

Intervention Group (CCE)

See Appendix D for the study flow of the intervention group participants and Appendix K for a description of the patient course.

Patients who accept participation in the study will be asked if it's possible to complete the faecal sample for the FIT sampling and to start bowel cleansing according to the instructions (Appendix I). Twice a week, the included patients will attend the in-hospital clinic in groups of five persons. They will bring their completed FIT sample, completed questionnaire, and the signed consent form. At the clinic, it will also be available blank copies of the forms in case patients need other ones. A project nurse will administer the capsules to the patients in the morning, and the patients can leave after. When the capsule investigation is completed (excretion of capsule) or the day after capsule ingestion (whichever occurs first), patients must return their belt and receiver to the Department of Surgery, OUH. After a few days, the patient will receive an electronic letter

(per routine clinical practice) from the project doctor with the results and information regarding upcoming steps (Appendix D). Those with positive findings or an incomplete investigation will be given a new appointment according to the current clinical routine. A second questionnaire, Q2 (Appendix G), will be sent to the patient 2 weeks after the completed procedure.

Control Group

See (Appendix J) for the study flow of the control group participants.

Patients who <u>accept</u> participation in the study will be asked to start bowel cleansing according to the instructions. They will bring their completed questionnaire and the signed consent form to the scheduled colonoscopy. At the clinic, it will also be available blank copies of the forms in case patients need other ones. They will continue to follow the routine clinical setup for outpatient colonoscopy and will only receive, by digital post, after 2 weeks from the procedure, an extra second questionnaire Q2 (Appendix G).

Data Collection and Management

Intervention group

A paper-based questionnaire (Q1) is handed to the patients, asking about basic personal information (including name, social security number, contact info, transport to hospital, age, and sex) and procedural information (CCE or OC). The patients complete the Q1 questionnaires. They are handed over to the nurse handling the patient's examination at the endoscopic unit, after which it is forwarded to the SATC-C research unit. A questionnaire concerning the post-investigation period (Q2) (including questions about occupation and consequences of the procedure) will be electronically distributed to participants on the public communication platform "Digital Post" two weeks after the procedure. All clinical data retrieved from the electronic patient journals and the Q1 will be manually entered into a RedCap database by SATC-C project staff. Patient replies from Q2 will automatically be entered in the RedCap database. The CCE videos will be reviewed by trained doctors from the Department of Surgery, OUH.

Control group

For control group participants investigated by OC, the medical record will be examined for colonoscopy findings, pathology results and reported complications (both during and after the procedure) approximately four weeks after the examination. A paper-based questionnaire received before the colonoscopy procedure (Q1), the same as received by the intervention group, will be collected by nurses at the endoscopic unit and forwarded to the SATC-C research unit. A questionnaire concerning the post-investigation period (Q2) (including questions about occupation and work-related consequences of the procedure) will be electronically distributed to participants on the public communication platform "Digital Post" two weeks after the procedure. All clinical data retrieved from the electronic patient journals and the Q1 will be manually entered into a RedCap database by SATCC project staff. Patient replies from Q2 will automatically be entered in the RedCap database.

Stool samples & microorganisms

Participation in the study is not conditioned by taking the FIT test. If patients agree to submit the faecal sample, it will only be analysed for traces of blood, and the haemoglobin concentration and the microbiota composition. We will conduct this analysis considering that recent studies suggested these this values can be useful biomarkers for colorectal cancer or precursor lesions (15-20). The FIT sample collection KIT is already an integrated part of colorectal cancer screening in Denmark. The collection kits contain a vial, a spatula for collection of stool and minor collection aids. Patients will be asked to collect one sample containing approximately 1 gram of faeces.

The stool sample will be analysed at the Department of Biochemistry at Vejle Hospital in accordance with standard analytical protocols. After the samples have been tested for traces of faecal haemoglobin and the concentration determined, the samples will be frozen and transported to the laboratory in Aalborg (DNASense, Aalborg, Denmark). Here it will be examined of all DNA from microorganisms in the sample (no human DNA will be examined) to determine the entire composition of the microbiome. A similar examination of microorganisms of tissue samples from colonoscopy (from both intervention and control group) will be undertaken. After pathological assessment (clinical routine), these samples will be frozen and shipped to the laboratory in Aalborg (DNASense, Aalborg, Denmark), where the DNA of microorganisms on the samples will be analysed. The results of all analyses will be used to study whether either blood or microbiome composition predicts diagnostic outcomes (cancer or precursor lesions) and could be used in future interventions for this purpose.

After this analysis, the biological material (stool sample and tissue) will be destroyed. The bacterial DNA (non-biological material) will be stored for research purposes in accordance with current data protection legislation in freezing facilities at the Department of Microbiology, OUH. No human DNA or biological material will be stored, hence no biobank is needed. The electronic test results from both laboratories will be transferred electronically to secure storage at OUH for further statistical analyses.

Patient journal information

We need to include 800 patients. We expect a 10% to decline participation or be ineligible for inclusion. Therefore, we theoretically need to access 880 journals in total, whereof we expect approximately 100-120 of these to be accessed before written consent is obtained during the inclusion period.

Before written consent:

The status of patients with symptoms that need a colonic investigation will be confirmed during a phone call with the secretaries after oral information about the project and interest in participating are manifested. The conversation will inform and identify eligible patients (based on inclusion or exclusion criteria). The secretaries will be assisted at any point by the clinical research staff. The name, CPR-number and procedure date of the patient is registered in the hospitals electronic patient management system (EPJ/Bookplan) on a procedure schedule. Those in the intervention arm will be registered on a separate CCE list, where research staff will have access to this basic information. Those in the control arm will be registered as per standard clinical practice. No information will be collected by researchers from the patient journals before written consent is obtained, but it may become necessary to confirm or elaborate on patient input on inclusion/exclusion criteria based on the phone call, at which time the patient journal may be accessed for the following information:

1. History of gastrointestinal surgery (incl. stenosis) (ICD10: KJ)
2. History of colonoscopy procedures (incl. stenosis) (ICD10: KUJF)
3. Implanted pacemaker/defibrillator (ICD10: KFPF, KFPH)
4. Allergies to bowel preparation (ICD10: Z88)
5. Severe kidney disease (ICD10: DN17-DN19)
6. Chronic obstipation (ICD10: DK590A)

Here information will be passed on to research doctors with the purpose of evaluating inclusion/exclusion criteria.

After written consent:

Data relating to the clinical procedures conducted in the study will be collected from patient journals. This data is not accessible outside the patient journal system, and access will be necessary to ensure that we can meet both the primary and the secondary aim(s). Patient consent gives the principal investigator and in need, sponsors and sponsors representatives, as well as any control authority, direct access to obtain information in the patient's medical record, including electronic medical records, to see information about the subject's health conditions necessary in the implementation of the research project as well as for control purposes including self-monitoring, quality control and monitoring, which they are obliged to perform.

The following types of data will be collected from the patient journals:

1. Procedural information and results from OC
2. Procedural information and results from CCE
3. Pathology report from OC specimens
4. Lab results relating to the performed procedures
5. Follow-up procedures (OC after CCE, Computer tomography colonography, Magnetic resonance investigation)
6. Information from the GP referral
7. Result from the FIT analysis (Haemoglobin concentration, microbiome components)
8. Reported complications from OC or CCE, both during and after the procedure
9. Administrative information (Expenses - for bowel preparation kit and delivery, consumables used per patient; manpower – time spent by any medical and connected staff member on every task project-related; time and expenses for cleaning and maintaining the scopes and related information).

Outcomes

The primary outcome is the costs of the suggested CCE-based pathway compared to the routine clinical pathway. Secondary outcomes include the clinical quality parameters, PDR, FIT concentration, microbiome composition, diagnostic performance, and reinvestigation rate. All outcomes are detailed in **Table 3** below:

Table 3: Aims with correspondent outcomes, defined by groups and data type. Blue represents the primary aim, and red represents the secondary aims.

Study arm	Outcome	Description
Both	Cost of CCE-pathway compared to OC-pathway	Cost analysis
Intervention	Diagnostic tool evaluation / Performance evaluation	NPV, PPV, Sensitivity, Specificity
Intervention	Reinvestigation rate of CCE	Technically insufficient examinations or plus number of examinations followed by second-stage OC due to positive CCE findings
Both	Comparative analysis of detection rates for CCE and OC	PDR in both pathways, categorized as “<6 mm”, “6-9 mm” and “>9 mm”
Intervention	Predictive value of FIT	Concentration of faecal haemoglobin and the risk of findings
Intervention	Gut microbiome	The composition of the microbiome and the risk of findings

ABBREVIATIONS: *CCE*: Colon/Camera capsule endoscopy; *OC*: Optical Colonoscopy; *PDR*: Polyp detection rate

Pathway-cost analysis

The objectives of the cost analysis encompass each aspect of the process for patients and staff and scrutinize the direct costs associated with both pathways, evaluating factors such as dropout rates and cancellations. The cost analysis will be measured in various ways, dependent on tool-specific aspects, as presented in **Table 4**. The main focus of the pathway cost analysis is hospital-related costs to identify possible cost benefits/deficits of CCE appliances in routine clinical practice.

Relevant factors for analysis

Timeline (No. of day from GP referral)	**Hospital-related costs of CCE**	**CCE-related cost-factors**	**Hospital-related costs of OC**	**OC-related cost-factors**
Day 1	Secretary allocates referred patients to vetting doctor	Sample-size to estimate time spent for patients allocated to triage by doctor	Secretary allocates referred patients to vetting doctor	Sample-size to estimate time spent for patients allocated to triage by doctor
	Doctors time spent on vetting referred patients to CCE pathway	Sample-size to estimate time spent for patients allocated to CCE	Doctors time spent on vetting referred patients to OC pathway (normal practice)	Sample-size to estimate time spent for patients allocated to OC
Day 2	Secretary calls patient for inclusion and study information	Not relevant for cost-analysis	Secretary calls patient for inclusion and study information	Not relevant for cost-analysis
Day 6-7	Expenses for bowel preparation medication		Expenses for bowel preparation medication	
	Nurse calls patient for CCE bowel preparation information.	Sample-size to estimate time spent calling CCE patients	Nurse calls patient for OC bowel preparation information.	Sample-size to estimate time spent calling OC patients
Day of Investigation	Collection of Q1		Collection of Q1	
	Pre-procedural tasks	[1]Nurse-time spent on group information before capsule administration [2]Nurse-time spent on administrate the capsule, per patient (retracted from "Bookplan")	Pre-procedural tasks	**Materials:** [1]Maintenance of scope [2]Blanket for patient **Secretaries:** [1]Time spent on bookings and patient contact **Nurses:** *(Two nurses at each operating room)* [1]Time spent preparing patient, equipment, logging in patient journal, etc. **Doctors:**

				[1]Time spent informing and preparing patient
	Procedural tasks	[1]Nurse-/doctor-time spent on procedural questions per phone	Procedural tasks (Normal/Negative OC)	**Materials:** [1]Procedural items; gloves, plastic apron/cover, glasses, masks, plastic for colonoscope, IV cannula, paper cover for bed, exploration gel, hand disinfection, soap, valves, suction equipment, **Nurses:** *(Two nurses at each OR)* [1]Time spent at OR **Doctors:** [1]Time spent on colonoscopy
			Procedural tasks (Abnormal/Positive OC)	**Same as above for staff and material, and the additional cost-factors specified for the below mentioned abnormality* **For incomplete procedure:** [1]Second OC with double bowel prep. [2]OC and hospital admission [3]CT-colonography [4]OC in full anaesthesia **For biopsies:** [1]Forceps, sample glass [2]Time spent by doctor marking samples and filing pathology requisition [3]Pathology resources **For polypectomies:** [1]Simple; snare [2]Advanced; EMR **For cancers:**

				[1]Surgery, chemotherapy, etc.
	Post-procedural tasks (Normal/Negative CCE)	**Doctors:** [1]Time spent evaluating CCE video, CCE report and uploading report to EPJ [2]Time spent dictating or writing a note in patient journal	Post-procedural tasks	**Materials:** [1]Wipes for cleaning OR [2]Cleaning endoscopy equipment (water, chemicals, machines **Secretaries:** [1]Time spent writing patient pathway summary ("epikrise") and procedure-related reporting in patient journal **Nurses:** *(Two nurses at each OR)* [1]Time spent reporting in patient journal [2]Time spent cleaning and preparing OR [3]Time spent observing patient post-operative **Doctors:** [1]Time spent informing the patient [2]Time spent reporting in patient journal [3]Time spent uploading video to Endobase
	Post-procedural tasks (Abnormal/Positive CCE)	******Same as above for staff and additionally:* **Doctors:** [1]Contacting patients by phone (if relevant; cancers) [2]Referring patient to secretary for follow-up OC **Secretaries:** [1]Referring patient to OC		
Day after Investigation	Post-procedural tasks	**Secretaries:**		

		[1]Time spent processing monitor from delivery at Svendborg or Odense to Nyborg by internal mail (*sample size evaluation*) **Nurses:** *(Two nurses at each OR)* [1]Time spent cleaning monitor and uploading video to EPJ		
Days after Investigation	Collection of Q2		Collection of Q2	

ABBREVIATIONS: *CCE*: Colon/Camera capsule endoscopy; *OC*: Optical Colonoscopy; *Q1*: Questionnaire 1; *OR*: Operating Room; *Q2*: Questionnaire 2

ADDITIONAL: Sample sizes: 25-30 procedures

Statistical Analysis of Secondary Outcomes

Descriptive statistics, X^2 for categorical outcomes and a t-test for numerical outcomes will be employed to compare the intervention and the control arm. Fischer's exact test will be employed to compare the results of the metagenomic analyses of the microbiome. A multivariate logistic regression model will be employed to allow adjustments of potential confounding factors. Due to the risk of clustering by GP unit, we will consider robust statistical models to address this issue.

Sample Size Estimation

To meet the primary aim and compare the costs of the CCE-based pathway to standard clinical practice, the major unsolved issue is the reinvestigation rate and cost compared to OC and to build a practical integration of the pathway into the routines of the endoscopy unit. Compared with OC, there is a wish to verify PDR in a Danish cohort. A standard sample size calculation is irrelevant. The cost analysis is based on the reinvestigation rate and the number of patients with positive findings in each group. It is estimated from the Scottish and English experience that the frequency of relevant positive pathological findings is 10-20%. The frequency of technically unacceptable examinations will be 10-15%. Polyps are allocated into three groups of approximately equal size: <6 mm, 6-9 mm and >9 mm. The number of cancers will be too low, and we would need to include several thousand to achieve > 10 cases. In discussions with health economics, it has been agreed that at least ten in each group will allow for a fairly accurate and detailed cost analysis. Including 2x400 patients will ensure at least ten patients in the smallest group.

Interim Analysis & Monitoring

We will perform an interim analysis to assess quality (video quality, completion rate, and adverse events), reinvestigation rates, complications, clinical routines, and pathways after including 100 CCE patients. The project steering group will then decide whether to continue or shut down the study based primarily on the reinvestigation rate, which should never exceed 35%.

Quality control on the capsule video readings will be conducted during the study to ensure consistent quality on the manual CCE assessment. In addition, we will also seek to employ a set of newly developed diagnostic AI algorithms, developed in a collaboration between OUH and the University of Southern Denmark, on all videos as an extra precaution. The algorithms are developed and validated as part of the AICE project (www.AICEproject.eu). The algorithms will strictly be used as a quality assurance and support tool and will not be part of the clinical decision-making process.

Deviation from standard treatment and care

All patients will receive a colonoscopic investigation following clinical routine guidelines indications. The only deviation will be regarding timelines (deviation only for a few days) in case the patients need a second investigation due to findings requiring therapeutic actions. We should also consider that delays can happen per clinical routine due to non-responders, poor bowel preparation, uninterrupted anticoagulants, etc.

Study group & feasibility

The described platform has been developed as a collaboration of the Surgical Research Unit SATC-C, the Department of Surgery, OUH in partnership with the board of OUH directors and the Region of Southern Denmark. It is built upon solid research and experience we have collected during the last 9 years (21), combined with published results from international partners and colleagues. The CCE research has been developed through numerous trials, including the activity of our Centre of Excellence 'CICA' (CICA-research.com) and the Horizon Europe project 'AICE' (aiceproject.eu).

The SATC-C has a long history of delivering studies on CCE and has recently completed a seminal trial on using CCE in the screening population (CareforColon 2015). (12) Therefore, both SATC-C and CICA are ideally placed, in terms of expertise and vision, to deliver this study. Eventually, the study's outcome will allow a much-needed cost-benefit analysis that will pave the way for integrating CCE into regular clinical routine.

The unit, under the guidance of Professor Koulaouzidis, is known internationally for CCE expertise, and the overall benefit of the study will provide continuous development for the medical & nursing staff. Lastly, the overall CCE process platform will be integrated into the clinical routine if acceptable cost is proven.

Ethics

Patients will receive information before providing consent and will only be included in trial-related procedures after both oral and written consent has been obtained. They will be allowed to withdraw their consent at any time with no consequence to their further diagnostics. Patients will receive no compensation for participation.

Colon camera capsules have been on the market for around 15 years. They are CE-marked. European guidelines exist for their use in selected cases (but not for the indication of this study). Tens of thousands of colon capsule investigations have been conducted, and CCE is now implemented in routine clinical diagnostics in Scotland and England. Existing evidence suggests that the quality in terms of sensitivity, complication rates, and patient preference is equal to or superior to OC. The procedure is considered safe and ethical. Patients in the intervention arm of the trial will gain a therapeutic advantage by being given the chance to undergo CCE instead of OC, allowing them a less straining, less invasive and clinically efficient mode of undergoing diagnostics. Should the study results prove acceptable, future patients will hopefully be given the same op-

tion as patients in the DanCap trial, potentially with the addition of predictive biomarkers (FIT and microbiome composition analysis) that can further improve the quality of the diagnostic procedure. Patients in the control arm will use healthcare facilities as normal, and the quality of their diagnostic course will not be impacted. Patients will not be compensated for the participation but will be covered by "patienterstatningen".

Before inclusion, potential participants will be offered information from project staff (secretaries, nurses, doctors, researchers). When included, the participants will receive information regarding the investigation and have the opportunity to change their decision and receive standard treatment at all times.

If additional findings are detected during quality control, a project doctor will assess them, and subsequent patient management will be in accordance with the established clinical standards dictated in the protocol.

The microbiome analyses using genome sequencing will not be conducted on human DNA. The analyses will only include the DNA of the microorganisms of the faecal sample. The material will be destroyed immediately after we conduct the stool sample analysis.

Data Management

The trial will be initiated after approval from the regional ethics committee. It will be conducted according to the Helsinki Declaration. All data will be handled according to the General Data Protection Regulation (GDPR) and the Data Protection Act. The project is registered internally in the Region of Southern Denmark (intern fortegnelse over forskningsprojekter).

Data on participants will be collected from electronic patient charts. Only relevant and required information for conducting the study is collected and entered into a RedCap electronic database via OPEN at OUH. Participation is always completely voluntary, and patients can exit the study. The Data Protection Regulation and the Data Protection Act are complied with.

The CCE examinations, including all intestinal images taken by the camera capsule, will be stored in the established GAIA database (19/30116). The results of the metagenomic analyses will be transferred to the GAIA database and stored in a secure storage environment. These results will be coupled with the other data from the project for research purposes.

Only project staff with a legitimate research purpose will be granted access to the database. This access will be limited to essential staff. The Data Protection Regulation and the Danish Data Protection Act will be complied with.

Procedure-related risks and disadvantages

Some patients report difficulties swallowing the capsule because of its size. Fluid displacement can happen due to bowel preparation. Complications of CCE are expected to be minimal following the existing literature. In a large meta-analysis, complications were reported in 4.1% of CCE examinations, and all were documented as mild to moderate, the most common being nausea and abdominal pain (22). Other possible side effects of the bowel preparation are dizziness and general discomfort. Severe complications in terms of capsule aspiration (blocking the respiratory tract) and retention (blocking the GI tract) are extremely rare. These patients cannot undergo MR-investigations while the capsule is retained in the body. These complications can sometimes lead to endoscopic or surgical removal of the capsule. The existing evidence suggests that the rate of major complications related to CCE is significantly lower than that of colonoscopy.

One of the disadvantages of CCE is that if the patient needs a subsequent colonoscopy (due to significant findings or incomplete/inadequate CCE investigation), he/she will be exposed to a new bowel preparation and the risks associated with colonoscopy. Severe bleeding after polypectomy and bowel perforation are serious complications of colonoscopy, with an incidence of less than one out of 1000 examinations.

To diminish possible side effects and complications of CCE, we screen the patients, excluding those at risk for developing complications (e.g., capsule retention). Furthermore, we inform and thoroughly explain the entire process and procedure to the patients. We also carefully monitor the patients undergoing a CCE or OC. Patients undergoing colonoscopies are offered sedatives during the examination to diminish discomfort.

Realistic medicine perspectives

There is currently a discussion on the "*Realistic Medicine*" aspect of diagnostic procedures in Denmark and other European countries (23, 24). There is accumulating evidence that over-treatment, defined as providing high-risk procedures without a clear benefit for the patient, increases dramatically in frequency. It is internationally acknowledged that the higher sensitivity of diagnostic tests must go together with sound definitions of the treatment thresholds (25). Therefore, the existing national guideline that recommends removing all polyps seen during colonoscopy is outdated (26). Polyps with no or very little risk of harm can now be identified before resection and should be left untreated. The combination of CCE and "*Realistic Medicine*" will improve patient outcomes without increasing treatments with no clear patient benefit. The DanCap protocol employs *Realistic Medicine*, leaving diminutive polyps (<6 mm) untreated. This prevents an increase in therapeutic colonoscopies, which will improve patient safety, preference, and the healthcare economy. During the next 2-4 years, this approach will be further developed by the pragmatic use of Artificial Intelligence (AI) in image analysis (www.aiceproject.eu/www.cica-research.com).

Combining the established higher sensitivity of CCE for advanced lesions with a decision to disregard low-risk polyps will result in a favourable diagnostic course for patients. It will lead to the resection of approximately the same number of polyps as in current practice but with a higher percentage of high-risk polyps and a lower percentage of low-risk polyps.

Dissemination

After completion of the study, we plan to publish two articles in (preferably) high-impact journals. One article on primary and secondary outcomes and another on the study protocol**.** Results will be published in case of positive, negative or inconclusive results. The trial will be registered at clinicaltrial.gov.

Financial Considerations Initiative for the study was taken by Trial Manager Anastasios Koulaouzidis. The trial protocol originates from the Surgical Research Unit, Department of Surgery, Odense University Hospital, Svendborg. The study costs will be covered by OUH, Region of Southern Denmark, with a grant of 1.8 million DKK and funds from CICA (a tentative budget is attached). Funding is administered by an account subject to public audit. The Trial manager has no financial affiliation with study subjects. Participants will not receive any monetary compensation for their participation. Loss of earnings and transportation costs will not be covered. Patients will not be compensated or receive any monetary benefits for participating in the study.

Cooperation

The project will be conducted in close cooperation with OUH. Who will deliver the capsules and bowel preparation and withstand the patients during CCE, while the research unit will internally analyze the CCE videos

and report the findings. Endoscopic capsules are received from Medtronic at a reduced price without conditions or involvement in the protocol or operation of the project.

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Appendices

Overview

A. Protocol Summary

B. GP Clinics

C. Workflow DanCap staff

D. CCE flowchart

E. CCE patient information

F. Questionnaire 1

G. Questionnaire 2

H. Consent

I. Bowel preparation

J. Colonoscopy flowchart

K. CCE patient course

L. Recruitment letter