

Prospective Study of a Novel Diagnostic
Algorithm for Investigating and Managing
Gastrointestinal Disease Through The
Appropriate Use of Biomarkers and Wireless
Based Capsule Endoscopy

Doctor in Medicine (MD)

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Declaration, online access, and the General Data Protection Regulation

I declare that this thesis has not been submitted as an exercise for a degree at this or any other university and it is my own work. I have also collaborated with other researchers for studies conducted as part of this thesis whom I have and will acknowledge.

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Chapter 1: Thesis outline

This chapter gives a general outline of the thesis for better understanding of issues surrounding research areas and studies that have been performed. Lower Gastrointestinal (GI) Symptoms are common and often warrant further investigations which may include colonoscopy. Currently the demand for colonoscopy far exceeds the capacity to perform them. This results in prolonged waiting lists and unfortunately delays in diagnosis. Possible strategies for patient triaging would include symptoms based triaging systems, use of biomarkers and minimally-invasive colonoscopy which includes Colon Capsule Endoscopy (CCE) and CTC (Computed Tomography Colonography). The use of CCE for investigating the symptomatic lower GI patient is still under investigation and we wish to explore this further in this thesis.

Chapter 2 highlights the current literature review on the topic of the symptomatic lower gastrointestinal (GI) patient. This is a common problem and warrants further investigations. We outline in this chapter the current strategies that has been employed to select and triage patient for further investigations which includes the need for colonoscopy. This chapter also explores the role of symptoms based triaging systems, biomarker use and minimally-invasive colonoscopy, which we have divided into CT Colonography (CTC) and Colon Capsule Endoscopy (CCE) in the diagnosis of the symptomatic patient.

Chapter 3 is a retrospective study performed to assess the value of symptoms in picking up Clinically Significant Disease (CSD). We compared the diagnostic yield of each lower GI symptoms and the likelihood of picking up CSD based on symptoms. We then applied the National Institute for Health and Care Excellence (NICE) guidelines for Colorectal Cancer (CRC) and Inflammatory Bowel Disease (IBD) as a means of classifying these patients into low risk versus high risk to assess whether fulfilling the criteria will increase diagnostic yield. This study has been published in *BMJ Open Gastroenterol.* 2020 Mar 31;7(1): e000221. DOI: 10.1136/bmjgast-2018-000221 [1]. The study has also been presented at the 26th United European Gastroenterology Week (UEGW) which was held on October 20-24, 2018, in Vienna, Austria as a poster presentation.

Chapter 4 outlines the use of biomarkers in assessing GI related disease.

The first subchapter outlines the role of different types of faecal and urine biomarkers in diagnosis and management of small bowel diseases. This subchapter has been published as a review article in *Curr Opin Gastroenterol*. 2021 May 1;37(3):284-294. doi: 10.1097/MOG.0000000000000730 [2].

The second subchapter is a study that we have performed to investigate the use of C-Reactive Protein (CRP), Faecal Immunochemical Test for Haemoglobin (FIT) and Faecal Calprotectin (FC) to assess for mucosal healing and disease activity in patients with Inflammatory Bowel Disease (IBD). We correlate the diagnostic accuracy of biomarkers with findings on endoscopy of IBD patients. The results of this study were presented at the 15th Congress of ECCO, 12-15 February 2020 and published as an abstract publication in *Journal of Crohn's and Colitis*, Volume 14, Issue Supplement_1, January 2020, Page S240, <https://doi.org/10.1093/ecco-jcc/jjz203.332> [3]. A full journal article has been written and has been planned for submission for peer-review in the *Irish Medical Journal*.

Chapter 5 explores the use of CCE in the symptomatic patient and also some other aspects of CCE.

- The first subchapter is a pilot study that investigates the use of biomarkers and CCE in low to moderate risk patients complaining of lower GI symptoms. The study outlines the diagnostic accuracy of biomarkers and CCE compared to colonoscopy. This subchapter has been published as an original research in *Endosc Int Open*. 2021 Jun;9(6):E965-E970. doi: 10.1055/a-1401-9528. Epub 2021 May 27 [4]. Colon capsule endoscopy is a viable alternative to colonoscopy for the investigation of intermediate- and low-risk patients with gastrointestinal symptoms: results of a pilot study. Ismail MS, Semenov S, Sihag S, Manoharan T, Douglas AR, Reill P, Kelly M, Boran G, O'Connor A, Breslin N, O'Donnell S, Ryan B, McNamara D. This study has also been presented as an oral e-poster podium presentation at ESGE Days 2019 meeting in Prague.
- The second subchapter explores the different bowel preparation regimens that are used for CCE and the effect on bowel cleansing and capsule excretion. The first part describes the change from a 4 litre Polyethylene Glycol (PEG) (KleanPrep) based bowel preparation to a 2 litre Polyethylene Glycol + Ascorbic acid (AA) (Moviprep). This study has been presented as an e-poster at the Virtual UEGW 2020 meeting and has been published as abstract form in *Endoscopy* 2020; 52(S 01): S274. DOI: 10.1055/s-0040-1704865 [5]. Improving Quality in Colon Capsule Endoscopy; Effects of Different Bowel Preparation Regimens. M Syafiq Ismail, S Semenov, S Sihag, N Breslin, A O'Connor, B Ryan, D McNamara. The second part of this

subchapter explores the addition of castor oil to the CCE booster medications and effects on bowel cleansing and capsule excretion. This study has been published in *World J Gastrointest Pharmacol Ther*. 2021 Nov 5;12(6):103-112. DOI: 10.4292/wjgpt.v12.i6.103, Semenov S, Ismail MS, O'Hara F, Sihag S, Ryan B, O'Connor A, O'Donnell S, McNamara D. Addition of castor oil as a booster in colon capsule regimens significantly improves completion rates and polyp detection [6]. It was also presented at the Virtual UEGW 2020 meeting as a e-poster.

- The third subchapter explores the patient preference between colonoscopy and CCE. We assess patients' comfort, satisfaction, and preference between CCE and colonoscopy. The patients from this subchapter were recruited from the study conducted in subchapter 5.1. This subchapter has been published in *BMC Gastroenterol*. 2022 Jan 24;22(1):31. DOI: 10.1186/s12876-021-02081-0, Ismail MS, Murphy G, Semenov S, McNamara D. Comparing Colon Capsule Endoscopy to colonoscopy; a symptomatic patient's perspective [7]. This study has also been presented as a e-poster at the ESGE Days 2019 meeting in Prague.

Chapter 6 explores the potential role of CCE as a response to the Covid-19 Pandemic.

- The first subchapter introduces the effects of the pandemic to endoscopy waiting lists in general and how CCE will be able to help reduce the waiting list. This subchapter has been submitted as a correspondence letter to *Endoscopy International Open* and is awaiting editor decision.
- The second subchapter outlines the impact of the Covid-19 pandemic to Colorectal Cancer Screening. This subchapter has been published as correspondence letter in *Lancet Gastroenterol Hepatol*. 2021 Jun;6(6):426. doi: 10.1016/S2468-1253(21)00136-9. Semenov S*, Ismail MS*, McNamara D. Impairment of colorectal cancer screening during the COVID-19 pandemic [8]. Ismail MS and Semenov S are co-first authors to this paper.

Chapter 7 is our conclusion to the thesis, which outlines summaries of studies presented and published. This chapter also outlines possible future directions for CCE and triaging systems of patients with lower GI symptoms.

List of Peer-Review Publications in this thesis (in order of appearance)

- 1) Lower gastrointestinal symptoms and symptoms-based triaging systems are poor predictors of clinical significant disease on colonoscopy. Mohd Syafiq Ismail, Olufemi Aoko, Sandeep Sihag, Eimear Connolly, Joseph Omorogbe, Neil O'Morain, Anthony O'Connor, Niall Breslin, Barbara Ryan, Deirdre McNamara. *BMJ Open Gastroenterol.* 2020 Mar 31;7(1):e000221
- 2) The Utility of Faecal & Urine Biomarkers for Small Bowel Diseases. M Syafiq Ismail, Serhiy Semenov, Deirdre McNamara. *Current Opinion in Gastroenterology: May 2021 - Volume 37 - Issue 3 - p 284-294*
- 3) Colon capsule endoscopy is a viable alternative to colonoscopy for the investigation of intermediate and low risk patients with gastrointestinal symptoms, results of a pilot study. Ismail MS, Semenov S, Sihag S, Manoharan T, Douglas AR, Reilly P, Kelly M, Boran G, O'Connor A, Breslin N, O'Donnell S, Ryan B, McNamara D. *Endosc Int Open* 2021; 09(06): E965-E970. DOI: 10.1055/a-1401-9528
- 4) Comparing Colon Capsule Endoscopy To Colonoscopy; A Symptomatic Patient's Perspective. Ismail MS, Murphy G, Semenov S, McNamara D. *BMC Gastroenterol.* 2022 Jan 24;22(1):31. doi: 10.1186/s12876-021-02081-0
- 5) The addition of castor oil as a booster in colon capsule regimens significantly improves completion rates and polyp detection. S. Semenov, MS. Ismail, F. O'Hara, S. Sihag, B. Ryan, N. Breslin, A. O'Connor, S. O'Donnell, D. McNamara. *World J Gastrointest Pharmacol Ther.* 2021 Nov 5;12(6):103-112. doi: 10.4292/wjgpt.v12.i6.103
- 6) Consider using Colon Capsule Endoscopy to reduce waiting list due to Covid-19 pandemic. M Syafiq Ismail, Serhiy Semenov, Deirdre McNamara. Correspondence letter sent to *Endoscopy International Open*, awaiting review
- 7) Impairment of colorectal cancer screening during the COVID-19 pandemic. M Syafiq Ismail*, Serhiy Semenov*, Deirdre McNamara. *The Lancet Gastroenterology & Hepatology.* Volume 6, Issue 6, P426, June 01, 2021. [Correspondence letter submitted to *Lancet Gastroenterology and Hepatology* regarding the use of CCE for catch-up colorectal cancer screening. (*MSI and SS are co-first authors)]

List of abstract publications (in order of appearance)

- 1) Lower Gastrointestinal Symptoms And Symptom-Based Triaging Systems Are Poor Predictors Of Clinical Significant Disease On Colonoscopy - M.S. Ismail, O. Aoko, J. Omorogbe, S. Sihag,

- A. O'Connor, B. Ryan, N. Breslin, D. McNamara. United European Gastroenterology Journal 6(8S)
- 2) FIT and FC as a surrogate non-invasive marker for mucosal healing in inflammatory bowel disease. M S ISMAIL, G Murphy, C Kelly, F O'Riordan, S Semenov, S Sihag, N Breslin, O Anthony, B Ryan, D McNamara. Journal of Crohn's and Colitis, Volume 14, Issue Supplement_1, January 2020
 - 3) Colon Capsule Endoscopy With Or Without Biomarkers As A Viable Alternative To Colonoscopy In Unselected Patients With Lower Gi Symptoms: Results Of A Pilot Study. MS Ismail, S Semenov, A O'Connor, N Breslin, B Ryan, D McNamara. Endoscopy 2019; 51(04): S161
 - 4) Improving Quality In Colon Capsule Endoscopy; Effects Of Different Bowel Preparation Regimens. M Syafiq Ismail, S Semenov, S Sihag, N Breslin, A O'Connor, B Ryan, D McNamara. Endoscopy 2020; 52(S 01): S274
 - 5) The Addition of Castor Oil As a Booster In Colon Capsule Regimens Significantly Improves Completion Rates And Polyp Detection. S Semenov, R Atiyekeogbebe, MS Ismail, S Sihag, E McCarthy, B Ryan, N Breslin, A O'Connor, D McNamara. Endoscopy 2020; 52(S 01): S285
 - 6) Comparing Colon Capsule Endoscopy to Colonoscopy; A Patient's Perspective. G Murphy, MS Ismail, C Msaky, D McNamara. Endoscopy 2019; 51(04): S218

List of presentations of studies performed in thesis (in chronological order)

- 1) International Presentation
 - a. Oral Presentation
 - i. ESGE e-poster podium Study Days 2019 in Prague - Colon Capsule Endoscopy with or without biomarkers as a viable alternative to colonoscopy in unselected patients with lower GI symptoms: results of a pilot study.
 - b. Poster Presentation
 - i. UEGW 2018 - Lower Gastrointestinal Symptoms And Symptom-Based Triaging Systems Are Poor Predictors Of Clinical Significant Disease On Colonoscopy
 - ii. ESGE Days 2019 – Comparing Colon Capsule Endoscopy to Colonoscopy
 - iii. ECCO 2020 – FIT and FC as a surrogate marker for mucosal healing
 - iv. Virtual UEGW 2020 – Improving Quality In Colon Capsule Endoscopy; Effects Of Different Bowel Preparation Regimens.

- v. Virtual UEGW 2020 – The Addition of Castor Oil As a Booster In Colon Capsule Regimens Significantly Improves Completion Rates And Polyp Detection.

2) National presentation

a. Oral Presentation

- i. ISG winter meeting 2018 - Colon Capsule Endoscopy with or without biomarkers as a viable alternative to colonoscopy in unselected patients with lower GI symptoms: results of a pilot study.

b. Poster Presentation

- i. ISG winter meeting 2017 – Symptoms Are A Poor Predictor Of Clinically Significant Disease On Colonoscopy
- ii. ISG meeting 2018 - Comparing Colon Capsule Endoscopy to Colonoscopy
- iii. ISG meeting 2019 – FIT and FC as a surrogate marker for mucosal healing
- iv. ISG meeting 2019 – Improving Quality In Colon Capsule Endoscopy; Effects Of Different Bowel Preparation Regimens.
- v. ISG meeting 2019 – The Addition of Castor Oil As a Booster In Colon Capsule Regimens Significantly Improves Completion Rates And Polyp Detection.

Chapter 2: Background Literature Review – Current Investigation and Management Strategies for Patients Presenting with Lower Gastrointestinal Symptoms.

Introduction

Lower gastrointestinal (GI) symptoms are very common, they account for about 10% of all GP referrals, and while most complaints are self-limiting, some may require further referral to a specialist gastroenterologist for further management [9, 10]. Lower GI symptoms include abdominal pain, diarrhoea, constipation, bloating, and bleeding Per Rectum (PR). Other symptoms that may be grouped with lower GI symptoms albeit not always due to lower GI pathology includes weight loss and symptoms related to iron deficiency anaemia.

When referred to a gastroenterologist, patients are interviewed with a full medical history taken, including any family history of lower GI pathology, have a physical examination performed and be referred for more investigations/tests in order to arrive at a diagnosis. These tests often include routine blood tests, including a) a full blood count checking for a low Haemoglobin (Hb) level indicating anaemia and a high white cell count indicating possible infection/inflammation; b) inflammatory markers including Erythrocyte Sedimentation Rate (ESR) and C-Reactive Protein (CRP) again indicating possible infection/inflammation. In addition, stool assessments are also regularly requested particularly for faecal calprotectin and microbiological assessments. If a lower GI pathology is suspected based on patient's demographics, clinical history, and examination, they are then often referred for a colonoscopy for direct visualisation of the colon and triaged in terms of priority. Apart from this more traditional pathway of referral, Open or Direct access endoscopy has been available to GPs to refer patients directly to the endoscopy department [11]. This type of referrals is also usually triaged by gastroenterologist in terms of priority for colonoscopy either urgent or routine.

Colonoscopy is the gold standard investigation for colonic disease. It offers direct visualisation of the colon and apart from its diagnostic capabilities including taking tissue samples for histology, it also enables the endoscopist to perform therapeutic measures for example polypectomies. Even though colonoscopy is usually well tolerated, it does come with its own limitations including potential complications for example bleeding and bowel perforation, and patients perceived anxiety, inconvenience, discomfort, or embarrassment [12-14]. Colonoscopies are only performed by

specialist endoscopists in specific endoscopic units. Patients undergoing a colonoscopy need to modify their diet several days prior to colonoscopy avoiding slow transit foods and often need to stop certain medications including iron tablets that may predispose to constipation in order to ensure an adequate colonic cleansing. They then need to take a bowel purgative agent to achieve sufficient bowel preparation for the colonoscopy and need to be fasting at least 4-6 hours prior to colonoscopy. Patients often need to be given some form of sedation and anxiolytic pre-procedure in order to ensure adequate comfort throughout the colonoscopy. In Ireland, colonoscopy is performed under conscious sedation with a combination of a benzodiazepine (most commonly Midazolam) and an opioid (most commonly Fentanyl). Patients often need to miss 1-2 days of work due to the bowel preparation, procedure itself and as an effect of the sedation.

Even though colonoscopies are generally well tolerated and considered safe, they come with potential risks. Levin et al reported that the incidence of adverse events from mostly diagnostic colonoscopies performed in an integrated healthcare system in the United States was 5 per 1000 procedures (95% CI, 4.0-6.2) [15]. General complications associated with colonoscopies are usually related to sedation, bowel perforation and a risk of haemorrhage. A recent review article by the American Society of Gastrointestinal Endoscopy (ASGE) found a pooled perforation rate of 5.8 per 10,000 colonoscopies (95% CI, 5.7- 6.0), bleeding rate of 2.4 per 1000 colonoscopies (95% CI, 2.4- 2.5), and death rate of 3 in 100,000 colonoscopies [16]. Furthermore, there is a risk of causing pain and discomfort to the patient during colonoscopy. This is often associated with air insufflation, looping of the colonoscope, and traversing through bends in the colon. The risk of causing pain is often worse in younger, female patients with lower Body Mass Indices (BMI) or in patients who have had previous abdominal and pelvic surgery [17].

Apart from the risks of complications, there are also patient factors to be considered. Patients can be reluctant to undergo this invasive procedure due to their perceived embarrassment, inconvenience, or discomfort associated with colonoscopy [12, 18]. In a study about anxiety related to colonoscopy in 1336 patients, Shafer et al found very high anxiety scores (>70/100) reported by 29% of patients relating to the procedure itself by using a self-reported Visual Analog Scale in a survey done just prior to their outpatient colonoscopies [19].

Currently the need for colonoscopy far exceeds our ability to perform them, resulting in prolonged waiting lists and unfortunately delays in diagnosis and treatment. The demand for colonoscopy is also increased due to the widespread introduction of colorectal cancer screening programmes [20, 21]. In the UK, 90% of units in Northern Ireland and 22% of acute services in England failed to meet urgent non-cancer waiting list targets, while 20% in English sectors, 42% in Welsh sectors and 40% in Scottish sectors failed to meet urgent cancer targets [22]. Even in Ireland, based on national waiting-list data there was a total of 66 601 patients awaiting endoscopy at the end of Nov 2019 [23]. Due to limited resources, a better means of patient selection and triage are badly needed, as current symptoms-based triaging systems are failing to accurately select patients with significant disease and are unsustainable. Apart from colonoscopy, there are newer technologies that are less invasive which may be used for colonic investigation which include CT Colonography (CTC) and Colon Capsule Endoscopy (CCE). These newer technologies are less often employed compared to colonoscopy and are further described in subchapter 2.3.

The main goal of colonoscopy is to diagnose and subsequently manage Clinically Significant Disease (CSD). CSD can be defined as Colorectal Cancer (CRC), High Risk Polyps (HRP), Inflammatory Bowel Disease (IBD), and Colonic Vascular Lesions (CVL – for example colonic angiodysplasia). HRP can be divided into High-Risk Adenomas (HRA – presence of 5 or more adenomas, adenomas more than 10mm, or adenomas with high grade dysplasia) and High Risk Sessile Serrated lesions (SSL – sessile serrated lesions greater than 10mm or with a focus of dysplasia). Inflammatory Bowel Disease (IBD) can be divided into Crohn's Disease (CD), Ulcerative Colitis (UC), Indeterminant Colitis (IC) or Microscopic Colitis (MC). Despite the need to detect CSD, colonoscopy also has a valuable role as a means to rule-out CSD. This provides both patients and physicians reassurance, alleviating anxiety and reducing stress [24, 25]. However due to the limitations of colonoscopy combined with prolonged waiting lists, there is a growing sense that colonoscopy is not the ideal rule-out test and that other investigations need to be considered.

2.1 Symptoms and triaging

Symptoms based triaging has been traditionally used to prioritise referrals for colonoscopies. The different available systems usually consider a patients age, demographics, family history and the duration of symptoms as a basis for triaging referrals.

In terms of lower GI symptoms themselves, not all symptoms are equal. Some symptoms for example Per Rectum (PR) bleeding, altered bowel habit including chronic diarrhoea, weight loss and the presence of a mass on examination are considered to be more serious, alarm symptoms and need more urgent assessment [26-31]. However, despite being considered as alarm symptoms, they still have a low sensitivity and specificity [32-34]. Other symptoms for example abdominal pain, constipation and bloating may be less specific [35-38].

2.1.1 Triage systems

Symptoms based triaging symptoms covered in this subchapter:

- Appropriate use of GI endoscopy by ASGE 2012
- NICE guidelines for CRC and IBD
- Victorian Triage guidelines for colonoscopy
- Triage system used in Irish Hospital

2.1.1.1 – American Society of Gastrointestinal Endoscopy (ASGE) guidelines

The American Society of Gastrointestinal Endoscopy (ASGE) had published guidelines regarding the appropriate use of Gastrointestinal (GI) endoscopy [39]. This guideline includes the optimal use of colonoscopy in investigating symptomatic patients presenting with lower GI bleeding, unexplained anaemia, and clinically significant diarrhoea. Apart from saying which indication for colonoscopy is appropriate or not, the guideline itself does not include triaging criteria nor recommend criteria which warrant an urgent prioritisation for colonoscopy. Despite this, several studies have evaluated their own service in terms of appropriateness of colonoscopies following the ASGE guidelines, and adherence to the guideline ranges from 58%-85% [40-45]. An Italian study looking into these guidelines has also found that the diagnostic yield of colonoscopy was significantly higher for appropriate colonoscopies (26.94% vs 10.6%, $P < 0.001$) than for inappropriate colonoscopies [43].

2.1.1.2 – National Institute for Health and Care Excellence (NICE)

NICE is an executive non-departmental public body of the Department of Health in England whose role is to improve health and wellbeing by putting science and evidence at the heart of health care decision making (nice.org.uk). NICE has published guidelines which define criteria for patients with

suspected IBD and CRC for urgent referral for investigations which include colonoscopy (Table 1 and 3) [46, 47]. Regarding the CRC guideline, NICE made their recommendation based on their own meta-analysis of Positive Predictive Value (PPV) of certain lower GI symptoms (Table 2). A patient fulfilling the criteria will need to have a colonoscopy performed within 2 weeks.

NICE CRC referral guideline (NG – NICE Guidelines 12)	
Refer patients using CRC pathway (for an appointment within 2 weeks) if:	
• Age $\geq$ 40 with weight lost AND abdominal pain. • Age $\geq$ 50 with unexplained PR bleeding. • Age $\leq$ 50 with PR bleeding AND one of the following symptoms: abdominal pain, weight loss, change in bowel habit, iron deficiency anaemia. • Age $\geq$ 60 with iron deficiency anaemia or change in bowel habit. • Test show occult blood in faeces (2015 update). • Presence of rectal/abdominal mass on examination.	

Table 1: Adapted from NICE guidelines for Suspected cancer: recognition and referral (updated 29 January 2021) (NG12)

It is interesting to note that based on NICE's meta-analysis, PR bleeding only has a PPV of 4.8%, anaemia 5.87%, diarrhoea 0.94-1.5% (n=2093), constipation 0.42-0.81% (n=2093), and change in bowel habit 2.8-2.9% (n=621321 in males) for CRC (Table 2) [48].

Symptoms	Total Patients	PPV % (95%CI)
Rectal Bleeding	132701	4.88 (3.48-6.79)
Abdominal Pain	371703	2.04 (0.53-7.55)
Anaemia	35949	5.87 (2.64-12.)
Weight loss	42338	3.00 (0.32-22.89)
Dyspepsia	4476	0.60 (0.27-1.35)

Table 2: Adapted from – Colorectal Cancer: Meta-analyses

(<https://www.nice.org.uk/guidance/ng12/evidence/full-guideline-pdf-2676000277>) [48]

Regarding the NICE referral guidelines for IBD, patients fulfilling the criteria for referral would need an urgent specialist assessment within 4 weeks (Table 3) [46]. The prioritised symptoms include bloating, change in bowel habit, and abdominal pain and would need to be present for more than 6 weeks to warrant a referral. These symptoms are however not specific for IBD and can often overlap with symptoms of Irritable Bowel Syndrome (IBS). Specialist assessment enables consideration of a possible diagnosis of IBD, out ruling IBS, which includes clinical evaluation and a combination of biochemical, endoscopic, radiological and histological investigations to confirm a diagnosis [46].

People with **ANY** of the following symptoms that have been present for ≥ 6 weeks should be suspected of having IBD:

- abdominal pain or discomfort
- bloating
- change in bowel habit (such as diarrhoea with or without rectal bleeding).

Table 3: Adapted from - Symptoms requiring specialist referral for suspected IBD based on NICE (QS – Quality Statement 81) [46].

2.1.1.3 Victorian Triage Guidelines for colonoscopy

The Health and Human services of the Victoria State Government has published guidelines for referral for colonoscopy in 2017. These guidelines include for Indication A (symptoms and investigation), indication B (surveillance), and Indication C (therapeutic). The triage is broken down into four categories, Category 1 (for colonoscopy <30 days), Category 2 (for colonoscopy <60 days), Category 3 (for colonoscopy <180 days) and Not Indicated. The guidelines specifically mention that single symptoms have a poor sensitivity for detecting advanced colorectal neoplasia, hence factors are combined along with age for increased sensitivity [49]. Indication A based on this guideline is found in Table 4. They defined critical factors as positive FIT, anaemia, rectal bleeding, and age 60 years or older.

Category 1 (<30 days)	Category 2 (<60 days)	Category 3(<180 days)	Not Indicated/ comments
Positive FIT (Faecal Immunochemical Test)			
Anaemia and either - Any other critical factor - One or more other symptoms	Anaemia and all of: - no other critical factor or other symptom - no likely cause - any age	Anaemia and all of: - no other critical factor or other symptom - likely non-GI tract cause - age $\geq$ 50 years	Anaemia and all of: - no other critical factor or other symptom - untreated likely Non-GI tract cause such as menorrhagia/diet - age < 50 years If no response to treatment or recurrence, recommend Category 2 colonoscopy. Consider upper gastrointestinal endoscopy
Rectal bleeding and any one of: - any other critical factor < 12 months' duration, age $\geq$ 50 years < 12 months, one or more other symptom, age < 50 years	Rectal bleeding and all of: < 12 months' duration - no other critical factor or other symptom - no likely anorectal cause found (such as normal rigid/flexible sigmoidoscopy) or	Rectal bleeding and all of: > 12 months, occasional - no other critical factor or other symptom - no likely anorectal cause found (such as normal rigid/flexible sigmoidoscopy) - any age	Rectal bleeding > 12 months, occasional and all of: - no other critical factor or other symptom - likely cause found after specialist assessment including rigid/ flexible sigmoidoscopy such as haemorrhoids

	failed treatment of haemorrhoids • age < 50 years		• If no response to treatment or recurrence, recommend Category 2 colonoscopy.
Altered bowel habit (> 6/52 and < 12 months) and: • any critical factor	Altered bowel habit (> 6/52 and < 12 months) and both: • no critical factor and • one or more other symptom	Altered bowel habit (> 6/52 and < 12 months) and: • no critical factor or other symptom	Altered bowel habit of less than six weeks' duration should be fully assessed and treated. If no response to treatment or recurrence, recommend Category 2 colonoscopy. Chronic diarrhoea or constipation (> 12 months) with no critical factor or other symptom should undergo specialist review with consideration to colonoscopy only after full assessment
Abdominal pain (unexplained) and: • any critical factor	Abdominal pain (unexplained) and both: • no critical factor • one or more other symptom	Abdominal pain (unexplained) and: • no critical factor or other symptom	Abdominal pain of less than six weeks' duration should be fully assessed and treated with consideration of colonoscopy if no response or persistence. Colonoscopy is not

			indicated in a resolved episode of acute abdominal pain or diverticulitis with typical CT features and both no critical factor and no other symptom.
Weight loss (unexplained) and either: • any critical factor or • one or more other symptom			Weight loss and all of: • no critical factor or other symptom • normal examination • normal MCH/MCV/iron studies
Mass palpable (abdominal or rectal) or present on rigid/flexible sigmoidoscopy			Some masses (such as on the superficial abdominal wall) should be assessed by CT prior to consideration of colonoscopy.
Possible inflammatory bowel disease (IBD) and any one of: • any critical factor or other symptom • calprotectin (+) • raised CRP or ESR • iron deficiency • low albumin	IBD reassessment for change in treatment	Possible IBD and all of: • no critical factor or other symptom • calprotectin (-) • normal CRP and ESR • no iron deficiency • normal albumin • specialist assessment (including normal rigid/flexible sigmoidoscopy)	Symptoms of IBD may mimic those of irritable bowel syndrome and include abdominal bloating, non-specific abdominal pain and irregular bowel habit.

• abnormal rigid/flexible sigmoidoscopy			
Low MCV/MCH or ferritin and: • any critical factor	Low MCV/MCH or ferritin and both: • no critical factor • one or more other symptom	Low MCV/MCH or ferritin and both: • no critical factor or other symptom • age ≥ 50 years	Low MCV/MCH or ferritin and both: • no critical factor or other symptom • age < 50 years If no identifiable likely cause, no response to treatment or recurrence, consider Category 2 colonoscopy

Table 4: Adapted from Indication A, Colonoscopy Categorisation Guidelines 2017, Victoria State Government [49]

A recent validation study by Emery et al found that following the Victorian Guidelines reduce the proportion of Category 1 colonoscopies by 10% without adversely affecting detection rates [50].

2.1.1.4 Symptoms based triaging in Ireland.

Currently in Ireland, a specific national triage guideline does not exist to aid endoscopist for prioritising colonoscopies. Each individual endoscopy unit may implement their own triaging system. The majority employ NICE Criteria: however, individual centres have developed their own based on available evidence.

An example of this is the triaging system used in Beaumont Hospital and adapted in other Royal College of Surgeons Ireland (RCSI) group Hospitals (Table 5) [51]. To the best of our knowledge, no validation or diagnostic accuracy studies have been performed for this guideline.

Urgent (within four weeks) referral for colonoscopy is generally indicated in:

- Palpable abdominal or rectal mass
- Unexplained iron deficiency anaemia
- > 60 years persistent rectal bleeding for six weeks or more and or a change in bowel habit to looser stools
- > 40 years with rectal bleeding and a change in bowel habit tending to looser stools persisting for six weeks or more
- Abnormal abdominal imaging
- < 40 years with rectal bleeding and a change in bowel habit towards looser stools with a family history of colorectal cancer or inflammatory bowel disease

Routine referral for colonoscopy is generally indicated in:

- <60 years with a history of chronic diarrhoea
- Assessment of disease and extent of established IBD

Table 5: Adapted from Endoscopy Referral Guidelines, Beaumont Hospital [51]

Biomarkers

The use of biomarkers to assist in diagnosing patients complaining of lower GI symptoms have been used by clinicians and gastroenterologist for quite some time. This would include more traditional serum-based biomarkers which include serum Haemoglobin (Hb) to check for anaemia and Erythrocyte Sedimentation Rate (ESR) and C-Reactive Protein (CRP) to check for inflammation. More recently, faecal / stool-based biomarkers have been introduced in the diagnostic pathway. This includes Faecal Immunochemical Test for Haemoglobin (FIT) which detects the presence of occult blood in the stool and also Faecal Calprotectin (FC) which detects the presence of enteric inflammation.

2.2.1 Serum Haemoglobin (Hb)

Serum Haemoglobin (Hb) is used to detect the presence of anaemia. Normal Hb levels differ between males and females. The World Health Organization (WHO) defines anaemia as a Hb concentration below 13 g/dl in males, below 12 g/dl in non-pregnant women, and below 11 g/dl in

pregnant women [52]. Iron Deficiency Anaemia (IDA) is a subset of anaemia defined as the presence of anaemia with low iron parameters. This is often picked up on a Full Blood Count (FBC) showing a low Mean Corpuscular Volume (MCV), low Mean Corpuscular Haemoglobin MCH and a microcytic hypochromic erythrocyte pattern on a blood film.

IDA could be due to loss of blood from the GI tract but the presence of IDA by itself does not specifically point to a lower GI pathology where upper GI and small bowel pathologies could also be the culprit. These pathologies include vascular malformations, and coeliac disease. A low dietary intake of Iron could also cause IDA. Apart from that, patients with haemoglobinopathies for example Sickle Cell Anaemia and Thalassemia would often have an IDA picture in their blood. Blood loss from other organs for example in patients with Menorrhagia could also cause IDA.

The British Society of Gastroenterology (BSG) has recommended patients with IDA to undergo coeliac testing, OesophagoGastroDuodenoscopy (OGD) and colonoscopy [53].

As mentioned above in subchapter 2.1.1.2, the presence of iron deficiency anaemia has been incorporated in the NICE suspected CRC referral pathway. Based on their meta-analysis of several studies, NICE had concluded that the PPV of anaemia for CRC is 5.87% (95% CI [2.64-12]) which tended to increase with age [48, 54-61]. When excluding Panzuto et al from their meta-analysis following secondary analysis due to concerns that their study population has a higher risk than the unselected population, the PPV for anaemia dropped to 4.09% (95% CI [2.24-7.34]) [48, 59].

Anaemia is also the most common systemic complication and extraintestinal manifestation of IBD and the cause can be a combination of IDA and anaemia of chronic disease [62-66]. The prevalence of anaemia in IBD patients ranges from 8.8% to 73.7% depending on the patient subpopulation and about two thirds of patients have anaemia at diagnosis [67].

2.2.2 Serum C-Reactive Protein (CRP) and Erythrocyte Sedimentation Rate (ESR)

Serum C-Reactive Protein (CRP) and Erythrocyte Sedimentation Rate (ESR) are commonly used markers of systemic inflammation. CRP is an acute phase reactant protein produced primarily by hepatocytes in response to tissue injury, including infection, trauma, myocardial infarction, surgery, and cancer [68]. ESR represents the rate at which erythrocytes fall through plasma which depends

largely on the plasma concentration of fibrinogen and is an indirect measurement of plasma acute-phase protein concentrations [68].

Normal values of CRP and ESR will vary between different laboratories. In Tallaght University Hospital (TUH) normal values of CRP is 0-5 mg/L and ESR is 1.0-15.0 mm/hr.

Chronic inflammation has been implicated in the aetiology of CRC through a few different mechanisms including the effects of oxidative stress and subsequent DNA damage, as well as the effects on cellular proliferation and apoptosis being hypothesized [69-72]. Kantor et al found in their study of adolescents who underwent a compulsory conscription assessment for the Swedish military, those with high ESR (15+ mm/hr) had a 63% higher risk of CRC (HR: 1.63; 95% CI: 1.08, 2.45) than those with low ESR (<10 mm/hr) (p-trend:0.006) (total cohort = 239658, CRC cases = 885) [73]. In a meta-analysis of 11 studies, Zhang et al did not find that CRP was associated with a higher risk of developing colorectal adenomas [OR (95% CI): 1.15 (0.94-1.40)] [74]. However, Zhou et al in their meta-analysis of 18 studies found that the pooled relative risk (RR) of colorectal cancer for one unit change in CRP was 1.12 [95 % CI (1.05–1.21)] indicating a link between high CRP and CRC [75].

Being a marker of inflammation, ESR and CRP may have a role to help in the diagnosis of patients with IBD. In a meta-analysis by Menees et al, an elevated CRP level of ≥ 1.7 mg/dl had a >52% predictive probability of IBD, while levels >2.7 mg/dl have more than a 90% likelihood of IBD [76]. For ESR they found that an elevated level of ESR was not predictive of IBD and did not discriminate IBD patients from those with IBS or healthy controls [76]. In a meta-analysis of different biomarkers in a paediatric setting, Holtman et al found that ESR had a pooled Area Under the Curve (AUC) for diagnosis of IBD of 0.84 (95% CI, 0.82-0.87) while CRP had a lower AUC at 0.79 (95% CI, 0.73-0.85) [77].

These studies would indicate that serum biomarkers alone would be an insufficient means of selecting patients for referral for direct colonic visualisation and identifying high risk subjects who would require a more urgent colonoscopy.

2.2.3 Faecal biomarkers

As serum biomarkers can be non-specific for lower GI disease, more recently there has been increasing research for the use of faecal based biomarkers. The two most commonly used and readily available are the Faecal Immunochemical Test for Haemoglobin (FIT) and Faecal Calprotectin (FC).

Stool collection for FIT and FC requires two separate collection bottles (Image 1 and 2). Patients are often asked to collect the samples themselves and return the bottles to the hospital. Stool collection for FC involves scooping a small amount of fresh faeces in a standard collection bottle. FIT involves inserting the included probe which is attached to the bottle cap into fresh faeces (Image 1). The FC collection bottle especially cannot be sent by post due to the risk of breakage and possible leakage of stool collected. FIT collection bottle, however, is sturdier and may be safely sent in the post as used in the Irish National Colorectal Cancer Screening Program. The process of stool collection and return can often be seen by patients as embarrassing and cumbersome [78].

FIT detects the presence of occult blood in the stool. Conventional Faecal Occult Blood test (FOB) detects the presence of guaiac and pseudoperoxidase activity and is therefore not specific for human blood [79]. FIT is specific for intact human Hb and its early degradation products [80, 81]. There are two types of FIT available: qualitative (based upon immunochromatography and providing a positive or negative result) or quantitative (based upon latex agglutination immunoturbidimetry and giving a numerical result for the faecal Hb concentration). Quantitative FITs have been recommended over qualitative FIT to remove reader variability, inter-batch variability and to improve the diagnostic accuracy of the test [79, 81]. Based on the assumption that many significant colonic conditions are associated with some form of bleeding which may be occult, a positive FIT has been advocated as a selection criterion for the need for direct colonic visualisation. FIT has been used successfully as a means of detecting CRC and advanced colonic polyps in national colorectal screening programs with different cut-offs values (15–67 µg/g) [80, 82, 83].



Image 1: FIT collection bottle

Faecal Calprotectin (FC) is a calcium and zinc binding neutrophil cytosolic protein with a wide array of functions, including anti-bacterial and anti-fungal defence, regulation of neutrophil and monocyte chemotaxis and induction of apoptosis [84]. The detection of FC in stool reflects neutrophil cellular degranulation during an inflammatory response and FC concentrations strongly correlate with the migration of 111-indium-radiolabeled granulocytes through the gut wall [84, 85]. FC is stable at room temperature for up to 7 days and can be accurately measured by using a laboratory-based enzyme-linked immunosorbent assay (ELISA) or by point-of-care rapid detection assays [85-88]. This point of care test uses quantitative immunochromatographic or quantitative enzyme immunoassays and studies have found that some test kits (Quantum Blue®, EliA™, RIDASCREEN®) to be comparable to a lab-based ELISA [87, 89]. Current NICE and manufacturers guidelines have suggested a cut off value of <50 µg/g to exclude active inflammation in the GI tract [90].



Image 2: Standard stool collection bottle used for FC. Scoop is attached to the lid to assist stool collection.

A few studies have investigated the use of FIT and FC to improve triage and investigation of patients with lower gastrointestinal related symptoms [91-99]. FIT shows the most promise as a possible means of prioritising patients for further investigations. In a cohort of 1043 patients, Mowat et al found that with a cut-off of any detectable faecal Hb on FIT, the PPV for any Clinically Significant Disease (CSD) was 20.6% and the Negative Predictive Value (NPV) for CRC, High Risk Adenoma (HRA) and IBD of 100%, 97.8% and 98.4%, respectively [97]. For FC, using a cut-off of 50 µg/g, the PPV for any significant bowel disease was 16.9% and the PPV for IBD was 6.4%. On the other hand, the NPV for IBD was 98.9% [97]. Widlak et al found in their study of 430 symptomatic patients, at a cut-off point of detectable FIT and FC ≥ 50 µg/g, the NPV of FIT alone or both markers (FIT and FCP) in combination was similar at 99% for CRC, with a sensitivity and specificity of 84% and 93%, respectively [96].

In a meta-analysis of 17 studies involving 6755 symptomatic patients, Stonestreet et al, found that at a cut-off of 20µg/g, FIT had an overall pooled sensitivity and specificity to detect CRC of 0.90 (95% CI 0.87-0.92) and 0.87 (95% CI 0.83-0.90) respectively [100]. Walker et al have found in their study that an FC with a cut off value of <100 µg/g had a PPV of 50% distinguishing IBD from functional disease despite having alarm symptoms [101]. A summary of these studies can be found in Table 6.

However, faecal biomarkers are still non-diagnostic and may still have a high positivity rate which would warrant further investigations. Mowat et al had a FIT positivity rate of 58.3%, FC positivity rate of 62% [97]. Of importance they had found three patients with CRC with a FIT less than 10 µg/g in a symptomatic cohort [97]. Hence, in order to not miss a clinically significant diagnosis, biomarkers alone would not be enough as a triage tool for patients complaining of lower GI symptoms. Further methods of pre-screening should be introduced as part of the diagnostic process including the use of minimally-invasive colonoscopy.

Author	Study design	Biomarkers and cut off	Diagnostic value
Mowat et al [97]	1043 symptomatic patients referred by GP for colonoscopy	Detectable FIT Cut-off of 50 µg/g of FC	PPV for any CSD = 20.6% and NPV for CRC = 100%, HRA = 97.8% and IBD = 98.4% FC, PPV for CSD = 16.9% and IBD = 6.4%. NPV for IBD = 98.9%
Widlak et al [96]	430 symptomatic patients	Detectable FIT Cut-off of 50 µg/g of FC	NPV of FIT alone or both markers (FIT and FCP) in combination was similar at 99% for CRC, sensitivity 84% specificity 93%
Stonestreet et al [100]	Meta-analysis of 17 studies involving 6755 symptomatic patients	Cut-off of 20µg/g of FIT	Pooled sensitivity for CRC = 0.90 (95% CI 0.87-0.92) Pooled specificity for CRC = 0.87 (95% CI 0.83-0.90)
Walker et al [101]	789 symptomatic young adults	FC with a cut off value of <100 µg/g	PPV of 50% distinguishing IBD from

	with/without alarm symptom		IBS despite alarm symptoms
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Table 6: Biomarkers and diagnostic values

2.3 Minimally-invasive colonoscopy

2.3.1 Computed Tomography Colonography (CTC)

CTC is a minimally-invasive imaging method that uses computed tomography (CT) for data acquisition combined with specialized imaging software to examine the colon [102]. CTC is performed in the radiology department using pre-existing CT scanners. Patients are still required to take some form of purgative agent (usually 1-2L of Polyethylene Glycol) for bowel preparation, and they also have to take a radiocontrast agent pre-procedure. A rectal tube is usually inserted for air insufflation. Scans takes about 20-25 minutes. It also involves giving some Intravenous contrast and a small radiation exposure risk to patients. Standard CTC will result in radiation doses of 10–12 mSv, while smaller series operating 4-slice scanners with low-dose protocols have reported effective doses of 2.1–7.8 mSv [103-105]. Apart from that, there is also a small risk of colonic perforation (0.005%-0.03%) with CTC related to the insertion and air insufflation of the intrarectal tube [106].

The accuracy of CTC for both CRC and large/advanced polyps has been shown to be similar to that of optical colonoscopy in symptomatic and asymptomatic patients [107]. In a meta-analysis by Pickhardt et al including 34 studies with a total of 41 680 participants, CTC sensitivity for detection of colorectal cancer was 93 % among older patients (>65 years) and 92 % among younger patients [108]. In a separate meta-analysis Pickhardt et al found significant extra-colonic findings of 5.2 % in a cohort with symptoms and of 2.8% in a cohort of patients without symptoms [109].

In a recent joint guideline update by European Society of Gastrointestinal Endoscopy (ESGE) and European Society of Gastrointestinal and Abdominal Radiology (ESGAR), CTC has been recommended as an acceptable and sensitive alternative to colonoscopy for patients complaining of alarm and non-alarm symptoms, an option for CRC screening, and following an incomplete or infeasible colonoscopy [110].

A major drawback to the widespread use of CTC is that most radiological departments would not have a specific CT scanner used solely for CTC. The CT scanners would also need to be used for other types of scans including for elective and emergent cases and hence only small numbers would be able to be performed in an acute hospital setting.

2.3.2 Colon Capsule Endoscopy (CCE)

Colon Capsule Endoscopy (CCE – PillCam Colon 2, Medtronic, USA) based on wireless technology has been shown not only to offer an alternative to colonoscopy but also has the potential to assess the whole digestive tract [111]. CCE is an office-based test that does not need to be done in a specialist endoscopy unit nor by a specialist endoscopist or even in a hospital setting. ESGE in 2012 has approved the use of CCE in average risk patients as a minimally-invasive option for colonic investigation [112]. The recent updated ESGE-ESGAR guidelines for use of CCE will be further explored in subchapter 2.3.3.

Similar to colonoscopy, CCE involves the patient modifying their diet and taking a purgative agent for bowel preparation. CCE involves the patient swallowing a vitamin-sized capsule with cameras on both ends (Image 3). Pre-procedure, patients are connected to a recorder belt that will be able to receive and store the wireless video captured by the capsule. Upon confirming the position of the capsule in the duodenum with a real-time viewer, patients are then given booster medications to help propel the capsule through the digestive tract. A complete exam is signified by the capsule being excreted from the rectum. Patients are then instructed to return the recorders for video downloading. The videos that are downloaded are then read by trained CCE readers. Unlike colonoscopy, patients do not need to be sedated for the procedure and may resume normal activities after taking their booster medications.

Regarding the potential risk of CCE, apart from taking bowel preparation and boosters, the risk is similar to other forms of capsule endoscopy. Wang et al reported in a recent meta-analysis that the rate of capsule retention, swallow disorder, aspiration, technical failure, and procedural adverse events were 0.73% (95% confidence interval [CI] 0.59–0.89%), 0.75% (95% CI 0.43–1.13%), 0.00% (95% CI 0.00–0.00%), 0.94% (95% CI 0.65–1.28%), 0.67% (95% CI 0.32–1.10%), respectively [113].



Image 3: Colon Capsule Endoscopy

Over the recent years, there has been increasing evidence in support of CCE which includes its use to detect both neoplastic and non-neoplastic disease in selected patient cohorts including Inflammatory Bowel Disease patient assessment, average, and low risk screening, after incomplete colonoscopy and for polyp surveillance [114-120].

A recent meta-analysis by Vuik et al involving 13 studies and 2485 patients, showed that CCE had a Polyp Detection Rate (PDR) of 24-74% in a mix of diagnostic and FIT based screening cohort [121]. They also found that the sensitivity and specificity of CCE for polyps > 6 mm was 79% - 96% and 66% - 97%, while for polyps $\geq$ 10 mm the sensitivity of CCE was 84% - 97% [121].

2.3.3 CCE VS CTC

There have been several recent studies comparing the effectiveness of CTC versus CCE. Utano et al compared 30 patients referred for Endoscopic Submucosal Dissection (ESD) for large polyps (>20mm) found initially on CCE with colonoscopy and CTC [122]. They found that CCE has a higher per patient [0.89 (24/27) by CCE and 0.70 (19/27) by CTC ($p = 0.02530$)] and per lesion sensitivities compared to CTC [0.87 (26/30) and 0.67 (20/30) respectively ($p = 0.0143$)] [122]. In a multicentre, prospective, randomised study comparing the diagnostic yield of CCE versus CTC in a screening population involving 286 patients, Cash et al found that CCE was superior to CTC in detecting polyps of ≥ 6 mm (diagnostic yield 31.6% vs 8.6%, sensitivity 79.2% vs 26.8%, and specificity of 96.3% vs 98.9%) and of ≥ 10 mm (diagnostic yield 13.5% vs 6.3%, sensitivity 85.7% vs 50%, and specificity of 98.2% vs 99.1%) [123]. In a FIT positive surveillance cohort, Pioche et al found the PDR of CCE to be superior to CTC, 60% vs. 28.6 [124]. Rondonotti et al found that in a cohort of 50 FIT positive

patients, the sensitivity, specificity, Positive Likelihood Ratio (PLR) and Negative Likelihood Ratio (NLR) between CCE and CTC to be comparable (88.2% vs 88.2% sensitivity, 87.8 vs 84.8% specificity, 3.75 vs 3.0 PLR , and 0.06 vs 0.07 NLR) but 78% preferred CCE to CTC [125]. Meanwhile, González-Suárez et al randomized between CTC and CCE in 349 FIT-positive patients and found that CCE compared to CTC had a higher sensitivity and NPV (98.1%, 92.0% for CCE vs 64.9%, 57.7% for CTC) but lower specificity and PPV (76.6%, 93.7% for CCE vs 95.7%,96.8% for CTC) [126]. They also found that CCE was superior to CTC (100% vs. 93.1%) for the detection of advanced adenomas (AA) and for the detection of any neoplastic lesion (AL) (CCE 100% vs. CTC 81%) [126]. A summary of this findings can be found in Table 7.

Study	Patient Population	Findings CCE	Findings CTC	Conclusion
Utano et al [122]	30 patients referred for ESD found on CCE	Per patient sensitivity = 89%	Per patient sensitivity = 70%	Favours CCE
		Per lesion sensitivity = 87%	Per lesion sensitivity = 67%	
Cash et al [123]	286 patients randomized to CCE vs CTC	Polyps $\geq 6\text{mm}$ = 31.6%	Polyps $\geq 6\text{mm}$ = 8.6%	Favours CCE
		Polyps $\geq 10\text{mm}$ = 13.5%	Polyps $\geq 10\text{mm}$ = 6.3%	
		Sensitivity polyp $\geq 6\text{mm}$ = 79.2%	Sensitivity polyp $\geq 6\text{mm}$ = 26.8%	
		Specificity polyp $\geq 6\text{mm}$ = 96.3%	Specificity polyp $\geq 6\text{mm}$ = 98.9%	
		Sensitivity polyp $\geq 10\text{mm}$ = 85.7%	Sensitivity polyp $\geq 10\text{mm}$ = 50%	
		Specificity polyp $\geq 10\text{mm}$ = 98.2%	Specificity polyp $\geq 10\text{mm}$ = 99.1%	
Pioche et al [124]	378 positive gFOBT patients who refused colonoscopy	PDR = 60%	PDR = 28.6%	PDR favours CCE (p=0.04)

	offered between CCE vs CTC (19 CCE vs 29 CTC)			
Rondonotti [125]	50 FIT positive patients had both CCE and CTC	Sensitivity = 82 %	Sensitivity = 82 %	Both modalities effective but patient prefers CCE
		Specificity= 87.8%	Specificity= 84.8	
		PLR = 3.75	PLR = 3.0	
		NLR = 0.06	NLR = 0.07	
		Preference = 78%	Preference = 22%	
González-Suárez [126]	209 FIT positive patients randomly allocated, 147 CCE 143 CTC	Sensitivity = 98.1%	Sensitivity = 64.9%	Favours CCE
		Specificity = 76.6%	Specificity = 95.7%	
		PPV = 93.7%	PPV = 96.8%	
		NPV = 92.0%	NPV = 57.7%	
		AA detection = 100%	AA detection = 93.1%	
		AL detection = 98.6%	AL detection = 81.0%	

Table 7: Comparison between CCE and CTC

Despite available evidence favouring CCE to CTC, the most recent ESGE-ESGAR guidelines [110] still favours CTC over CCE. CCE has not been recommended as a method of investigation for patients with alarm symptoms but may be considered with patients with no alarm symptoms. CTC has been recommended for both subgroups. CTC has also been recommended over CCE as an option for CRC population screening, and in FIT positive patients with an incomplete or unfeasible colonoscopy [110]. The main reason for these recommendations was the smaller population sizes in available CCE studies compared to CTC.

Similarly, the American Gastroenterological Association (AGA) in their position statement in 2017 has recommended against the routine substitution of colonoscopy with CCE apart from in the subgroup of patients who are unwilling to undergo colonoscopy [127].

The American Society of Gastrointestinal Endoscopy (ASGE) Technology Committee has recently published an update on use of CCE where they concluded that CCE, for the detection of colorectal neoplasia, has acceptable performance characteristics and is an emerging screening modality for those unable or unwilling to consider colonoscopy for screening [128]. Potential hurdles cited in this guideline to wider adoption of CCE would include the extra bowel preparation that patients need to take, capsule transit time and capsule excretion rate. Currently, the most optimal bowel preparation that would lead to an excellent bowel cleansing, capsule excretion rate, patient acceptance and tolerability is still under investigation. There have also been few, if any, patient preference studies between colonoscopy and CCE in the symptomatic cohort. We will try to explore these two issues in our thesis in the following chapters.

Despite these recommendations, interest in an expanded role for CCE remains. Mainly because of the significant potential advantages of CCE including being an office-based test thereby providing true additional non-hospital-based capacity combined with accuracy and a good safety profile. Providing an outpatient, community based service is also key part of Sláintecare, a 10-year cross party initiative to improve healthcare in Ireland which will be further explored in chapter 3 [129].

We hope to explore all these issues presented in this chapter within this thesis. As outlined in Chapter 1, our thesis will continue with Chapter 3, assessing symptoms and symptoms-based triaging for diagnosis of clinically significant disease. We then continue with describing the role of biomarkers in different GI diseases in Chapter 4. In Chapter 5, we will be looking at the use of CCE with and without biomarkers in the diagnosis of patients complaining of lower GI symptoms. In this chapter we will also look at patient reported satisfaction, comfort, and preference between CCE and colonoscopy, and the effect of different bowel preparation and booster regimens in the quality of CCE. In Chapter 6 we will describe the effect of the Covid-19 pandemic on endoscopy waiting list and how CCE may offer a solution to deal with the increasing wait list. Finally, chapter 7 will conclude our thesis and make further recommendations regarding potential studies to be conducted in the future.

Chapter 3: Lower Gastrointestinal Symptoms and Symptoms-Based Triaging Systems are Poor Predictors of Clinically Significant Disease on Colonoscopy

This chapter has been presented at the United European Gastroenterology Week 2018 meeting in Vienna, Austria. It has also been published in *BMJ Open Gastroenterol.* 2020; 7(1): e000221 [1].

Introduction

Over 10% of presentations to general practitioners (GP) are for gastrointestinal (GI) complaints; while most of these are dealt with by GPs many would require a referral to gastroenterology services [9]. Traditionally when patients present with lower GI symptoms, including change in bowel habit (diarrhoea, constipation, or alternating symptoms), bloating, abdominal pain, bleeding per rectum (PR) or anaemia) they are seen by a gastroenterologist in an outpatient clinic, where a clinical history, physical examination and routine blood tests are often performed. For a majority of patients as part of the subsequent workup, based on initial assessment, they are then triaged to either a routine or urgent appointment for a colonoscopy before arriving at a specific diagnosis. More recently, a significant proportion of patients referred by their GPs are sent directly for endoscopy procedures [11]. Patients on this open/direct access endoscopy pathway are also normally triaged based on their symptomology and demographics.

Previous studies have suggested that a combined clinical history and physical exam is a poor tool to predict clinically significant disease (CSD), defined as colorectal cancer (CRC), high-risk adenoma (HRA) and inflammatory bowel disease (IBD) [130]. More recently, systems have been developed to improve patient triage, thereby identifying patients for early investigations, and minimising unnecessary procedures. Including the National Institute for Health and Care Excellence (NICE) guidelines, which triages patients based on symptoms and age for a diagnosis of CRC and IBD [46, 131]. Although some symptoms employed are more specific, for example, unprovoked PR bleeding in someone over 50 years of age and the presence of a mass on examination for the diagnosis of CRC, others are vaguer, which includes a change in bowel habit in patients above 60 years old for possible CRC and ongoing symptoms of bloating longer than 6 weeks period for a potential diagnosis of IBD.

Different triaging systems used worldwide have been also described in subchapter 2.1.1.

The use of serum and stool biomarkers have been increasing in the past number of years to assess a wide variety of GI diseases. This ranges from the use of faecal immunochemical test (FIT) in population screening for bowel cancer to the use of faecal calprotectin (FC) to help assess disease activity in patients with IBD [80, 85, 132]. Data on their efficacy in symptomatic patient stratification are limited, still under investigation and has been described in subchapter 2.2.3 with a summary given in Table 6. Further studies are required to set a universal cut-off for CSD. As such, symptom-based triaging remains the standard of care in clinical practice.

Colonoscopy is considered the gold-standard test to assess for bowel disease. It is performed in a dedicated fully-staffed endoscopy unit. Even though colonoscopy is usually well tolerated, it does come with its own limitations including potential complications which include bleeding and bowel perforation, and patients perceived inconvenience, discomfort, or embarrassment [12, 13]. Currently the need for colonoscopy far exceeds our ability to perform them, resulting in prolonged waiting lists and unfortunately in some cases delays in diagnosis and treatment. Based on national waiting-list data, there are a total of 54 625 patients awaiting endoscopy in Ireland by end of February 2018 and specifically in our hospital, 4591 patients are on a waiting list [133]. Similar problems have been encountered nationally and internationally in other centres. More up-to-date national data will be presented in subchapter 6.1.

Due to limited resources, better means of patient selection and triage are badly needed, as current symptoms-based recommendation is unsustainable, results in prolonged waiting lists, and may lead to catastrophic delays in diagnosis.

We would like to draw attention to the tragic case of SL that happened between 2005-2007, a then 40-year-old lady from Kilkenny, who had presented to her GP in 2005 with symptoms of diarrhoea and occasional PR bleeding [134, 135]. Due to her symptoms, SL's GP referred her on for a colonoscopy which unfortunately due to prolonged public waiting list only occurred after 7 months despite her worsening alarm symptoms [135]. On her colonoscopy SL was diagnosed with CRC, underwent surgery and at a subsequent PET scan, lung metastases was diagnosed [135]. SL then had chemotherapy and in one of her sessions, she had discovered that another patient, who had private insurance, had been diagnosed with CRC within 3 days of being referred and was going to recover

[134]. In her letter and following interview with a national radio station, SL highlighted the two-tier discrepancy between public and private care in Ireland at that time, garnering national and political interest and ultimately allocation of more resources to the public system [134, 135]. Sadly, SL succumbed to her illness on 12th October, 2007 leaving behind 2 teenage children and her husband [134].

Although since SL's case, the situation in the Irish public health system has significantly improved, there are still further rooms for improvements. As we will outline in subchapter 6.1, the Covid-19 pandemic has made the waiting list for endoscopy procedures longer, which will possibly cause cases like SL to re-occur. Hence, we will try to explore in this chapter and the following chapters, possible ways to deal with triaging colonoscopy for patients complaining of lower GI symptoms to prioritise referrals and how to possibly reduce the burden on the endoscopy departments.

Aim

The aim of this study was to assess within an unselected group of patients how symptoms correlate with findings of CSD on colonoscopy and to evaluate whether using a high-risk triaging system (NICE guidelines) improves prediction and detection of CRC and IBD in our cohort of patients.

Method

Study design

A retrospective observational study based on our endoscopy records of an unselected symptomatic cohort referred for colonoscopy, over a 2-year period (2015–2016). Endoscopy reports were obtained from Unisoft Endoscopy reporting database. We recorded patients' symptoms prompting the colonoscopy and also the findings of the colonoscopy. We excluded patients with known IBD (either disease surveillance or assessment), patients for polyp surveillance, CRC surveillance, screening colonoscopy for a family history of CRC and a prior colonoscopy within 5 years. We also documented patients' demographic details. We defined CSD as CRC, inflammation (either IBD, microscopic colitis or indeterminate inflammation), (HRA—where one adenoma is larger than 10 mm, the presence of more than three adenomas or adenomas with high-grade dysplasia [136]) and presence of angiodysplasia.

Based on patients symptomology and demographic details, patients were then categorised into high-risk and low-risk groups based on the NICE guidelines for CRC and IBD [46, 131].

We did not discriminate based on source of referral, either from primary or secondary care. All referrals to our endoscopy service are triaged by consultant gastroenterologists using appropriate guidelines. The criteria used by our gastroenterologists are widely available and are already in use in general practice. Our study included all patients irrespective of urgency of referral.

Analysis

Data analysis was performed using MedCalc (MedCalc Software Ltd, Belgium). We calculated the overall diagnostic yield and OR of all symptoms. We also calculated the diagnostic yield and OR based on NICE guideline positivity in terms of diagnosing IBD and CRC. A $p < 0.05$ was considered to be statistically significant.

Results

Study population

In total, 1116 patients were identified who underwent a colonoscopy for symptomatic assessment during our study period. Of this, 493 (44%) were male and mean age is 54.3 years (range 16–91). Indications included were abdominal pain in 104 (9.3%) patients, diarrhoea in 188 (16.8%), weight loss in 37 (3.3%), constipation in 57 (5.1%), anaemia in 212 (19%), alternating constipation with diarrhoea in 79 (7%), PR bleeding in 148 (13.3%) and others 291 (26%). In terms of quality indicators for colonoscopy, based on our local data and audit, the caecal intubation rate in our centre is 95.3% and adenoma detection rate is 12% in the symptomatic cohort over this time period.

CSD occurred in only 162 (14.5%) of our cohort; CRC in 19 (1.7%), HRA in 40 (3.6%), inflammation in 97 (8.7%) (IBD in 65 (5.8%), microscopic colitis in 9 (0.8%) and indeterminate inflammation in 23 (2%)), and angiodysplasia in 6 (0.5%).

Diagnostic yield and symptoms

With regard to the predictive value of symptoms for CSD, diarrhoea gave the highest diagnostic yield of 5.3% (n=59/1116); (OR 3.15, 95% CI 2.2 to 4.47, p<0.001), similarly PR bleeding also had a reasonable diagnostic yield of 2.9% (n=32/1116); (OR 1.9, 95% CI 1.24 to 2.9, p=0.003). Conversely weight loss and constipation gave the lowest diagnostic yields overall of 0.4% (n=4/1116); (OR 0.79, 95% CI 0.28 to 2.24, p=0.65) and 0.4% (n=5/1116); (OR 0.57, 95% CI 0.22 to 1.44, p=0.12), respectively, and did not correlate with significant disease. The breakdown of diagnostic yield by symptom are given in Table 8.

Symptoms (total)	Findings	No (%)	Diagnostic yield	OR (95% CI, p value)
Diarrhoea (total=188)	CRC	5 (3)	5.3% (n=59/1116)	3.15 (2.22 to 4.47, p<0.0001)
	HRA	7 (4)		
	Angiodysplasia	2 (1)		
	Inflammation— IBD	31 (16)		
	Inflammation— Microscopic Colitis	7 (4)		
	Inflammation— non-specific	7 (4)		
	Negative	129 (69)		
PR bleeding (total=148)	CRC	9 (6)	2.9% (n=32/1116)	1.9 (1.24 to 2.9, p=0.003)
	HRA	12 (8)		
	Inflammation— IBD	6 (4)		
	Inflammation— microscopic colitis	1 (1)		
	Inflammation— non-specific	3 (2)		
	Angiodysplasia	1 (1)		
	Negative	116(79)		

Anaemia (total=212)	CRC	4 (2)	2.2% (n=25/1116)	0.83 (0.53 to 1.29, p=0.4)
	HRA	12 (6)		
	Inflammation— IBD	5 (2)		
	Inflammation— non-specific	2 (1)		
	Angiodysplasia	2 (1)		
	Negative	187 (88)		
Weight loss (total=37)	HRA	3 (8)	0.4% (n=4/1116)	0.79 (0.28 to 2.24, p= 0.65)
	Inflammation— IBD	1 (3)		
	Negative	35 (94)		
Constipation (total=57)	HRA	2 (4)	0.4% (n=5/1116)	0.57 (0.22 to 1.45, p=0.12)
	Inflammation— IBD	1 (2)		
	Angiodysplasia	1 (2)		
	Negative	53 (93)		
Alternating constipation and diarrhoea (total=79)	CRC	1 (1)	1% (n= 12/1116)	1.23 (0.65 to 2.33, p=0.52)
	HRA	2 (3)		
	Inflammation— IBD	6 (8)		
	Inflammation— microscopic colitis	1 (1)		
	Inflammation— non-specific	2 (3)		
	Negative	67 (85)		
Abdominal pain (total=104)	CRC	1 (1)	0.8% (n=9/1116)	0.7 (0.37 to 1.33, p=0.28)
	HRA	1 (1)		
	Inflammation— IBD	4 (4)		
	Inflammation— non-specific	3 (3)		
	Negative	95 (91)		

Table 8: Clinically significant disease frequency based on predominant symptom/indications

In all, when looking at the break down of individual symptoms and the risk of CSD, of all patients with diarrhoea as their predominant symptom CRC occurred in 5 (3%) cases, inflammation in 45 (38%) cases (IBD in 31 (16%), microscopic colitis in 7 (4%), indeterminate inflammation in 7 (4%)), HRA in 6 (3%) angiodysplasia in 2 (1%) and 144 (78%) patients had a normal colonoscopy. For PR bleeding as the predominant symptom, CRC was diagnosed in 9 (6%) cases, HRA in 10 (7%), IBD in 10 (7%), microscopic colitis in 1 (1%), angiodysplasia in 1 (1%), indeterminate inflammation in 3 (2%) and 114 (79%) patients had a normal colonoscopy. While in anaemic patients, CRC was diagnosed in 4 (2%) cases, HRA in 12 (6%), IBD in 5 (2%), angiodysplasia in 2 (1%), indeterminate inflammation in 2 (1%) and negative in 187 (88%). Further breakdown is given in Table 8.

When looking at the likelihood of finding CSD based on each symptom, as expected, the symptom of diarrhoea was strongly associated with a diagnosis of IBD compared with other symptoms (diarrhoea alone—OR 2.22, 95% CI 1.25 to 4.4, $p=0.007$ and any diarrhoea (including symptom of alternating diarrhoea with constipation) OR 2.08, 95% CI 1.14 to 3.84, $p=0.01$). Meanwhile the symptom of PR bleeding was strongly associated with a diagnosis of CRC compared with other symptoms (OR 3.9, 95% CI 1.54 to 9.7, $p=0.005$). The symptom of anaemia was not statistically associated with a diagnosis of CRC or IBD compared with other symptoms (OR 1.17, $p=0.49$ and OR 0.33, $p=0.02$).

For the cohort with CSD, a similar pattern was identified. In addition, anaemia was the most common indication in patients with HRA (30%). Further breakdown can be seen in Table 9.

CSD	Indications (%)	Total (%)
CRC	PR bleeding – 9 (47)	19 (1.7)
	Diarrhoea— 5 (26)	
	Anaemia—4 (21)	
	Abdominal pain—1 (5)	
HRA	Anaemia—12 (30)	40 (3.6)
	PR bleeding—12 (30)	
	Diarrhoea—7 (18)	
	Weight loss—3 (8)	

	Constipation—2 (5)	
	Alt. constipation w diarrhoea—2 (5)	
	Abdominal pain—1 (3)	
	Others—1 (3)	
Inflammation— IBD	Diarrhoea—31 (48)	65 (5.8)
	PR bleeding—6 (9)	
	Alt constipation and diarrhoea—6 (9)	
	Anaemia—5 (8)	
	Abdominal pain—4 (6)	
	Weight loss—1 (2)	
	Constipation—1 (2)	
	Other—11 (17)	
Inflammation— microscopic colitis	Diarrhoea—7	9 (0.8)
	PR bleeding—1	
	Alt. constipation with diarrhoea—1	
Vascular— angiodysplasia	Diarrhoea—2	6 (0.5)
	Anaemia—2	
	PR bleeding—1	
	Constipation—1	

Table 9: Symptoms frequency according to CSD

Impact of NICE guidelines

Based on patients' symptoms and demographics, 592 (53%) patients fitted the criteria for urgent referral for CRC and 517 (46%) for IBD based on the NICE guidelines. Only 19% (217) of our total patient cohort fitted neither criterion nor would not have needed an urgent colonoscopy.

For patients meeting NICE criteria for CRC, the diagnostic yield for CRC was 3% (n=17/592) and the diagnostic yield for those not meeting the criteria was 0.4% (n=2/524). Fitting the criteria for CRC statistically increased the diagnostic yield compared with not fitting the criteria (OR 7.71, 95% CI 1.77 to 33.56, p=0.0064). For patients meeting the NICE criteria for IBD, the diagnostic yield was 9% (n=48/517) and the diagnostic yield for those not meeting the criteria was 2.8% (n=17/599). Fitting

the criteria for IBD also statically increased the diagnostic yield compared with not using the criteria (OR 3.5, 95% CI 1.99 to 6.17, $p<0.0001$).

Although the diagnostic yield remained low, applying NICE criteria did increase the diagnostic yield from baseline; 1.7% ($n=19/1116$) to 3% ($n=17/592$) for CRC and from 5.8% ($n=65/1116$) to 9% ($n=48/517$) for IBD.

Being any NICE criteria positive versus any NICE negative gave an overall diagnostic yield for any CSD of 15% ($n=133/889$) vs 13% ($n=28/217$). If we were to consider being NICE positive as high risk, having a high-risk criterion does not statistically correlate with CSD (OR 1.44, 95% CI 0.919 to 2.278, $p=0.11$) Table 10.

	Diagnostic yield of CRC	Diagnostic yield of IBD	Overall diagnostic yield	OR
CRC NICE criteria positive ($n=592$)	3% ($n=17$)	n/a	n/a	7.71 (95% CI 1.77 to 33.56, $p=0.0064$)
CRC NICE criteria negative ($n=524$)	0.4% ($n=2$)	n/a	n/a	
IBD NICE criteria positive ($n=517$)	n/a	9% ($n=48$)	n/a	3.5 (95% CI 1.99 to 6.17, $p<0.0001$)
IBD NICE criteria negative	n/a	2.8% ($n=17$)	n/a	
CRC +IBD NICE criteria positive ($n=899$)	n/a	n/a	15% ($n=133$)	1.44 (95% CI 0.919 to 2.278, $p=0.11$)
CRC +IBD NICE criteria negative ($n=217$)	n/a	n/a	13% ($n=28$)	

Table 10: Impact of NICE guidelines

Figure 1 shown below will summarise findings presented in this study including patient demographics, indications for referral for colonoscopy, diagnostic yield for CSD, effect of NICE guidelines and diagnostic yield based on symptoms.

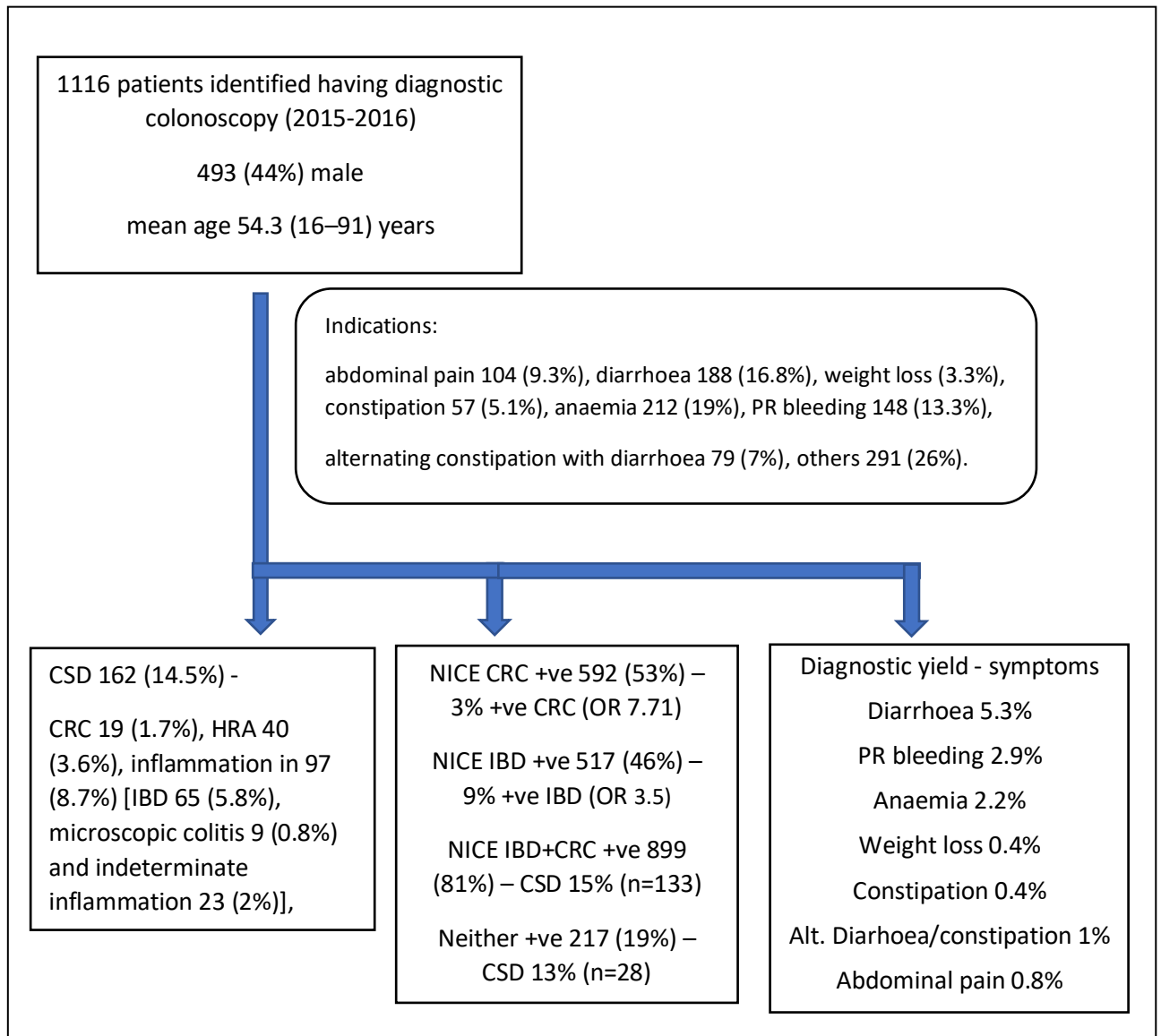


Figure 1: Flowchart of demographics, symptoms and diagnostic yield, and NICE positivity

Discussion

The results of our study suggest that symptoms remain a poor determinant of significant bowel disease on colonoscopy. The diagnostic yield for CSD was only 14.5% in our symptomatic patient cohort. While there are established optimum detection rates for screening colonoscopies, the same

cannot be said for the symptomatic cohort. More studies are needed to establish an optimum detection rate. Diarrhoea was the best indication for colonoscopy with a diagnostic yield of 5.3% (n=59/1116) and an OR of 3.15 followed closely by PR bleeding with a diagnostic yield of 2.9% (n=32/1116) and OR of 1.9. While using NICE guidelines for CRC and IBD improved diagnosis for each disease, overall diagnostic yield remained low, 3% vs 0.4% in CRC with (OR 7.71) and 9% vs 2.8% in IBD (OR 3.5). In agreement with our findings, NICE reported a PPV of 3% for CRC criteria positive patients [131].

While most physicians agree that a 'negative test' is often helpful to exclude CSD, the purpose of this study was not to prevent patients having a procedure but to better identify at risk patients requiring urgent referrals. We do not feel that colonoscopy is the most ideal negative test for reassurance based on its restrictions. Other potential candidates include faecal biomarkers (FIT and FC), CT Colon and Colon capsule endoscopy, all of which are considered minimally-invasive compared with colonoscopy and maybe a better means for excluding CSD. As mentioned in chapter 2, while there are clear guidelines from the European Society of Gastrointestinal Endoscopy on the use of colon capsule endoscopy [112] as a diagnostic test for bowel disease, the role of biomarkers are less clear and warrants further investigations.

Our findings are similar to previous papers published by Selinger et al [137] who found that colonic investigations will not explain isolated abdominal pain in 92% of patients. In addition Mowat et al [97], used a combination of symptoms and stool biomarkers to detect CSD. The diagnostic yield of symptoms in Mowat's cohort is quite similar to ours at 14%. In addition, their biomarker results would indicate that the absence of occult blood in the stool could potentially exclude significant disease. The use of FIT as a population screening for bowel cancer has been widely adopted internationally [80]. Different FIT cut-off's have been suggested for cancer screening, in some countries going as high as 250 µg/g [82, 138-140]. It is interesting that in Mowat's study [97], they identified three patients with a FIT of less than 10 µg/g who had CRC, suggesting further studies are needed to set a cut-off point in the symptomatic patients.

While there is evidence that FC is helpful to assess for IBD activity [132], its use for the screening of symptomatic patients for IBD is less clear and the limited data available suggests that it is less effective especially for borderline results (50–150 µg/g) [141]. Mowat et al found, using a cut-off of

50 µg/g, the PPV for any CSD was only 16.9% and 6.4% for IBD [97]. However, the role of combined biomarkers may be an effective approach in the future.

While our study is based in secondary care, all referrals were vetted by a consultant gastroenterologist using standard criteria. In addition, all referrals to the gastroenterology OPD are also vetted and referred directly to colonoscopy if needed. These criteria are employed widely in primary care as well and currently remain the best way to triage patients. Based on the evidence to date, we feel that there is a clear need for a more holistic method of predicting which patients presenting with lower GI symptoms would require further investigation by means of a colonoscopy. We have clearly demonstrated in our large retrospective study that symptoms alone are poor at doing this. Despite using high-risk criteria such as the NICE guidelines, the diagnostic yield remains low. In the future, a combination of all traditional tools, that is, symptomology, physical examination, and blood parameters with more novel methods of diagnosis including stool biomarkers (FIT and FC) and minimally invasive endoscopy (Colon capsule endoscopy or CT Colonoscopy) may be used to improve patient selection; improving access to colonoscopy while avoiding adverse events and warrants further investigations.

In the introduction section of this chapter, we have highlighted the case of SL [134, 135], who had a delayed diagnosis of CRC due to prolonged waiting list and discrepancies between the public and private health care in Ireland. Sláintecare is a 10-year cross-political-party initiative developed in 2017 to reform the health system in Ireland and potentially develop a universal, single-tier healthcare system [129]. There is a big emphasis in Sláintecare to move services from their current hospital-based settings to a more primary and community-based setting, emphasizing on an integrated care approach [129]. The use of faecal biomarkers in the primary care referrals, like the case of Mowat et al [97], would be in keeping with the principles of Sláintecare. We will explore the use of biomarkers in the following chapters. CCE also has the potential to be outsourced from a hospital setting to a community-based setting in line with Sláintecare, but this needs to be further studied and cost benefit analyses need to be performed to determine its feasibility.

Conclusion

Our study clearly shows that symptoms alone remain a poor predictor of CSD on colonoscopy, although it still remains the most common method to triage referrals. A more holistic and novel

approach needs to be studied and formulated using a combination of symptoms, blood and stool biomarkers and potentially minimally invasive colonoscopy in order to reduce the need for a 'negative' colonoscopy which would hopefully improve access, reduce waiting times, and avoid unnecessary adverse events.

Chapter 4: The use of biomarkers in different GI diseases

4.1 The utility of faecal and urine biomarkers for small bowel diseases

This subchapter has been published as a review article in Curr Opin Gastroenterol. 2021 May 1;37(3):284-294. doi: 10.1097/MOG.0000000000000730. PMID: 33769381. The utility of faecal and urine biomarkers for small bowel diseases. Ismail MS, Semenov S, McNamara D [2].

Purpose of review

Small bowel diseases pose a unique diagnostic and management challenge and often requires tertiary specialist referral. The use of biomarkers may provide a cheap, non-invasive tool to assess the small bowel in terms of diagnosis, offering a better way to triage referrals and select patients for early management. This review looks at the most recent evidence behind the use of several faecal and urine biomarkers for small bowel diseases.

Recent findings

Faecal calprotectin shows the most promise, with evidence to support its role in predicting relapse post-surgery and monitoring treatment response in patients with Crohn's disease. A faecal calprotectin less than 50mg/g may also be used as a cut-off to triage further investigation. Faecal lactoferrin also appears promising as a marker of small bowel inflammation. A positive faecal immunochemical test pre-capsule may help to prioritize referrals for obscure bleeding.

Summary

The use of biomarkers in the diagnosis and management of small bowel disease is still controversial and remains unclear. More studies are required to further develop their potential and before societal guidelines can be developed to direct their appropriate use in clinical practice.

INTRODUCTION

Diseases of the small bowel poses a unique diagnostic and management challenge to gastroenterologists. The European Society of Gastrointestinal Endoscopy, American Society of

Gastrointestinal Endoscopy and American Gastroenterological Association recommends the use of small bowel capsule endoscopy (SBCE) and device-assisted-enteroscopy to assess for small bowel disease [127, 142-144]. With most gastroenterologist and endoscopists being proficient at Oesophago-Gastro-Duodenoscopy and colonoscopies, endoscopy of the small bowel is considered a subspeciality and access to this service at a tertiary level may not be freely available. There is also a need to develop screening pathways as the demand for small bowel investigation increases.

The use of biomarkers may provide a cheap, non-invasive tool to assess the small bowel in terms of diagnosis, offering a better way to triage referrals and select patients for early management. At present, no gastrointestinal societal guidelines exist in terms of the use of faecal and urine biomarkers in small bowel diseases.

The current review article aims to assess the use of several commercially available faecal and urine biomarkers in small bowel diseases.

FAECAL CALPROTECTIN

Faecal calprotectin is a calcium and zinc binding neutrophil cytosolic protein with a wide array of functions, including antibacterial and antifungal defence, regulation of neutrophil and monocyte chemotaxis and induction of apoptosis [84]. The detection of faecal calprotectin in stool reflects neutrophil cellular degranulation during an inflammatory response and faecal calprotectin concentrations strongly correlate with the migration of ¹¹¹-indium-radiolabeled granulocytes through the gut wall [84, 85]. Faecal calprotectin is stable at room temperature for up to 7 days and can be accurately measured by using a laboratory-based ELISA or by point-of-care rapid detection assays [85-88]. This point of care test uses quantitative immunochromatographic or quantitative enzyme immunoassays and studies have found that some test kits (Quantum Blue Calprotectin kit [BÜHLMANN Laboratories, Basel, Switzerland], EliA Calprotectin [Phadia AB, Uppsala, Sweden], RIDASCREEN Calprotectin kit [R-Biopharm AG, Darmstadt, Germany]) to be comparable with a lab-based ELISA [87, 89].

The role of faecal calprotectin in diagnosing and managing small bowel diseases is controversial. Being a marker of inflammation, it's most probable use it to distinguish between organic versus

nonorganic bowel disease. von Roon et al. [145] in their meta-analysis of 30 studies involving 5983 patients found that the faecal calprotectin levels in inflammatory bowel disease (IBD) patients were higher by 219.2 mg/g compared with normal patients ($P < 0.001$). They have also found that the overall area under the curve (AUC) in distinguishing patients with Crohn's disease from patients with irritable bowel syndrome (IBS) and healthy control patients at a cut-off value of 50mg/g was 0.97 [standard error 0.01, diagnostic odds ratio (DOR) 129.00, 95% confidence interval (CI) 44.12–377.18] [145].

Faecal calprotectin as a diagnostic tool

When considering the use of faecal calprotectin as a diagnostic tool, several factors need to be considered, pre-test probability, differences in levels of faecal calprotectin in different age groups, differences in cut-off values. The interpretation of faecal calprotectin in diagnosing Crohn's disease is dependent on the pre-test probability, where Conroy et al. [146] evaluated 410 patients referred by their primary care physicians undergoing faecal calprotectin testing; 148 patients (36.1%) had faecal calprotectin more than 50mg/g of which less than 20% of colonoscopies were abnormal and only three patients were confirmed to have Crohn's disease. This study concludes that faecal calprotectin measurements without having a high enough pre-test probability has low positive predictive value (PPV), sensitivity and specificity for diagnosing Crohn's disease [146]. The differences in normal values of faecal calprotectin between age groups has been reported in several studies, suggesting a higher value of faecal calprotectin of around 100 mg/g as a normal reference range in healthy individuals over 60 and also in the paediatric population [147, 148]. Lastly, the difference of setting a cut-off value of a normal faecal calprotectin has huge impacts on determining who should be referred for investigation. Setting a higher threshold will probably increase the number accurately diagnosed with Crohn's disease but with a greater risk of some cases being missed. Alternatively setting a lower threshold will increase the negative predictive value (NPV) but may result in more unnecessary colonoscopies [149, 150].

Faecal calprotectin in small bowel versus colonic disease

When comparing Crohn's disease between colonic and small bowel disease, further conflicting data have been reported. In a systemic review by Simon et al. of an initial 5619 studies where a final total of eight studies were included, sensitivities of faecal calprotectin at small bowel and large bowel locations ranged from 42.9 to 100% and 66.7 to 100% respectively while corresponding specificities

were 50 to 100% and 28.6 to 100% respectively. They suggested that faecal calprotectin measurements in Crohn's disease at different disease locations were too diverse and that no firm conclusion can be made regarding normal or abnormal values by disease site [151].

Most isolated small bowel studies use a cut-off point off of 50mg/g to indicate inflammation and a positive result. Considerable variability has been observed among different cohorts of patients using the cut-off of 50mg/g, with sensitivity, specificity, PPV and NPV ranging from 59 to 88.9%, 23 to 71%, 14.3 to 56% and 83 to 94.1%, respectively [152-154]. Furthermore, Kopylov et al. [153] has suggested that with a faecal calprotectin less than 50mg/g, the likelihood of a positive diagnosis is very low. A systemic review by Vernia et al. [155] suggests that faecal calprotectin less than 50mg/g may prove useful for avoiding unnecessary SBCE procedures with many studies reporting low sensitivity in detecting or confirming active small bowel Crohn's disease.

In summary, based on evidence provided above, the use of faecal calprotectin in diagnosis of small bowel Crohn's disease is still controversial but a faecal calprotectin level of less than 50mg/g may be used as a cut-off to triage the need for further small bowel investigations.

Faecal calprotectin in monitoring Crohn's disease activity

When using faecal calprotectin to monitor disease activity, the role of faecal calprotectin may be better utilized [84, 156]. Most endoscopic scores including the simple endoscopic score for Crohn's disease (SES-CD) assess the colon as well as the small bowel when calculating the severity of Crohn's disease. When comparing faecal calprotectin with SBCE scores, Koulaouzidis et al. [157] concluded that faecal calprotectin does not really correlate with capsule Crohn's disease scores, with a moderate correlation only with the Lewis score and not with the Capsule Endoscopy Crohn's Disease Activity Index being reported ($r=0.448$, $P=0.0014$ versus $r=0.245$, $P=0.089$).

Most SBCE studies by their nature exclude patients with small bowel strictures due to the risk of capsule retention, representing a potential for bias. Of interest, in a small sample size of 20 patients, Matsuura et al. [158] performed small bowel evaluation by means of double balloon enteroscopy (DBE) and correlated this with faecal calprotectin in patients with small bowel Crohn's. Employing their specifically designed Double Balloon Endoscopic Score (DES-CD) to fully assess the small bowel,

they found a good correlation between their proposed DES-CD score with faecal calprotectin ($\gamma = 0.691$, $P=0.001$) and C-reactive protein (CRP) ($\gamma = 0.631$, $P=0.003$) levels [158]. Similarly, when assessing small bowel disease endoscopically with DBE, Iwamoto et al. [159] found that faecal calprotectin levels correlated with their proposed extended SES-CD ($r=0.607$, $P < 0.001$). They also found that for mucosal healing a cut-off value of 92 mg/kg, had a sensitivity of 87%, specificity of 88%, PPV of 96%, NPV value of 64% and AUC of 0.85 [159].

In a recent European multicentre observational study examining a newer panenteric Crohn's capsule (PillCam Crohn's) in 93 patients with known or suspected Crohn's disease, Tai et al. [160] found that a raised CRP and faecal calprotectin were both poor predictors of active disease (48 and 59%, respectively). This article found a faecal calprotectin value greater than 200 mg/kg had only a 59% sensitivity and 65% specificity in detecting active disease demonstrated on Crohn's capsule. PillCam Crohn's capsule is a novel technology that allows for visualization of both the small bowel and the colon in a single test. In a prospective multicentred study of 158 patients, Bruining et al. [161] found that the sensitivity of PillCam Crohn's was superior to magnetic resonance enterography (MRE) for enteric inflammation in the proximal small bowel (97 versus 71%, $P=0.021$), and similar to MRE and/or ileocolonoscopy in the terminal ileum and colon ($P=0.500-0.625$). There was however, one patient who developed bowel obstruction due to capsule retention at an ulcerated stricture.

Egea Valenzuela et al. [162] provides some explanation as to why faecal calprotectin may be falsely elevated in some patients with smoking, Non-Steroidal Anti-Inflammatory Drugs (NSAIDs) use and small intestinal bacterial overgrowth all identified as possible culprits.

Jones et al. [163] in a study assessing the correlation between faecal calprotectin and MRE using a receiver operating characteristic analysis showed an AUC of 0.77 (0.67–0.87, $P < 0.0001$), 69.3% (57.6– 79.5) sensitivity and 71.4% (53.7–85.4) specificity with an optimal faecal calprotectin cut-off of 145 mg/g for severe inflammation only on MRE. Details on milder disease was lacking.

In summary, when monitoring Crohn's disease activity, based on the evidence presented above, faecal calprotectin use is still controversial, with positive correlation reported with DBE and MRE but not Panenteric Capsule being reported.

FAECAL CALPROTECTIN IN ASSESSING TREATMENT RESPONSE

When assessing small bowel response to treatment specifically, the available data is limited. In one study, Dolinger et al. [164] found that faecal calprotectin correlated with improvement in small bowel ultrasound post induction with infliximab in 13 paediatric patients with Crohn's disease ($r=0.57$; $P=0.04$).

Several other studies carried out on a small series of Crohn's disease patients on a biologic agent using mainly ileocolonoscopy also support the concept that the measurement of faecal calprotectin (as well as faecal lactoferrin) may help to predict response to treatment at different time intervals, with Łykowska-Szuber et al. seeing correlation between faecal calprotectin and SES-CD, faecal calprotectin and Crohn's Disease Activity Index (CDAI) at all time intervals (before, 3 and 12 months post antitumour necrosis factor therapy) [165-167].

Our centre also looked at long-term response in 43 Crohn's disease patients with known small bowel disease treated with adalimumab using SBCE and found a significant median decrease in calprotectin from 195 (baseline) to 25mg/g (52-week assessment) ($P < 0.0224$ 95% CI 0.05–0.57) [168].

To summarize, although promising, more studies are needed to establish whether faecal calprotectin would be useful to assess long-term response to treatment and whether it correlates well with clinical, endoscopic, or radiological response.

FAECAL CALPROTECTIN IN PREDICTING RELAPSE

A recent systemic review and meta-analysis by Xiang et al. [169] of four studies in predicting relapse of small bowel Crohn's disease showed faecal calprotectin at a threshold of 100–140 mg/g had a pooled sensitivity of 0.68, specificity of 0.91 and AUC was 0.77 (95% CI: 0.73–0.81) at predicting relapse (relapsed defined either as a Lewis score > 135 , computed tomography enterography > 1 , SES-CD score 3 or Rutgeerts > 1). They did not comment on total number of patients included, disease duration, what treatment patients in their analysis were on or whether all patients were preop or postop Crohn's.

In a recent prospective study in 61 patients by Ben-Horin et al. [170] evaluating the use of clinical, biomarkers and SBCE in predicting relapse, they found that 17 (28%) patients had a flare during the 24-month follow-up. They also found that the AUC for faecal calprotectin to predict a flare occurring within 24 months was 0.62 (95% CI 0.49–0.74; $P=0.17$), but progressively increased in accuracy as the target time-to-flare was shortened, reaching 0.76 (0.70–0.81; $P < 0.0001$) within 6 months and 0.81 (0.76–0.85; $P < 0.0001$) within 3 months [170]. They also found that a Lewis score increase of 383 points or more from baseline on SBCE predicted imminent disease exacerbation within 6 months (AUC 0.79, 0.65–0.89; $P=0.011$). In their study, 10 (16%) patients had previous bowel resection and all flares were managed by intensification of medical therapy and none required surgery for Crohn’s disease during follow-up [170].

Tham et al. [171] performed a systemic review and meta-analysis of studies evaluating postoperative recurrence in Crohn’s disease which reported Rutgeert’s score and faecal calprotectin levels. They found that the optimal diagnostic accuracy was obtained for faecal calprotectin value of more than 150 mg/g, with a pooled sensitivity of 70% (95% CI 59–81%), specificity 69% (95% CI 61–77%), DOR of 5.92 (95% CI 2.61–12.17). They concluded that serial faecal calprotectin evaluations may eliminate or defer the need for colonoscopic evaluation in up to 70% of postoperative Crohn’s disease patients [37]. Their analysis unfortunately did not specifically mention what type of surgery their enrolled patients underwent.

In an abstract publication by Rowan et al. [172] on 15 Crohn’s disease patients with an ileostomy, they found no correlation between faecal calprotectin and endoscopic scores ($R=0.312$; $P=0.19$).

In summary, when assessing faecal calprotectin for relapse in Crohn’s disease, based on evidence above, at a higher cut-off of faecal calprotectin 150 mg/g, faecal calprotectin does appear to have some role in predicting post-surgery relapse but may not have any role in patients with an ileostomy. However, with limited data, further prospective validation studies will be required before any clinical recommendations could be made (Table 11).

Paper	Study Description	Accuracy
Diagnosis of small bowel Crohn’s disease		
Simon et al [151]	Systematic review	Sensitivities 42%-100%

	Any Small Bowel CD	Specificities 50%-100%
Hale et al [152]	SBCE diagnosis	Cut-off >50 µg/g Sensitivity 88.9% Specificity 25.0%
Kopylov et al [153]	Meta-analysis of 7 studies of small bowel diagnosis	Cut-off >50 µg/g Sensitivity 83% Specificity 53% Cut-off >100 µg/g Sensitivity 68% Specificity 71% Cut-off >100 µg/g Sensitivity 42% Specificity 94%
Egea-Valenzuela et al [154]	SBCE diagnosis	Cut-off >50µg/g Sensitivity 96% Specificity 23% Cut-off >100 µg/g Sensitivity: 96% Specificity: 23%
Monitoring CD activity		
Koulaouzidis et al [157]	Correlation with SBCE Lewis and CEDCAI Scores	Lewis r = 0.448, p = 0.0014 CEDCAI r = 0.245, p = 0.089
Matsuura et al [158]	Correlation with DBE (DES-CD)	$\gamma = 0.691$, p = 0.001
Iwamoto et al [159]	Correlation with DBE (eSES-CD)	r = 0.607, P < 0.001
Tai et al [160]	Panenteric Crohn's capsule and FC	Cut- off >200 mg/kg Sensitivity 59% Specificity 65%
Jones et al [163]	MRE and FC	Sensitivity 69% Specificity 71%
Treatment Response in CD		

Dolinger et al [164]	Correlation with Ultrasound	r=0.57; p=0.04
Łykowska-Szuber et al [167]	Correlation with Ileocolonoscopy , CDAI and SES-CD scores	0 months CDAI: r =0.431, p < 0.0001 SES-CD: r =0.420, p < 0.05 3 months CDAI: r =0.310, p < 0.05, SES-CD: r =0.420, p < 0.05 12 months CDAI: r =0.461, p < 0.0001 SES-CD: r =0.562, p < 0.0001
Hall et al [168]	Mucosal healing on SBCE	Ileitis FC Mean =195 µg/g Mucosal Healing FC Mean = 25 µg/g, p < 0.0224
CD Relapse post-surgery		
Xiang et al [169]	Systemic review and meta-analysis of 4 studies	Cut-off range 100-140 µg/g Pooled Sensitivity 68%, Pooled Specificity 91%
Tham et al [171]	Systemic review and meta-analysis – Ileocolonoscopy Rutgeert's score	Cut-off 150 µg/g Pooled sensitivity 70% Pooled specificity 69%

Table 11: Faecal Calprotectin as a biomarker in small bowel disease

FAECAL LACTOFERRIN

Lactoferrin is an iron-binding glycoprotein secreted from glandular epithelial cells and is a major component of inflammatory cells, mainly neutrophils, being part of its secondary granules [173]. Faecal lactoferrin can reflect neutrophil activity, being a specific and sensitive indicator of intestinal inflammation [174]. Faecal lactoferrin is resistant to proteolysis in faeces but is less stable than faecal calprotectin (2–5 versus 7 days for faecal calprotectin) [175, 176]. As with faecal calprotectin, faecal lactoferrin concentration quantification is usually done using an ELISA technique [177]. In a meta-analysis of 19 studies conducted by Mosli et al. [178] the pooled sensitivity and specificity for

endoscopically active IBD for faecal calprotectin were 88, 73% and for faecal lactoferrin were 82, 79%, respectively.

The role of faecal lactoferrin in small bowel disease is still under investigation with limited data available (Table 12).

Sipponen et al. [175] described a significant correlation between faecal lactoferrin and both SES-CD ($r=0.705$, $P < 0.001$) and histology for colonic or ileocolonic Crohn's disease ($r=0.543$, $P < 0.01$), but did not demonstrate an association with isolated ileal disease ($P=0.448$).

Further studies of faecal lactoferrin in small bowel disease include a retrospective study by Sorrentino and Nguyen [179] of 43 Crohn's disease patients, using a faecal lactoferrin cut-off of 7.24 mg/ml. They reported normal values in 28% preoperatively and 31.8% of patients postoperatively with positive SBCE findings.

In a prospective small bowel study by Bar-Gil Shitrit et al. [180] using faecal calprotectin (using cut-off of 95 mg/kg) and faecal lactoferrin (using cut-off of 1.05 mg/kg) to predict Crohn's disease (defined as >3 ulcers) on capsule endoscopy, the reported sensitivities, specificities, positive predictive and NPVs were similar; 77 and 73%, 60 and 65%, 50 and 50% and 84 and 84%, respectively.

While Sidhu et al. [181] found in another prospective study of 17 patients, faecal lactoferrin had a sensitivity, specificity, PPV and NPV of 71, 100, 100 and 83% for the diagnosis of small bowel Crohn's disease, detected by capsule endoscopy.

When assessing the accuracy of faecal lactoferrin in patients in clinical remission ($CDAI < 150$) from Crohn's disease, Aggarwal et al. [182] found that using the Capsule Endoscopy Scoring Index (CESI or Lewis score), of 26/43 (60%) patients with mucosal inflammation on SBCE, 85% had an elevated faecal calprotectin and 77% an elevated faecal lactoferrin. Suggesting both may have a role in detecting early disease relapse. In this study, CESI correlated significantly with both faecal calprotectin and faecal lactoferrin but not CDAI nor CRP [182].

While early data suggest faecal lactoferrin may be able to reflect small bowel inflammation, the available evidence is limited and cannot support its use in routine clinical practice.

Author	Study Description	Accuracy
Crohn's Disease Diagnosis		
Sipponen et al [175]	Correlation with Ileocolonoscopy with SES-CD	r=0,705, p <0.001
	Correlation with Ileocolonoscopy and histology	r=0.543 p <0,01
Sorrentino et [179]	Correlation with SBCE	Cut-off of 7.24 µg/ml false negative 28% preoperatively 32% post-operatively
Bar-Gil Shitrit et al [180]	SBCE	Cut-off of 1.05 mg/kg Sensitivity 73% Specificity 65%
Sidhu et al [181]	SBCE	Sensitivity 71% Specificity 100%

Table 12: Faecal Lactoferrin as a biomarker of small bowel disorders

GUAIAIC-BASED FAECAL OCCULT BLOOD AND FAECAL IMMUNOCHEMICAL TEST FOR HAEMOGLOBIN

Small bowel bleeding accounts for about 5–10% of gastrointestinal bleeding [142, 183, 184]. The use of SBCE to investigate obscure gastrointestinal bleeding is widely practiced [127, 142, 182]. Obscure gastrointestinal bleeding is usually defined as the presence of occult blood in the stool or persistent iron deficiency anaemia following a negative bidirectional endoscopy. Presence of occult blood in the stool is often demonstrated with guaiac-based faecal occult blood (gFOB) and faecal immunochemical test for haemoglobin (FIT).

Conventional FOB detects the presence of guaiac and pseudoperoxidase activity and is therefore not specific for human blood [79]. FIT for haemoglobin (Hb) is specific for intact human Hb and its early degradation products [80, 81]. There are two types of FIT available: qualitative (based upon

immunochromatography and providing a positive or negative result) or quantitative (based upon latex agglutination immunoturbidimetry and giving a numerical result for the faecal Hb concentration). Quantitative FITs have been recommended over qualitative FIT to remove reader variability, interbatch variability and to improve the diagnostic accuracy of the test [81, 185]. FIT has been used in national colorectal screening programs with different cut-offs values (15–67mg/g) [80, 82, 83]. Hb/haptoglobin (Hb/Hpt) complex testing is a variant of FIT that uses an immunoradiometric assay for the Hb/ Hpt complex; Hpt forms a soluble complex with Hb, which remains stable even following incubation with gastric juice and faecal extracts [186].

Faecal immunochemical test for detecting small bowel disease

FIT can help predict a small bowel bleeding source on capsule endoscopy. In a recent article, Judge et al. [187] performed a prospective study in 51 patients referred for SBCE to investigate anaemia or suspected small bowel bleeding and found that there was a statistically significant association between positive FIT (cut-off of 45mg Hb/g used) and disease on SBCE [OR 12, 95% CI (2.8–51.9), $P=0.001$], sensitivity 69% and specificity 84%.

In a systemic review and meta-analysis of six studies (four used FIT, one used FIT and gFOB, one used Hb/Hpt complex testing), Yung et al. [188] found the sensitivity for any small-bowel findings was 0.60 (95% CI 0.50–0.69), specificity was 0.72 (95% CI 0.52–0.86) and diagnostic ORs was 3.96 (95% CI 1.50–10.4). Specifically, for the four studies using only FIT (cut-off of 100 ng/ml), they found that the sensitivity and sensitivity was lower at 0.48 (95% CI 0.36–0.61) and 0.60 (95% CI 0.42–0.76), respectively [188]. Yung et al. [188] concluded that their meta-analysis did not find faecal occult blood testing to be a comprehensive tool for small bowel screening prior to SBCE.

In general, our review of the data supports this approach, with a lack of overall diagnostic accuracy for FIT/faecal occult blood test in small bowel disease. It remains a possibility that a positive FIT pre capsule may help prioritize patients for earlier investigation and warrants additional investigation.

OTHER FAECAL BIOMARKERS

M2-pyruvate kinase (M2-PK) is a cytosolic enzyme involved in glycolysis; it is a stable protein resistant to microbial endoproteases, excreted in faeces during leucocyte apoptosis and has

increased expression in undifferentiated tissues and cells with a rapid turnover [189]. Promising data is available to support a role for M2-PK in diagnosing several gastrointestinal cancers including colorectal cancer and gastric cancer. It has also been shown to be a useful prognosticator in pancreatic cancer and can help predict benign inflammation including inflammatory bowel disease. However, as with other faecal biomarkers more studies are needed to assess its use specifically in small bowel disease as to date there is no data looking specifically at small bowel diseases [190-193].

High mobility group box 1 (HMGB1) is a protein included in a group of endogenous molecules (also known as alarmins or damage-associated molecular patterns) with intestinal and systemic proinflammatory properties when secreted in the extracellular milieu [190]. Faecal HMGB1 has been described as a reliable marker of intestinal inflammation in paediatric and adult IBD (either in overt or subclinical status), where it significantly correlated with faecal calprotectin in adult IBD patients and predicted histologic inflammation in patients with IBD in clinical and endoscopic remission [194-197]. HMGB1 may also have a role in the management of coeliac disease, a study in the paediatric population by Palone et al. found a significantly raised faecal HMGB1 in children with coeliac compared with matched controls (Wilcoxon rank sum test with continuity correction $P < 0.001$). This article also suggested that persistence of detectable levels of faecal HMGB1 may hint to an underlying active low-grade enteropathy, not revealed by blood anti-tissue transglutaminase antibody levels [198].

In all, although, faecal M2-PK, HMGB1 seem to be promising biomarkers of intestinal inflammation, more and larger studies are needed to establish their role in small bowel disease.

URINE BIOMARKERS

Although faecal biomarkers are promising as a tool to assess for small bowel and gastrointestinal diseases, there are patients who feel reluctant to provide a stool sample due to perceived embarrassment and cumbersomeness [199]. Urine biomarkers may provide an alternative to patients and offer a different tool in the gastroenterologists' armamentarium.

Intestinal fatty acid (FA)-binding protein (IFABP) and liver FA-binding protein (L-FABP) are two of the nine known cytoplasmic proteins that regulate long-chain FA transportation intracellularly and both

are expressed along the gastrointestinal tract, with mature enterocytes in the jejunal villi generating higher levels than colonocytes [200, 201].

Ho et al. [202] evaluated urine samples for I-FABP, L-FABP, claudin-3 and calprotectin in 14 young adults (median age 25) with active Crohn's disease before and after exclusive enteral nutrition (EEN) therapy. Urinary I-FABP: Cr (standardized to urine Cr) levels were significantly reduced ($P=0.03$), urinary L-FABP: Cr levels increased ($P=0.03$), while Urinary CLND3: Cr and calprotectin: Cr levels were not significantly different following EEN therapy [202]. L-FABP: Cr levels in urine correlated positively with serum IGF-1 levels, $r=0.60$, $P=0.02$ [202]. There is evidence that IGF-1 levels are low in patients with IBD (reportedly attributed to malnutrition and/or gastrointestinal tract inflammation) and are increased within 1–2 weeks in children and adults with active Crohn's disease following EEN therapy [203-207]. Although not yet correlated with endoscopic disease activity, Ho et al. [202] concluded that urinary I-FABP is a potential urinary biomarker for disease activity in adults with Crohn's disease and urinary L-FABP may be an indirect marker of nutritional status in adults with Crohn's disease and warrants further larger studies.

There has been increasing data that suggests that small intestine permeability (SIP) plays a role in the development of IBS and Coeliac disease [208, 209]. Altered gut permeability may permit the passage of luminal contents into the underlying tissues and the bloodstream, resulting in both the activation of the immune response and the induction of gut inflammation [210, 211]. Current methods of assessing SIP includes the use of small sugar molecules of different sizes such as sucrose (Su), lactulose (La) and mannitol (Ma) [210]. Their urinary recovery may be affected by several nonmucosal factors (e.g. gastric emptying, intestinal transit and renal clearance) and the usage of La: Ma ratio in urine is considered a reliable parameter to evaluate the impairment of SIP [212]. Linsalata et al. [211] found a statistically significant difference between patients with Coeliac and healthy controls but not with diarrhoea predominant IBS (DIBS) when evaluating the use of urinary Su and La: Ma ratio ($P=0.0009$ and $P<0.0001$).

In terms of management of coeliac disease, a life-long strict gluten-free diet (GFD) is currently the only treatment strategy. However, due to the ubiquitous nature of gluten and the risk of contamination, adherence to GFD may not always be possible. As a result, some research has shown that about 25–40% of adults with coeliac disease have persistent enteropathy despite being on a

GFD for more than 2 years [213-215]. Currently, the use of coeliac antibody is widely used to assess for adherence to GFD, but these tests were never approved for this purpose and have low sensitivity in detection of persistent mucosal lesion in coeliac patients on a GFD [216]. The development of monoclonal antibodies (mAbs) that are capable of sensitively and specifically detecting gluten immunogenic peptides (GIP) have been used to detect inadvertent gluten consumption by measuring GIP in human samples (faeces and urine) [217-219]. Comino et al. [219, 220] has evaluated in several studies the use of faecal GIP in the diagnosis of coeliac disease and for monitoring adherence to GFD. They also found that the elevation of tissue transglutaminase antibody was more prolonged in patients with detectable gluten peptides ($P < 0.05$) [220]. Costa et al. [221] evaluated 44 patients prospectively over a 2-year period comparing both an ELISA and point-of-care tests for stool and urine GIP. They found that both types of tests were concordant in 67 out of 74 (90.5%) samples [221]. Stefanolo et al. [222] performed a prospective study on 53 patients assessing GIP in faecal and urine samples who have been on a GFD for more than 2 years. They found that patients with symptoms had more weeks in which GIP was detected in stool than patients without symptoms ($P < 0.05$). Although these studies are promising in terms of the use of a GIP as a noninvasive marker of GFD adherence, larger multicentred studies are needed prior to recommending its use. The role of urinary markers in small bowel disease in general remains unclear and they have no role currently in routine clinical practice.

Biomarker	Mechanism	Potential roles	Evidence
FC	Calcium and zinc binding neutrophil cytosolic protein that reflects neutrophil cellular degranulation during an inflammatory response	• Diagnosis of small bowel CD • Monitoring disease activity • Assessing treatment response • Predicting relapse post surgery	Conflicting data in diagnosing small bowel CD but a FC level of $< 50 \mu\text{g/g}$ may be used as a cut-off to triage further investigation. Monitoring disease activity – some evidence regarding correlation between

			DBE and MRE but not panenteric capsules Monitoring treatment response – evidence still lacking but has promising role with use of anti TNF agents. Predicting relapse – at cut off of 150 µg/g some evidence available to exclude relapse post-surgery
FL	Iron-binding glycoprotein that reflects neutrophil activity, being a specific and sensitive indicator of intestinal inflammation	Marker of small bowel inflammation	Data presented in this paper appears promising however further studies needed
FIT/gFOB	gFOB - detects the presence of guaiac and pseudoperoxidase activity FIT – based on immunochromatography or upon latex agglutination immunoturbidimetry and more specific for intact human Hb and its early degradation	Pre-screening tool for SBCE in patients referred for iron deficiency anaemia or obscure GI bleeding	FIT, as expected, appears better than gFOB however not enough evidence to recommend routine use and further studies needed
F M2-PK	Cytosolic enzyme excreted in faeces during leucocyte apoptosis and has increased	Marker of inflammation in IBD	Further studies needed to assess roles in small bowel disease

	expression in undifferentiated tissues and cells with a rapid turnover	and possible cancer detection	
F HMGB1	Endogenous molecules (alarmins) with intestinal and systemic pro-inflammatory properties	Marker of intestinal inflammation in IBD and Coeliac disease	Further evidence needed
Urinary I -FABP	Cytoplasmic proteins that regulate long-chain fatty acid transportation intracellularly	Monitoring disease activity in adults with CD	Further evidence needed
Urinary L-FABP		Indirect marker of nutritional status in adults with CD	Further evidence needed
Urinary Su, La/Ma ratio	Small intestine permeability	Differentiating coeliac, IBS	Further evidence needed

Table 13: Potential biomarkers of small bowel disease

CONCLUSION

Biomarker use can potentially aid in the diagnosis and management of several small bowel diseases. Several biomarkers are available which could have a potential role in the diagnosis and monitoring of a variety of small bowel conditions (Table 13). To date, faecal calprotectin shows the most promise, with evidence to support its role in both predicting relapse and monitoring treatment response in patients with small bowel Crohn's disease. The use of biomarkers in general though in the diagnosis and management of small bowel disease is still controversial and remains unclear. Biomarkers may provide a cheap, non-invasive tool to assess the small bowel offering a better way to triage referrals for dedicated small bowel investigation and also to monitor disease activity and help inform management decisions. More studies are required to further develop their potential and before societal guidelines can be developed to direct their appropriate use in clinical practice.

4.2 The use of CRP, FIT and FC as a surrogate marker for disease activity and mucosal healing in Inflammatory Bowel Disease.

Background

Ulcerative Colitis (UC) and Crohn's Disease (CD) are progressive chronic inflammatory conditions affecting the GI tract which could lead to serious and permanent effects for example bowel perforation, stenosis and fistulas if left untreated [223, 224]. Intestinal inflammation may result in significant ulceration of the mucosa, preventing water resorption and retention and promoting loss of electrolytes and protein and contact bleeding. Unchecked chronic inflammation can result in irreversible damage including fibrosis and is a recognised risk factor for subsequent cancer development. Some IBD patients despite being in symptomatic remission have ongoing active inflammation [225]. Over recent years, the goal of IBD therapy has expanded in order to achieve deep remission which may include symptomatic remission, biochemical remission, endoscopic remission, and histological remission [225, 226]. The definition of deep remission and mucosal healing (MH) however, is not unanimous [227]. Discrepancy between endoscopic remission and histological remission does exist and a standardised definition has yet to be achieved, but generally endoscopic remission can be equated to MH [228, 229].

There has been evidence that MH in CD leads to better outcomes in terms of reduction in hospitalisations, decreasing relapse rates and need for surgery [230-232]. Similarly in UC, MH is associated with long-term clinical remission, avoidance of colectomy, and corticosteroid-free clinical remission [233]. Currently, the only way to assess for MH is by performing a colonoscopy and obtaining histological biopsies. More recent data suggests that capsule endoscopy may also have a role to assess for MH [168, 170, 234].

Endoscopy for patients with IBD is also needed in cases of symptoms relapse, persistent disease activity, new unexplained symptoms, assessment of effects of therapy and for surveillance [228, 235]. Unfortunately, due to high demands for colonoscopy, not just in IBD patients but for the general symptomatic, surveillance and screening cohort, societal guidelines for the use of endoscopy in IBD including the assessment of MH may not always be adhered to.

A non-invasive, readily available biomarker which could act as a surrogate for colonoscopy to assess MH is badly needed. Serum CRP has a low sensitivity in determining mucosal disease in UC, with serum levels frequently within normal limits even in active disease [178]. In CD, the correlation between CRP and MH is variable, with some evidence of reasonable correlation in some studies but not others [178, 236, 237].

As explained in subchapter 4.1, Faecal Calprotectin (FC) concentrations in stool strongly correlate with the migration of ¹¹¹-indium-radiolabeled granulocytes through the gut wall which can be a marker of intestinal inflammation [84, 85]. For CD, there has been evidence of FC correlation with DBE and MRE but not Crohn's Capsule [158-160, 163]. Iwamoto et al concluded that at a cut-off value of 92 mg/kg, FC had a sensitivity of 87%, specificity of 88%, PPV of 96%, NPV value of 64% and AUC of 0.85 for MH [159]. For UC, several recent studies have concluded that FC may be a reliable surrogate marker for assessment of MH [238-240]. These studies have led to the joint recommendation by European Crohn's and Colitis Organization (ECCO) and ESGAR for the use of FC to assess for MH in UC [235]. Interestingly, a specific cut-off point however has not been recommended.

Faecal Immunochemical Test for Haemoglobin (FIT) is specific for intact human Hb and its early degradation products [80, 81]. The hypothesis of using FIT to assess MH is that if the intestinal mucosa has fully healed, it will no longer be inflamed and bleed. Hence a biomarker that assess for occult bleeding will be useful as a surrogate marker for MH. Several studies have looked at the use of FIT to assess MH, with data favouring its use in UC and colonic CD but not small bowel CD [241-251]. Most Japanese based studies [241-246, 248], Ma et al [247], and Ryu et al [250] used a FIT cut-off of <100 ng/ml as being normal, while Shi et al [249] used a cut-off of < 50 ng/ml and Kim et al [251] used a value of 10 ng/mL. A recent meta-analysis by Dai et al of 6 studies consisting of 625 UC patient, showed at a cut-off of <100 ng/ml, the sensitivity and specificity for predicting MH in UC were 0.77 (95% CI 0.72-0.81) and 0.81 (95% CI 0.76-0.85) respectively and an AUC of 0.88 (standard error 0.02) [252]. However, a specific agreed upon cut-off point of FIT for MH has yet to be determined.

Aim

The aim of this study was to assess the use of CRP, FIT and FC as surrogate markers of disease activity and MH in an Irish IBD cohort.

Methods

Patient population

IBD patient aged 16-80 undergoing colonoscopy in Tallaght University Hospital (TUH) were prospectively identified and recruited from a dedicated outpatient clinic to the study over a 6-month period (Dec 2018-June 2019). Exclusion criteria included patients with known small bowel disease without terminal ileal activity, a GI malignancy, regular NSAID use or known peptic ulcer disease, a known coagulopathy, patient referred for a sigmoidoscopy only, patients unable to give informed consent, and pregnancy.

In TUH, IBD patients generally undergo colonoscopy based on the indication of IBD assessment or IBD surveillance. Generally speaking, patients referred with an indication of IBD assessment are usually symptomatic, and the colonoscopy is undertaken to assess severity and map disease location. However, the indication of IBD assessment is very broad and would sometimes include assessment following therapy. For the purpose of this study, this subclassification was not performed. Both subgroups of patients (IBD assessment and surveillance) were included in this study. Following informed consent, patient demographics including type of IBD was collected and documented.

Study procedure

Serum samples were obtained at maximum 4 weeks prior to colonoscopy for CRP and sent to the laboratory for analysis. CRP was reported as mg/l and >5 mg/l was considered abnormal.

Patients were asked to collect stool samples for FIT and FC prior to their scheduled colonoscopy and to bring the collection bottles with them on the day of endoscopy. FIT and FC were processed in TUH laboratory. FC was reported as $\mu\text{g/g}$ of stool and FIT was ng/ml. A normal value of FC was defined as ≤ 50 $\mu\text{g/g}$. At present there is no normal range for FIT in IBD, an arbitrary value of ≤ 50 ng/ml was considered normal.

For the purpose of the study, only completed colonoscopies were included. All colonoscopists were blinded to results of faecal biomarkers as these results were not available prior to colonoscopy.

All colonoscopies were performed by experienced endoscopists who meet national quality standards. Histology samples were processed as standard within the hospitals laboratory and assessed by qualified histopathologists.

Electronic colonoscopy reports and histology results if available were obtained. For the purpose of this study, MH was defined as no visible activity on colonoscopy for both UC and CD patients. Quiescent disease on histology was defined as normal histology even if the endoscopist described evidence of inflammation on colonoscopy. Patients without any active ulceration, has minimal inflammation endoscopically but had a normal representative histology was also deemed to have MH. In those without MH, they were considered to have active disease.

We opted not to include any endoscopy scoring systems for unanimity and for ease of interpretation as these scoring systems were not readily available in our endoscopy reporting system (Unisoft – Enfield UK) used at the time of the study. If there was any activity either endoscopically or histologically, this was divided into mild, moderate, or severe. For the purpose of this study, deep healing is defined as both a normal endoscopy and normal histology.

Collected data was stored on a secure hospital computer and server. Statistical analysis was performed by MedCalc (MedCalc Software Ltd, Belgium). Parametric data was compared using the student t-test where a p value of <0.05 considered to be significant. Diagnostic accuracy of each biomarker was calculated. A receiver operating characteristic curve (ROC) was also calculated to determine a specific cut-off for MH. Correlation between biomarkers and biomarker with disease severity was assessed using Pearson Correlation Co-efficient where a r value >0.7 was considered a strong correlation.

Results

Patient Demographic

A total of 108 patients were recruited to the study. 1 (0.9%) patient had an incomplete colonoscopy and was excluded. 107 patients had a full colonoscopy and were included in the analysis.

The mean age of patients was 45.5 (17-79) and 51% (55) were males. In all, a total of 35% (38) of patients had UC, 60% (64) had Crohn's, and 5% (5) had IBD-undifferentiated (IBDU). 87% (n=93) of patients had a colonoscopy for IBD assessment. A summary of these results is available in Table 14.

Biomarker, colonoscopy, and histology

Of the 107 colonoscopies performed, CRP was returned and available for analysis in 96% (103), FC in 95% (102) and FIT in 86% (92) respectively. Mean CRP was 6.7 mg/l (0-83), mean FC was 1281.4 µg/g (<19-43285) and mean FIT was 758ng/ml (0-6610).

In the 107 colonoscopies, endoscopically, 30% (32/107) had no activity, 34% (36/107) had mild activity, 29% (31/107) had moderate, and 7% (8/107) had severe activity. While histologically, 30% (32/107) had no activity, 38% (41/107) had mild disease, 26% (28/107) had moderate disease and 6% (6/107) had severe disease.

Using our definition, MH was seen in 36% (38/107) patients and deep healing was seen in 30% (32/107).

Biomarkers and MH

In patients with MH, the mean CRP was 3.3 mg/l (0-78), mean FIT was 99.8 ng/ml (0-1439) and mean FC was 295µg/g (0-4328). While in active cases mean CRP was 8.7 mg/l (0-83), mean FIT was 1221.9 ng/ml (0-6610) and mean FC was 1028.2µg/g (0-10664).

All biomarkers were significantly lower in MH cases compared to active cases, CRP (3.3 vs 8.7, $p=0.0220$, FIT (99.8 vs 1221.9, $p=0.00003$), and FC (295 vs 1028.2, $p=0.016$).

Using our standard cut-off point of CRP ≤ 5 mg/l being normal; 30/103 (29%) had abnormal CRP and the sensitivity, specificity, Positive Predictive Value (PPV) and Negative Predictive Value (NPV) of CRP for disease activity is poor at 77%, 42%, 35%, 82% respectively.

Using our standard cut-off point of FC $\leq 50\mu\text{g/g}$ being normal; 78/102 (76%) had a positive FC and the diagnostic accuracy of FC for disease activity was, sensitivity 69%, specificity 63%, PPV 86% and NPV 38%.

Using a predefined cut-off of FIT ≤ 50 ng/ml being normal, 55/92 (60%) had a positive FIT and the diagnostic accuracy of FIT for disease was sensitivity 76%, specificity 68%, PPV 78% and NPV 66%.

Using at least 2 normal values (2N) (CRP ≤ 5 mg/l, FC $\leq 50\mu\text{g/g}$, FIT ≤ 50 ng/ml), the sensitivity, specificity, PPV and NPV was 80%, 68%, 80%, 68% respectively.

ROC analysis for each biomarker shows FIT (at our cut off 's given above) had the best ROC area with a fitted ROC area (Area Under Curve – AUC) of 0.788 (estimated standard error of 0.047), followed by FC 0.748 (estimated standard error of 0.05) then by CRP of 0.641 (estimated standard error 0.05).

A summary of these results is available in Table 15.

Correlation between each biomarker were weak; CRP and FIT $r=0.09$, CRP and FC $r=-0.033$, FIT and FC $r=-0.008$.

Correlation between specific values of each biomarker and disease severity seen endoscopically (none, mild, moderate, and severe) was also weak CRP $r=0.047$, FC $r=-0.04$, FIT $r=0.049$.

Total patients 108, 107 included (1 incomplete colonoscopy excluded)

- Mean age - 45.5 (17-79)
- 51% (55) males
- 35% (38) UC, 60% (64) Crohn's, 5% (5) IBDU
- 87% (n=93) had a colonoscopy for IBD assessment

Of the 107, biomarkers returned and analysed

- CRP – 103(96%), mean 6.7 mg/l (0-83)
- FC – 102(95%), mean 1281.4 µg/g (<19-43285)
- FIT – 92 (86%), mean 758ng/ml (0-6610)

Colonoscopy

- 30% (32/107) normal
- 34% (36/107) mild
- 29% (31/107) had moderate
- 7% (8/107) had severe

Histologically

- 30% (32/107) normal
- 38% (41/107) mild
- 26% (28/107) moderate
- 6% (6/107) severe

MH in 38/107 (36%) and deep healing in 32/107 (30%).

Table 14 – Demographics, biomarkers, and colonoscopy results

Biomarkers and deep healing

Using our definition of deep healing, although all biomarkers showed a trend of lower values in deep healing, only FIT was the only one that was statistically significant which could be due to small sample sizes; FIT (118.24 vs 1053.13, $p=0.000992$), CRP (3.66 vs 8.22, $p=0.066$), FC (242.62 vs 1505.7, $p=0.11$).

Diagnostic accuracy of each biomarker for deep healing is also given in Table 15.

	Mucosal Healing		Deep Healing	
Sensitivity		95% CI		95% CI
	CRP = 77%	58-90%	CRP = 81%	63-93%
	FIT = 76%	63-87%	FIT = 81%	70-90%
	FC = 69%	58-79%	FC = 72%	60-81%
	2N = 80%	68-89%	2N = 77%	65-87%
Specificity	CRP = 42%	31-55%	CRP = 31%	21-43%
	FIT = 68%	50-82%	FIT = 56%	36-72%
	FC = 63%	41-81%	FC = 32%	14-59%
	2N = 68%	51-81%	2N = 39%	23-58%
PPV	CRP = 35%	29-42%	CRP = 34%	29-39%
	FIT = 78%	68-85%	FIT = 76%	68-83%
	FC = 86%	78-91%	FC = 79%	73-84%
	2N = 80%	72-86%	2N = 72%	65-78%
NPV	CRP = 82%	69-90%	CRP = 79%	62-89%
	FIT = 66%	52-76%	FIT = 62%	47-81%
	FC = 38%	28-50%	FC = 24%	14-39%
	2N = 68%	55-83%	2N = 46%	54-74%
AUC	CRP = 0.641 (ESE – 0.05) FIT = 0.788 (ESE – 0.047) FC = 0.748 (ESE – 0.05)		n/a	

Table 15 - Diagnostic accuracy of each biomarker for Mucosal Healing and Deep Healing

Figure 2 below demonstrates the differences between values of each biomarker in active disease, mucosal healing, non-deep healing, and deep healing.

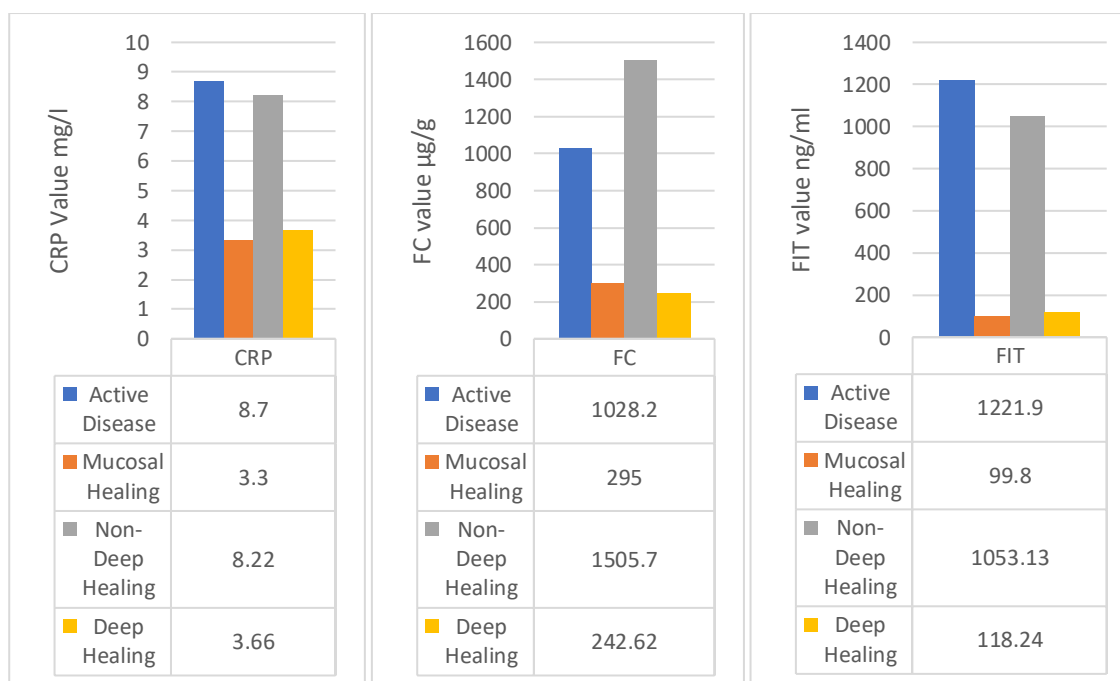


Figure 2: Values of biomarkers in Active Disease, Mucosal Healing, Non-Deep Healing and Deal Healing

Discussion

Our real-world study using readily available non-invasive biomarkers as a surrogate marker for MH in IBD patients is interesting and appears to be broadly in line with previously published data [238-251]. All three biomarkers in our study were significantly lower in patients with MH compared to those with activity, CRP (3.3 vs 8.7, $p=0.0220$, FIT (99.8 vs 1221.9, $p=0.00003$) FC (295 vs 1028.2, $p=0.016$). FIT appears to have the best data with AUC of 0.788, followed by FC (0.748) then by CRP (0.641).

Deep healing, as defined in our study as both a normal endoscopy and histology, occurred in 32/107 (30%) of patients. All biomarkers also tended to be lower in deep healing but only FIT showed a statistically significant difference, most likely due to low numbers in our study [FIT (118.24 vs 1053.13, $p=0.000992$), CRP (3.66 vs 8.22 $p=.066$), FC (242.62 vs 1505.7, $p=0.11$)].

MH is an important therapeutic target in managing patients with IBD. MH assessment should guide alterations in therapy with a view to achieving MH and reducing long-term complications. Our study adds to the body of evidence and suggests that in patients with lower values of non-invasive

biomarkers, MH is more likely to occur. However, their low accuracy in isolation, means direct mucosal visualisation remains necessary for the majority.

While our data suggests a combination of non-invasive biomarkers performs better, no one combination sufficiently predicts MH. Our study did not show that a higher value of each biomarker correlated with severity of disease seen endoscopically (CRP $r=0.047$, FC $r=-0.04$, FIT $r=0.049$). However, what is interesting in our data is that mucosal activity is predicted in those with high biomarker results, (Mean values significantly higher in mucosal activity compared to MH, CRP (3.3 vs 8.7, $p=0.0220$, FIT (99.8 vs 1221.9, $p=0.00003$) FC (295 vs 1028.2, $p=0.016$). This would suggest in those with high biomarker values, treatment escalation without the need for endoscopy may be considered.

The use of non-invasive biomarkers to assess for MH seems cost effective as patients would not need to undergo multiple repeated colonoscopies. In addition, it may be more preferable to have an alternative means to assess MH as there is some evidence to suggest IBD patients find colonoscopy more painful, and embarrassing compared to the general population [253]. A recent patient perspective survey by Ho et al also describes colonoscopy as the least comfortable test reported by IBD patients and generated the most worry [254]. A study by Ryhlander et al in IBD patients who have undergone more than 3 colonoscopies, revealed that multiple colonoscopies although giving an assurance of life also gives patients a reminder of life-long illness, is strenuous and interferes with daily life; with shame, inferiority and uncertainty enhancing the feeling of being exposed and vulnerable [255].

In our cohort of patients, serum CRP had the highest result return rate of 96%, followed by FC 95% and FIT had the lowest at 86%. Serum tests are known to be well tolerated and returned by IBD patients [254]. Even though our study had a high FC return rate, there are patients who feel reluctant to provide a stool sample due to perceived embarrassment and cumbersomeness [199]. A study by Kalla et al in 585 IBD patients had shown that 37% (165) find FC testing difficult, with 'sample collection' ($n = 106$) being the most common reason reported [256]. FIT testing is slightly more complicated and less common than FC testing, hence patients may not be familiar with this test and may be a reason why despite sending in a stool sample for FC, the rate of return of FIT was

lower. Better patient education and support may be needed in order to increase adherence with FIT and all stool tests.

A strength of our study is that it is among the first data of using a combination of CRP, FIT and FC to assess for disease activity and MH in a European based population (Table 2). Specifically for use of FIT in assessing for MH, most studies that we could find involved an Asian based cohort [241-251] and only Ma et al involved a Canadian cohort [247]. A specific cut-off for FIT in IBD has yet to be determined.

Limitations of our study include not using a validated scoring system to assess for MH. The reason for this is that on our electronic endoscopy reporting system (Unisoft – Enfield UK) does not have a specific drop down for validated scores. It only allows for a more subjective endoscopist assessment of severity being none, mild, moderate, and severe. Another limitation is that the number of our study cohort is small, and we did not have enough patients to differentiate between UC and CD for assessment of MH for each biomarker. We also did not perform a power calculation prior to the study being commenced. Apart from that, we did not specifically record each patients' symptoms prior to colonoscopy. We only recorded colonoscopy indication being either for IBD assessment or surveillance. Hence, we were not able to comment whether patients in our cohort had clinical remission and also in deep remission.

MH was also only seen in 38/107 (36%) of our patient cohort. This may reflect our current clinical practice in TUH of reserving colonoscopy for assessment of patients' symptoms/activity (in 87% of cases in this study) rather than for surveillance purposes or assessment of MH. Apart from that in our centre, we also employ the use of capsule endoscopy in selected IBD patients for intestinal visualisation [168]. The correlation between capsule endoscopy findings of MH and biomarkers still remains an area for future studies.

Unfortunately, due to low numbers of patients involved in the study we are not able to set a validated cut-off for each biomarker for MH. A similar issue has been raised by the most up-to-date joint guidelines by ECCO-ESGAR [235] guidelines. There also is not enough evidence to assess whether a specific cut-off of each biomarker (CRP, FC, FIT) will apply to all phenotypes of IBD. Future

prospective, multi-centre trials are needed to further set a proposed cut-off for each biomarker for all subtypes of IBD.

Conclusion

MH was only seen in 36% of patients which reflects our current clinical practice. FIT shows the most promise of predicting MH with an AUC of 0.788 followed by FC at 0.748. However, more prospective multi-centred studies are needed to set specific cut-offs of each biomarker for all subtypes of IBD. Mucosal activity can be predicted in those with higher biomarker values, which may suggest the need for treatment escalation without the requirement for direct intestinal visualisation.

Chapter 5: Colon Capsule Endoscopy: its use in symptomatic patients, improving bowel preparation and booster regimes, and patients' perspective regarding it

5.1 Colon capsule endoscopy is a viable alternative to colonoscopy for the investigation of intermediate- and low-risk patients with gastrointestinal symptoms: results of a pilot study

This subchapter has been presented as an oral podium e-poster presentation at the ESGE Days 2019 meeting in Prague. It has also been published in *Endosc Int Open* 2021 Jun;9(6):E965-E970. doi: 10.1055/a-1401-9528.

Introduction

Colon capsule endoscopy (CCE) is a recommended viable alternative to colonoscopy for colonic visualization in a variety of clinical settings [257]. In keeping with the evidence that patients without alarm symptoms are at low risk of colorectal neoplasia, the European Society of Gastrointestinal Endoscopy guideline of 2012 approved CCE use in average risk patients as a non-invasive option [112, 258]. Several non-invasive tests have been evaluated in this setting, including the use of faecal biomarkers, faecal calprotectin (FC) and faecal immunochemical test (FIT) and other imaging modalities, particularly CT colonography [97, 103]. Biomarkers are now widely incorporated into patient triaging and vetting procedures and are considered a useful means to prioritise cases [47, 90]. Biomarkers alone can rule-out significant disease in only a minority and imaging tests are still required in the majority of patients to detect both neoplastic and non-neoplastic conditions [103]. As such, evaluation of symptomatic patients still represents a significant burden for colonoscopy services and viable alternatives are needed to help meet increasing demand [1]. There is now an abundance of evidence to show CCE is an effective means to detect both neoplastic and non-neoplastic disease in selected patient cohorts including Inflammatory Bowel Disease patient assessment, average, and low risk screening, after incomplete colonoscopy and polyp surveillance [114-120]. However, the efficacy of CCE in an unselected average risk symptomatic cohort, with or without biomarker vetting is less clear. While CT Colonography is now an established alternative in symptomatic assessment, CCE could help to improve overall imaging capacity and offer additional advantages including a simple, non-radiation community-based alternative.

The aim of this study was to determine the feasibility of CCE imaging assessment in average risk symptomatic patients as an alternative to colonoscopy with and without additional biomarker assessment.

Patients and methods

Population

This is a prospective, single-centre comparative study conducted in Tallaght University Hospital, Ireland. At the time of study, we were the only CCE centre in Ireland and perform about 150 to 200 CCEs per year. Following ethical approval, patients aged 18 to 80 years, referred from primary care for investigation of lower gastrointestinal symptoms, who required a non-urgent colonoscopy based on vetting by a Consultant Gastroenterologist applying NICE criteria, were identified [47]. These patients are considered intermediate or low risk. Exclusion criteria for our study were, patients unable to give informed consent or with a contraindication to either study procedure (history of dysphagia, known or suspected small or large bowel strictures, recent abdominal surgery (within 6 weeks)), a contraindication to bowel preparation or allergies to any study medication, patients with coexisting serious medical illness, pregnant subjects, and patients with an ileostomy. Subjects on long-term non-steroidal anti-inflammatories (NSAIDs) could participate if willing to discontinue NSAIDs for 6 weeks prior to study commencement. As per departmental protocol, everyone on regular NSAID's had a patency test to exclude small bowel strictures.

Suitable candidates were invited to participate by phone and a study information leaflet was posted to all potential participants. At the first study visit informed consent was obtained, a medical history, physical examination and routine bloods performed, and study investigations scheduled.

Investigations

All CCE's were performed using PillCam COLON 2 (Medtronic, Minneapolis, United States). A low-residue diet was advised for 24 hours before the CCE. A standard split bowel preparation regimen was used prior to capsule ingestion and booster medications were employed to encourage capsule transit. The study was complete when the capsule was excreted, or the battery ran out. Experienced Capsule Endoscopists, using Rapid Reader Software Version 9, analysed all videos.

In keeping with our practice, all CCE's were reviewed at our institutions weekly capsule review board. During the period of this study our bowel preparation and booster regimen changed from KleanPrep (Norgine, Middlesex, UK) with Phospho-soda, "Fleet" (Casen Recordati, Zaragoza, Spain.) and Gastrograffin (Bayer, Reading, UK) boosters to Moviprep (Norgine, Mid Glamorgan, UK) bowel preparation and boosters. We changed our CCE bowel preparation and booster regimen due to a lack of availability of KleanPrep, having been substituted in our hospital pharmacy with Moviprep during the study and safety concerns regarding the use of Phospho-soda.

Colonoscopy was scheduled for all patients on average 4 weeks after their CCE. Experienced endoscopists, meeting national quality standards, performed all colonoscopies as a day case. The endoscopist was not blinded to the result of CCE. Colonoscopy reports were generated and stored on a national endoscopy database, Unisoft (HD Clinical, Hertfordshire, UK).

As per our departmental guidelines, for CCE we classified the preparation as being Good, Adequate, or Poor. This is slightly modified from the recommendation from ESGE guidelines for CCE 2012, where we combined the good and excellent rating as Good [112].

For colonoscopy, we had classified prep as being good, adequate/complete, and poor. This is based on pre-assigned prompts from the Unisoft endoscopy reporting system. This system is based on the Aronchick scale.

Significant polyps on CCE were defined, as per ESGE guidelines, as the presence of >3 lesions or a polyp greater than > 6 mm based on polyp size estimation [112]. Significant polyps on colonoscopy were defined as the presence of >3 polyps, and adenomas or sessile serrated lesions >10mm in size.

Any histology specimens were processed and reported as normal by our institution's pathology department.

Both FC and FIT samples were collected and delivered within 24 hours directly to the hospital laboratory and processed as standard.

Analysis

Basic demographics, presenting symptoms, initial blood work, biomarker levels, all CCE and Colonoscopy findings were recorded. For analysis, clinically significant colonic findings included colorectal cancer, high risk adenoma as defined by ESGE and inflammatory bowel disease. Clinically significant small bowel disease was defined as significant ulceration consistent with Crohn's disease or NSAID enteritis, suspicious submucosal masses and P1 vascular lesions in subjects with a suspicion of bleeding. A FIT of >10 ug/g and FC >50 ug/g were considered positive.

A per protocol analysis was performed in this study. For comparisons, colonoscopy was considered the gold standard investigation. CCE findings were compared to colonoscopy and CCE sensitivity, specificity and positive and negative predictive values determined, for any and clinically significant findings. Pearson Coefficient was also used to assess correlation between colonoscopy and CCE findings where an r value of ≥ 0.7 was considered a strong correlation. Similarly, the accuracy of both FC and FIT was determined.

Ethics approval

This study was approved by Tallaght University Hospital/St. James's Hospital Joint Research Ethics Committee (REC).

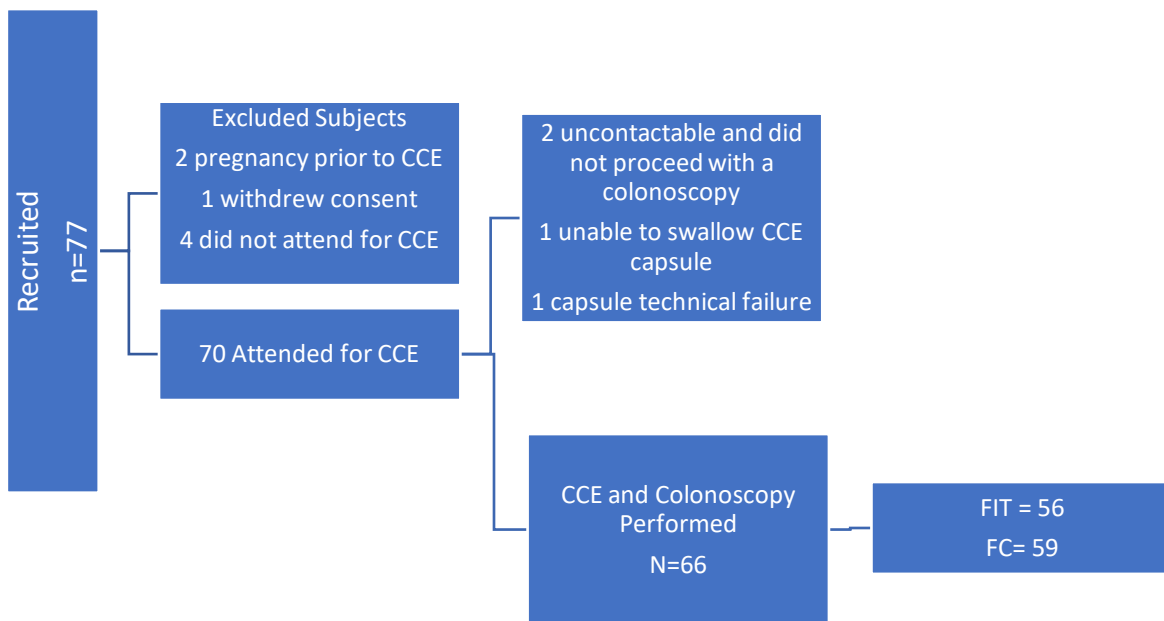
Results

Study population

In total, 77 patients were recruited. Of these, one withdrew consent prior to any investigation, two became pregnant after recruitment and four did not attend their CCE appointments. Of the 70 included patients, two did not have a colonoscopy after their CCE as they were not able to be contacted, one patient could not swallow the CCE capsule and in one case there was technical failure of the capsule on ingestion; all of these patients refused a colonoscopy. As a result, there were 66 patients with both CCE and colonoscopy tests available for analysis (Figure 3). Only one patient received and passed a patency capsule for a history of chronic NSAIDS use. The mean age of our cohort was 45.8 years (range 20–79) and 42% ($n=27$) were male. The predominant symptom in 22 (34%) patients was bleeding, 28 (44%) diarrhoea, seven (11%) alternating constipation and diarrhoea, five (8%) abdominal pain, two (3%) weight loss and one (1%) chronic constipation. As

expected only two patients (3 %) had anaemia detected on baseline bloods defined as Hb < 11.2 g/dL in women and < 12.8 g/dL in men. A C-reactive protein (CRP) was available in 62 patients (97 %) and 56 patients had an erythrocyte sedimentation rate (ESR). In all, 16 % (10/62) had a positive CRP (> 5 mg/L). Mean CRP was 4.1 mg/L (range 1–57.9). While 32 % (18/56) had a positive ESR (> 20 mm/hr). Mean ESR was 12.5 (1–47) mm/hr.

Figure 3: Study Population



Colonoscopy performance

The caecal intubation rate was 94 % (n=62). Bowel preparation was good in 39 % (n=26) adequate in 53 % (n=35) and poor in 8 % (n=5). In all, 64 % (n=42) of colonoscopies had a positive finding, with clinically significant disease reported in 24 % (n=16), including two with a histological diagnosis only (one lymphocytic, one TB colitis). Included as clinically significant disease were six cases of histologically confirmed IBD (3 UC, 3 CD), one case of radiation proctitis, seven patients with high-risk polyps (3 adenomas >10 mm, four >3 adenomas and one large >10 mm sessile serrated right colon lesion) and both microscopic colitis cases (Table 16).

Table 16: Diagnostic yield by test.

<i>Parameter N (%)</i>	<i>Colonoscopy</i>	<i>CCE</i>	<i>(+) FIT</i>	<i>(+) FC</i>
<i>Number</i>	66	66	31/56	23/57
<i>Completed Rate</i>	94 (62)	76 (50)	n/a	n/a
<i>Inadequate Preparation</i>	5 (8%)	5 (8%)	n/a	n/a
<i>Normal Study</i>	24 (36%)	26 (39%)	n/a	n/a
<i>Any Positive finding</i>	42 (68%)	40 (60%)	19/37 (49%)	16/39 (41%)
<i>Clinically significant disease</i>	16 (24%)	14 (21%)	8/14 (57%)	4/10 (40%)
<i>Polyps</i>	21 (32%)	23 (35%)	n/a	n/a
<i>Significant Polyp</i>	7 (11%)	8 (12%)	n/a	n/a
<i>Colitis</i>	6 (9%)	3 (5%)	n/a	n/a
<i>Diverticulosis</i>	11 (17%)	14 (21%)	n/a	n/a
<i>Haemorrhoids</i>	3 (5%)	0	n/a	n/a
<i>Microscopic Colitis</i>	2 (3%)	n/a	n/a	n/a
<i>Significant Small bowel disease</i>	3 (5%)	3 (5%)	n/a	n/a

CCE performance

In 66 of 68 (97 %) patients referred for CCE videos were available for review and compared to colonoscopy. The excretion rate was 76 % (n=50). Bowel preparation quality was good in 38 %

(n = 25), adequate in 55 % (n = 36) and inadequate in 8 % (n = 5). Overall, 40 (61 %) CCE's were positive. There were no procedure related complications (Table 1). CCE abnormalities included polyps in 23 (35 %), diverticulosis in 14 (21 %) and Colitis in n = 3 (5 %). Overall n = 8 (12 %) had significant polyps (>3 lesions or a polyp >6 mm). Any small bowel findings were reported in n = 15 (22 %) subjects, 3 (5 %) deemed clinically significant and was subsequently diagnosed with Crohn's disease. In all, 14 (21 %) had clinically significant disease detected on CCE. There was one false-positive and three false-negative CCEs in 16 patients with significant disease on colonoscopy. In all, there were two patients with distal colonic inflammation overlooked. In these cases, one had very distal radiation proctitis and the other case the capsule was incomplete. CCE by its nature misclassified the two patients with histologically diagnosed colitis; however, in one of these patients, they also had a significant polyp based on CCE. The only false- positive was accounted for by variation in classification of a polyp based on size. Of note, all significant polyps on colonoscopy reached the CCE threshold for excision. The sensitivity, specificity, positive and negative predictive values of CCE for significant disease were 81 %, 98 %, 93 % and 94 % respectively (Table 17). The overall correlation between colonoscopy and CCE was moderate, Pearsons $r=0.49$ but was strong for significant disease $r=0.83$.

Table 17: Diagnostic accuracy by test compared to colonoscopy for clinically significant disease.

	<i>Test</i>	<i>Sensitivity %</i>	<i>Specificity%</i>	<i>PPV%</i>	<i>NPV%</i>
<i>Clinically significant disease</i>	CCE	81	98	93	94
	FIT>10ug/g	57	60	32	81
	FC> 50ug/g	40	64	26	88
<i>Any positive finding</i>	CCE	79	71	83	65
	FIT>10ug/g	49	63	72	61
	FC> 50ug/g	41	37	70	66

Biomarker performance

In all, FIT and FC samples were available for 56 (85 %) and 59 (89 %) subjects. FIT was positive (>10 ug/g) in 31 cases (47 %), range 1–1992 ug/g. Within this cohort there were six false-negative FITs in patients diagnosed with clinically significant disease on colonoscopy (n = 14). Overall, the sensitivity, specificity, positive and negative predictive values of FIT for CSD were 57 %, 60 %, 32 %

and 81 %. FC was positive (>50 ug/g) in 23 patients (40 %), range < 19.5 to 1250 ug/g. There were four false-negative FCs in 10 patients with CSD. The sensitivity, specificity, and positive and negative predictive values of FC for CSD were 40 %, 64 %, 26 %, and 88 %, respectively (Table 17). With respect to the seven high-risk polyp cases specifically, four of six (67 %) returned a positive FIT and four of seven (57 %) a positive FC. Similarly, of the seven cases of colitis on colonoscopy FC was positive in five (71 %), unsurprisingly the FIT was also positive in five patients (71 %) with colitis. Neither CRP nor ESR were predictive of either CCE or Colonoscopy detected disease.

Discussion

Our pilot prospective single-centre analysis of CCE efficacy in an unselected symptomatic cohort suggests CCE is a viable alternative to colonoscopy. As expected only a small proportion of patients were found to have significant disease on colonoscopy, 16 (24 %). The majority of patients while needing and often benefiting from a negative test or low-risk diagnosis did not necessarily require an invasive colonoscopy. Viable alternatives, which offer similar diagnostic accuracy and enhanced capacity, would be of benefit to both patients and the health service alike.

After the CCE, colonoscopies were performed on average 4 weeks from the CCE procedure. The rationale for this is that previous blinded studies have assumed CCE findings not detected on the colonoscopy were a false negative, whereas recent evidence suggests that if the negative colonoscopy is repeated, unblinded, many polyps previously overlooked were found on the repeat procedure [116]. In addition, in the real world/clinical scenario, the capsule report is going to be available to the endoscopist before proceeding to colonoscopy.

In our cohort, CCE accurately detected all significant polyps and had a similar diagnostic accuracy for benign disease with PPV's and NPV's of 83 % and 65 % and 93 % and 94 % for any finding and clinically significant disease, respectively. However, detection rates for colitis were less than optimal compared to colonoscopy: three of seven (43 %). Only three of seven with colitis on colonoscopy ended up with a diagnosis of UC. This is difficult to explain as previous studies and those with modern capsules have found a high rate of diagnostic accuracy in IBD [114, 259]. For very distal limited proctitis the process of excretion may affect video interpretation, with distal inflammation being mis-classified as a normal rectal cushion. Initial analysis of our cohort would support this

supposition with two-thirds reclassified as showing disease on repeat reading. Enhanced awareness and training could improve future detection of proctitis and warrants additional investigation.

As expected, CCE was unable to diagnose both cases of microscopic colitis. Neither case had a positive biomarker result. Both had an established history of watery diarrhoea. As such, clinical acumen, and the adherence with biopsy protocols in suspected cases with a normal macroscopic colon is important to prevent overlooking microscopic colitis. A negative CCE should not have prevented further referral for biopsy.

Despite the overall good performance of CCE in our study, the capsule excretion rate remains low at 76 %. Analysis is in some way hampered by the required change in bowel preparation and booster regimen during this study. Optimising capsule excretion rates remains a priority and like others, we continue to adapt our preparation and booster regimens in line with current data [260]. Following study conclusion, audits of recent changes to our bowel preparation (2 L PEG solution) and booster regimen (PEG booster + Castor oil) has shown an 87 % capsule excretion rate and also improved image quality [5, 261]. The effect of these changes of bowel preparation regimen and booster regimen will be further explored in subchapter 5.2. Similarly, improving and standardising reporting of preparation quality in CCE is an area of ongoing research [262]. However, rates of suboptimal/inadequate bowel preparation were similar for both CCE and colonoscopy, five of 66 (8 %), highlighting the importance of this issue for both tests.

As with CT colonography, CCE has the potential to visualise more than just the colon, which may be particularly advantages in patients with chronic gastrointestinal symptoms. In this study, while small bowel abnormalities were detected in 15 (22 %) only three (4.5 %) were significant, all with enteritis, resulting in changed management.

The use of biomarkers is now commonplace in the assessment of patients presenting to hospital or community clinics. While they are helpful indicators of significant neoplasia and inflammatory bowel disease, they are not a replacement for direct colonic visualisation. Our study supports their role in selecting outpatients with a higher risk of clinically significant disease, with five of seven cases of colitis and four of seven with high-risk adenomas having a positive biomarker study. Their low

positive predictive value for clinically significant disease, FIT 32 % and FC 26 %, suggests referring all positive biomarker patients for a colonoscopy may not be warranted and alternatives such as CCE or CT colonography remain options. For biomarker negative individuals, based on our data, non-invasive imaging may be preferred. Both algorithms warrant further consideration.

The small size of our study is a drawback, but we felt the lack of available evidence for CCE use in a symptomatic unselected cohort warranted a further direct comparison of CCE with colonoscopy. This study design does hamper recruitment. We feel that in the setting of a pilot study assessing a novel aspect of CCE in investigating the symptomatic patient, where patients had to undergo both CCE and colonoscopy including two sets of bowel preparation, the sample size is adequate to draw some form of a conclusion as a proof of concept. We welcome bigger multi-centred studies in the future following this initial pilot study.

A strength, however, is that endoscopists were unblinded to the CCE result, which may account for the relatively low discrepancy rate in all polyp detection. Previous studies have suggested CCE accurately detects more polyps than colonoscopy, which can later be found on a targeted repeat colonoscopy [116]. As such, it remains a possibility that our colonoscopy polyp detection of 21/66 (32 %) was enhanced in our study by prior CCE. The CCE polyp detection rate was 35 %. Apart from polyp detection, all cases of terminal ileal Crohn's disease were initially picked up on CCE, if an endoscopist does not routinely perform terminal ileal intubation, these cases would have been missed. If borne out in additional studies this would represent another advantage for CCE patient selection.

It is also in our opinion that CCE would supplement but not replace the use of colonoscopy in endoscopy departments. An interesting aspect not covered in this study but would be open for future research is the workload, cost and time involved in setting up a colon capsule service, and training capsule readers.

Conclusion

CCE is a safe and effective alternative to colonoscopy in symptomatic average risk patients with or without the addition of biomarker screening.

5.2 Effect of different bowel preparation regimens on CCE excretion and bowel Cleansing

As mentioned in subchapter 5.1, an optimum bowel preparation that results in a good capsule excretion rate (CER) and bowel cleansing (BC) has yet to be determined. For colonoscopy, a caecal intubation rate of 90% which signifies a complete colonoscopy is acceptable. A similar quality indicator has yet to be determined for CCE completion. In this subchapter, we will explore the effects of changing bowel preparation and booster regimens in our CCE centre.

5.2.1 Improving quality in Colon Capsule Endoscopy; effects of changing from a 4L PEG to 2L PEG + ascorbic acid regimen.

This subchapter has been presented as an e-poster presentation the Virtual United Gastroenterology Week meeting 2020. It has also been published as an abstract publication in Endoscopy 2020; 52(S 01): S274. DOI: 10.1055/s-0040-1704865 [5].

Introduction

Allowing for variation between CCE centres, bowel preparation regimens are predominantly Polyethylene glycol (PEG) based [263]. Patients are initially given PEG to cleanse the colon, and this is followed by boosters to ensure CCE excretion. A complete study requires continuous image capture from the caecum to the haemorrhoidal plexus within the battery life of the capsule. Unfortunately, incomplete CCE remains problematic with significant variation in reported excretion rates ranging from as low as 70 to as high as 88% [260]. A further potential drawback of CCE is inadequate bowel cleansing. A recent meta-analysis reported median rates of adequate cleansing of 78% and 81% with CCE-1 and CCE2, respectively [264]. This can be explained by its inability to insufflate the colon, aspirate liquids, control its transit speed, and clean the mucosal surface [260]. Despite its technical limitations, CCE appears to have similar bowel preparation rates to colonoscopy [265].

As per ESGE guidelines in 2012 [112] our centre initially used a 4-Liter based PEG bowel preparation (KleanPrep). Most patients who participated in the pilot study in subchapter 5.1 had underwent their CCE based on this regimen which is further detailed in Table 18. This regimen was used in TUH until Dec 2018 and was changed to a 2-L PEG + ascorbic acid (MoviPrep). The reason for this change was twofold; (1) the pharmacy in TUH changed their stocked bowel preparation from KleanPrep to

Moviprep and (2) to improve CER as we noticed the suboptimal CER associated with KleanPrep highlighted in subchapter 5.1 (76%). A paper by Argüelles-Arias et al [266] found in their study that a 4-L PEG had a 70% CE rate compared to 2-L PEG + Ascorbic Acid (AA) which had a higher CER rate of 93% (p=0.043) without a significant difference in Bowel Cleansing (BC).

Table 18: Bowel Preparation Regimen for CCE and Colonoscopy in TUH prior to 2019.

Procedure	Bowel preparation	
CCE	1 week before test	Stop all iron tablets
	Day -2 (Day minus two, 2 days prior to study)	4 x 7.5mg Senna tablets at 7pm
	Day -1 (Day minus one, 1 day prior to study)	Liquid diet throughout the day (includes black tea, black coffee, broth (no particles) etc Drink at least 10 glasses of water 2 litres of KleanPrep (PEG) 7pm Fast from midnight
	Day 0 (test Day): 6am 9am	2 litres of KleanPrep (PEG) CCE is swallowed
	Small bowel reached	1 st booster of Sodium Phosphate (Fleet) 45mls (mix sachet

	(normally takes approx. 20-30mins, patient is encouraged to walk around, if delayed in the stomach 10mg of IV Metoclopramide can be given, failing that, options include endoscopic placement)	with standard 150mls of water and extract 45mls) + 50mls of Gastrograffin mixed with 1 litre of water Patient can leave the department. Instructions for 2nd booster should be explained prior to departure
	3 hours later 2nd bowel booster prepared by patient	2nd booster of Sodium Phosphate (Fleet) 25mls (prepare as per booster 1) + 25mls of premeasured Gastrograffin and 500mls of water Patient can eat and drink as normal at this point
	2 hours post 2nd booster	If capsule not passed, rectal bisacodyl suppository used
Colonoscopy	1 week before test	Stop all iron tablets
	Day -1 (Day minus one, 1 day prior to study)	Liquid diet throughout the day (includes black tea, black coffee,

		broth (no particles) etc) Drink at least 10 glasses of water 2 litres of KleanPrep (PEG) 7pm Fast from midnight
	Day 0 (test Day): 6am	2 litres of KleanPrep (PEG)

Aim

To assess the effect of changing from a 4L-PEG (KleanPrep) to a 2L-PEG + AA (MoviPrep) bowel preparation on CER and BC.

Method

In order to eliminate selection bias, 50 sequential patients who underwent CCE, pre and post change from 4L-PEG to 2L-PEG + AA bowel preparation regimen were included in the study. All patients were included in this study with no exclusions.

Patients' demographics, indications, BC score, CER and findings were recorded.

BC was divided into good, adequate, or poor. This as per subchapter 5.1 is our own units modified scale adapted from the ESGE guidelines for CCE 2012, where we combined the good and excellent rating as Good [112].

Capsule Excretion was defined as passage of CCE beyond dentate line indicating a complete colonic examination. A student t-test was used to calculate the mean differences between groups and a p value <0.05 was considered significant.

The booster regimen used throughout this study was similar in both groups and is outlined in Table 18.

Results

For the 4L-PEG group, the mean age was 50.1 (24-80) years, and 48% (n=24) were males. For the 2L-PEG + AA group mean age was 44.6 (16-77) years and 36% (n=18) were males.

Chronic diarrhoea was the most common indication for CCE in both groups (28%, n=14 in both).

For CER, there was a statistically significant difference favouring 2L-PEG over 4L-PEG; 72% (n=36) vs 54% (n=27), p=0.002).

For BC, there were no significant difference between good, adequate, and poor views in between the two groups; good 22% (n=11) vs 24% (n=12), p=0.8, adequate 66% (n=33) vs 62%(n=31), p=0.7, poor 12% (n=6) vs 14% (n=7), p=0.8.

Positive findings were reported in 50% and 56% respectively. These results are summarised in Table 19.

Table 19: Differences between 4L-PEG and 2L-PEG+AA

	4L-PEG	2L-PEG+AA	P value
CER	54% (n=27)	72% (n=36)	p=0.002
BC – good	22% (n=11)	24% (n=12)	p=0.8
BC – adequate	66% (n=33)	62%(n=31)	p=0.7
BC – poor	12% (n=6)	14% (n=7)	p=0.8

Summary

2L-PEG + AA did statistically improve CER compared to 4L-PEG [72% (n=36) vs 54% (n=27), p=0.002]] with similar bowel cleaning scores. However, CER in our study cohort remains low at 72% which is still not ideal. We will be exploring other potential cofounders which includes the booster regimes in improving CER in subchapter 5.2.2.

5.2.2 Addition of castor oil as a booster in colon capsule regimens significantly improves completion rates and polyp detection

This study has been published in World J Gastrointest Pharmacol Ther. 2021 Nov 5;12(6):103-112. doi: 10.4292/wjgpt.v12.i6.103 [6]. It was also presented at the Virtual UEGW 2020 meeting as a e-poster. Dr Serhiy Semenov is the main author of this study while Dr M Syafiq Ismail is the second author.

BACKGROUND:

In subchapter 5.2.1 we explored the effects of changing from a 4L-PEG to 2L-PEG + AA. Multiple booster and cleansing agents have been proposed in the literature in an attempt to improve CER and BC rates. Among these, a novel use of castor oil as an additional booster agent in CCE practice has been studied. Castor oil is a pale-yellow vegetable oil pressed from castor beans, produced by the *Ricinus* plant found mainly in tropical regions. Aside from its other medicinal uses, which include skin care, castor oil has been used as a laxative in traditional medicine for hundreds of years [267].

More recently, the use of castor oil in CCE has been described in several studies. In 2016, the addition of castor oil to CCE boosters has been trialled in a small number of dialysis patients with the aim of reducing liquid loading and resulted in 100% excretion rates (20/20) [260]. A further study looked at the addition of castor oil to a one-day bowel preparation protocol developed by a Japanese study group for an Ulcerative Colitis cohort, which yielded excretion rates of 93.9% (31/33) [268]. Finally, a multicentre retrospective study in Japan selecting 319 patients receiving a one-day PEG-based CCE regimen in a mixed cohort of faecal immunochemical test (FIT) positive, screening, and lower GI symptom patients, assessed excretion rates with and without castor oil. Of 152 patients receiving castor oil as a CCE booster, 97% excreted the capsule within the life of its battery compared to 81% (136/167) without castor oil [260]. Given this promising data, we aimed to

prospectively assess the effectiveness of adding castor oil as an additional booster to our CCE protocol in an unselected patient cohort.

Since end of December 2018 in TUH, as mentioned in subchapter 5.2.1, we have changed our bowel preparation regimen from a 4L-PEG to a 2L-PEG +AA with positive effects. In the mid-2019, we also changed our booster regimen from that outlined in Table 18 to a split dose of 2L-PEG + AA (Moviprep) based booster (similar as bowel preparation drug) due to safety concerns associated with the use of Sodium Phosphate which includes acute phosphate nephropathy, which has been shown to be an effective booster regimen in the available literature [269]. Due to small numbers, and recent changes to bowel preparation regimen at that time as per subchapter 5.2.1, we did not assess the impact of changing between the two booster regimens.

METHODS:

Study design & population:

This was a prospective open-label single-centre pilot study assessing the impact of castor oil on CCE performance. This study was approved as a service evaluation project by the process improvement department which is part of the quality safety and risk management directorate in our hospital. All patients referred routinely for CCE over a 5-month period (November 2019 to March 2020) received an additional 15ml of castor oil in conjunction to our standard booster regime. All patients were 18 years or older and had no contraindications to CCE or bowel preparation regimens. All patients with a history of IBD, chronic NSAID use, previous bowel surgery or any other risk for capsule retention, completed a capsule patency test prior to CCE. The outcome of this pilot was then compared to a control (non-castor oil) cohort identified retrospectively from our CCE database.

Procedure details:

Colon capsule endoscopy was carried out using the PillCam COLON2 (Medtronic, Minneapolis, MN, USA). Table 20 outlines the most up to date bowel preparation protocol used for each CCE procedure in our centre.

Two days prior to attending the capsule department for a CCE, all patients received four 12mg Senna tablets. This was followed by a two-litre split-dose bowel preparation with Moviprep® (PEG-3350, sodium sulphate, sodium chloride, potassium chloride, sodium ascorbate and ascorbic acid for oral solution; Norgine B. V, UK), a PEG-based solution used predominantly in our colonoscopy practice. The patients were instructed to ingest the 1st litre on the evening before, and the 2nd litre on the morning of the procedure. In the event of delayed gastric emptying, recorded as presence of capsule in the stomach 30 minutes post ingestion, all patients without contraindications received intravenous prokinetics; 10mg of metoclopramide followed by 250mg erythromycin, if unsuccessful.

Control booster regimen included Moviprep® with 750ml of water (booster 1) on reaching the small bowel. A further dose of Moviprep® with 250ml of water was given 3 hours later and a bisacodyl suppository (Dulcolax®) 10mg after 8 hours if the capsule was not excreted. Cases followed the same regimen with the addition of 15ml of castor oil given with booster 1. The studies were all read by trained CCE readers, unblinded to bowel preparation, and the final reports were reviewed and signed off at our local departmental capsule review board.

Table 20: Bowel Preparation Procedure

Time	Procedure/Patient instructions	Regimen/Medication	Dose/Volume
Day -7	Stop iron tablets		
Day -2: 19:00		Senna tablets	4 x 12mg
Day -1	- Liquid diet (e.g. black tea, black coffee, clear broth, soft drinks, jelly, ice cream, etc.) - Drink at least 10 glasses of water throughout the day - Clear fluids only from midnight		
Day -1: 19:00		Sachet A&B Moviprep® +Water	1L
Day of procedure			
07:00	Essential medications may be taken with sips of water	Sachet A&B Moviprep® + Water	1L
Time of appointment +30 minutes	- Capsule swallowed - Video checked for capsule passage into small bowel - Administer prokinetics if delayed gastric emptying	*Optional* IV Metoclopramide IV Erythromycin	10mg 250mg
Confirmation of capsule in small bowel	<u>Booster 1</u> (Only cases) - Patient can now drink fluids freely	Moviprep® A&B + Water Castor oil	750ml +15ml
+3 hours	<u>Booster 2</u> - Patient can now have a light meal and take remaining medications	Moviprep® A&B + Water	250ml
+5 hours	- Patient notes capsule excretion - Administer rectal suppository if capsule not visualised	*Optional* Dulcolax®suppository	10mg

Data analysis:

A nested case control design was employed with a 2:1 ratio (2 controls: 1 case) whereby controls were taken from our capsule database in chronological order without any selection bias.

We recorded patient demographics including age, gender, and indication for CCE. CCE excretion/completion was defined as uninterrupted image capture from the caecum to the dentate line within its battery life. In the event of failed capsule excretion, CCE was considered complete if images of the haemorrhoidal plexus were recorded.

Colonic image quality was based on the reader's overall impression of the bowel preparation and recorded as either "adequate" or "inadequate" at the time of reporting. All CCE procedures were read by trained capsule endoscopists, and reports reviewed at weekly capsule review meetings with at least one CCE expert reader present. The cleansing level was evaluated based on a previously validated scale and classified as poor (large amount of faecal residue), fair (enough residue to preclude a completely reliable examination), good (small amount of residue, not enough to interfere with examination) and excellent (no more than small amounts of adherent faeces) for each colonic segment. Examinations scored as 'poor' or 'fair' in any segment were considered 'inadequate', whereas those scored as 'good' or 'excellent' in all segments were considered 'adequate' [270, 271].

Colonic transit time was automatically generated by the PILLCAM™ SOFTWARE V9 and recorded directly from the CCE report. Findings were recorded and clinically significant findings included: colonic polyps, cancers, inflammation, and bleeding. Extra colonic findings were also documented where present. A CCE positivity rate was calculated by including studies with significant colonic findings as outline above. Adverse events and complications were documented.

Results were compared between the two groups of patients. Statistical analysis employed a student t test and "chi2" tests as appropriate, utilising the GraphPad online software. A p-value of less than 0.05 was considered statistically significant. Odds ratios, number needed to treat (NNT), and absolute risk reduction were calculated as required. Per protocol analysis was undertaken including patients only who were able to swallow the capsule and took at least some of the study medication.

RESULTS:

Patient demographics:

A total of 186 CCEs have been analysed; 124 controls and 62 cases receiving castor oil with booster 1. In all, the mean age was 60 years of age and 56% were females (104/186). The age and gender breakdown did not statistically differ between the two populations. The following were indications for CCE in order of prevalence; 96 polyp surveillance (51.6%), 42 lower gastrointestinal symptoms (22.6%), 28 due to incomplete colonoscopy (15%), 18 anaemia (9.7%) and 2 IBD surveillance (1.1%). Allowing for a slightly larger proportion of castor oil patients referred for anaemia work up; the indication breakdown did not significantly vary. Table 21 outlines the breakdown of demographics and indications between the two groups.

Table 21: Basic demographics of patients and indications for CCE.

	Total	With castor oil	Without castor oil	P-value
	186	62	124	
Age				0.2365
Mean	60.0	62.0	59.0	
Range	18-97	22-97	18-86	
Gender				0.8357
Male	82 (44%)	28 (45.2%)	54 (43.5%)	
Female	104 (56%)	34 (54.8%)	70 (56.5%)	
Indications				
Polyp surveillance	96	30/62 (48.4%)	66/124 (53.2%)	0.5362
Lower gastrointestinal symptoms	42	10/62 (16.1%)	32/124 (25.8%)	0.1382
Incomplete colonoscopy	28	11/62 (17.7%)	17/124 (13.7%)	0.4712
Anaemia	18	10/62 (16.1%)	8/124 (6.5%)	0.0355
IBD surveillance	2	1/62 (1.6%)	1/124 (0.8%)	0.6174

Assessing the effect of castor oil:

Overall CCE completion was 77% (144/186). Image quality was adequate and/or diagnostic in 91% (170/186). Mean colonic transit time was 3.5 hours with a range of 0.25-13. Overall CCE positivity (presence of significant colonic findings) was 59% (109/186) and the polyp detection rate was 57% (106/186). Additional pathology including colonic diverticulae, small bowel findings and gastric

findings were found in 63% (78/124), 22% (27/124) and 12% (15/124) of the overall studies, respectively. There were no cases of colorectal cancer recorded in this study.

Completion rates were significantly higher with castor oil, 87% (54/62) compared with 73% controls (90/124), ($p=0.01$). The NNT with castor oil to result in an additional complete CCE study was 7, absolute risk reduction = 14.52%, (95% CI 3.06- 25.97). Polyp detection rates were also higher in the castor oil group 82% (51/62) vs 44% (55/124), ($p<0.0001$), with an OR of 5.8, (95%CI 2.77-12.21). Similarly, overall positivity rates, which include studies with polyps, colitis and bleeding, were higher with castor oil, 84% (52/62) vs 46% (57/124), ($p<0.0001$), OR of 6.1, (95%CI 2.85 to 13.11).

Transit times were similar, 3.2 and 3.8 hours, with and without castor oil, respectively. Castor oil did not contribute to poorer image quality as rates were similar between the two groups; reported as adequate and/or diagnostic in 90% (56/62) vs 92% (114/124). Table 22 outlines comparisons between cases and controls.

Table 22: Effects of castor oil on CCE performance

Variables	Overall	With castor oil	Without castor oil	P-value
Capsule completion	144/186 (77%)	54/62 (87%)	90/124 (73%)	0.0128
Image quality (adequate/diagnostic)	170/186 (91%)	56/62 (90%)	114/124 (92%)	0.3558
Colonic transit time (hours) <i>Mean:</i>	3.5	3.2	3.8	0.1779
<i>Range:</i>	0.25-13	0.25-13	0.5-13	CI -2.90 to 0.54
CCE positivity	109/186 (59%)	52/62 (84%)	57/124 (46%)	<0.0001 CI 2.85 to 13.11 OR 6.1
Polyp detection rate	106/186 (57%)	51/62 (82%)	55/124 (44%)	<0.0001 CI 2.77 to 12.21 OR 5.8

Impact of gender, age, and indication on CCE completion:

Castor oil appears to improve completion rates. This effect is more significant in the over 60s, ($p < 0.03$). Similarly, the effect of the addition of castor oil is more pronounced in females, ($p < 0.025$). This is shown in table 23 below. The NNT with castor oil to have one more complete study was 6 for both female gender (absolute risk reduction 18.5%, 95% CI 1.94 - 34.36) and older age (absolute risk reduction 18%, 95% CI 1.65 – 34.46). The NNT with castor oil to have one more complete study was 5 for older females (absolute risk reduction 24.36%, 95% CI 1.23 to 47.48).

The male gender appears to be a predictor of higher excretion rates (83% vs 73%); however, this does not reach statistical significance, ($p = 0.0553$). Unsurprisingly, younger age is a significant predictive factor of higher excretion rates (86% vs 71%), ($p = 0.0094$).

Allowing for low incidence, castor oil did not appear to influence excretion rates in patients referred following an incomplete colonoscopy, anaemia work-up and IBD surveillance.

Table 23: CCE Completion vs non-completion

Variable	Total	With castor oil	Without castor oil	P-value
Overall capsule completion	144/186 (77%)	54/62 (87%)	90/124 (73%)	0.0128
<u>Age:</u>				
≤60	67/78 (86%)	24/26 (92%)	43/52 (83%)	0.1250
>60	77/108 (71%)	30/36 (83%)	47/72 (65%)	0.0253
<u>Gender:</u>				
Male	68/82 (83%)	25/28 (89%)	43/54 (80%)	0.1352
Female	76/104 (73%)	29/34 (85%)	47/70 (67%)	0.0251
<u>Indication:</u>				
Polyp surveillance	75/96 (78%)	28/30 (93%)	47/66 (71%)	0.0075

Lower gastrointestinal symptoms	36/42 (86%)	10/10 (100%)	26/32 (81%)	0.0450
Incomplete colonoscopy	19/28 (68%)	7/11 (63%)	12/17 (71%)	0.3502
Anaemia	12/18 (67%)	8/10 (80%)	4/8 (50%)	0.0899
IBD surveillance	2/2 (100%)	1/1 (100%)	1/1 (100%)	1.0

Adverse events:

There were no reported significant adverse events with castor oil and no documented events of patients refusing castor oil. There were also no significant complications associated with CCE procedure or the remainder of bowel preparation regimens, including capsule retention, bowel obstruction, severe abdominal pain, IBD flare and anaphylaxis to medications.

DISCUSSION:

With the increasing demand for solutions in tackling long colonoscopy waiting lists, CCE has become an attractive alternative. Given its potential, the importance of maximising CCE's performance has been recognised in the literature with a growing body of work looking into improving capsule excretion, image quality, detection of pathology and patient acceptance. Our study is the largest European study to date prospectively assessing the use of castor oil as an addition to a CCE booster regimen in an unselected cohort.

Our data suggests small volumes of cheap and readily available castor oil (15ml) can significantly increase excretion rates (87%) without compromising image quality or colonic transit times. This effect appears more significant in an older population and in females.

The significance of castor oil in completion rates is matched by other studies including the largest to date multicentre retrospective study from Japan, reporting rates as high as 97% [260]. Of note, the authors used a very different and complex preparation regimen comprising of 7 different agents (magnesium citrate, sodium picosulphate, Senna, Moviprep®, Mosapride, metoclopramide, Daikenchuto®) and up to 3L of bowel preparation in one day. This contrasts with our simple split-dose regimen requiring less bowel preparation volumes on the day of the procedure. Our protocol is based on evidence from Denmark showing no added value in adding gastrografin or magnesium

citrate in a split-dose regimen [269]. This study included Magnesium Citrate & Sodium Picosulphate (MCSP), a preparation highlighted in recent European guidelines for its safety concerns. Because of hyperosmolarity and magnesium content, solutions containing MCSP are contraindicated in patients with congestive heart disease, hypermagnesemia, rhabdomyolysis, gastrointestinal ulcerations, and severe impairment of renal function, which can lead to magnesium accumulation [272]. This could be one of the factors contributing to a lower excretion rate in our study (87% vs 97%). A further factor worth noting is that male gender has been identified as a significant predictor for capsule excretion in both studies and could be responsible for higher excretion rates in the Japanese study, which reports a male majority in its castor oil group of 66% (101 vs 51) as opposed to a female majority in our study of 54% (29 vs 25). Similar findings have been reported for standard colonoscopy [273]. Our study reveals that excretion rates also vary by indication, with polyp surveillance and lower GI symptom cohorts doing better, with 93% and 100% excretion rates, respectively.

Unlike other proposed booster agents like sodium phosphate which has been associated with nephropathy and electrolyte disturbances [274], castor oil appears safe and acceptable to patients with no significant side effects reported during the study period. Indeed, unlike other proposed booster regimens, castor oil has been used for thousands of years and is only contraindicated in pregnancy as it is known to induce uterine contractions [275]. Given its lower volume, castor oil has an advantage over larger volume ascorbic acid-based, magnesium-based, sulphate-based, or gastrografin-based booster preparations [269, 276, 277] as this is more likely to be acceptable to patients. It is important to note, our protocol added 15ml of castor oil to booster 1, contrasting with some other studies which have utilised higher doses of 30-60 ml with variable efficacy. The excretion rate in our study remains suboptimal, <90%, which is the minimum standard for caecal intubation rate in colonoscopy as recommended in recent European guidelines [272]. Whether increasing the dose of castor oil leads to further improvement in completion rates is unclear and warrants further investigation.

Oral ingestion of castor oil stimulates lipases in the small intestine to produce ricinoleic acid which in turn produces a strong laxative effect [267]. Reassuringly, this agent has not had an effect on the overall colonic transit rates as seen in our study. This finding is consistent with previous studies suggesting this effect is selective to small bowel mucosa, by activating intestinal EP3 receptors, and not the colon [275], in turn preserving the diagnostic value of CCE. It is also important to note that

overall image quality appears to be unchanged despite castor oil's effect on small bowel transit which can result in the capsule reaching the colon prematurely, i.e., before colonic cleansing is complete with a split dose PEG regimen.

The authors acknowledge limitations of this being a single centre study. This can, however, also be viewed as a strength as this ensured that all patients received a high quality and uniform CCE procedure in accordance with our departmental protocol. Secondly, this study incorporates a retrospective control cohort which can contribute to a selection bias. Thirdly, due to a departmental polyp surveillance initiative which overlapped with the period of this study, our patient cohort was skewed by a large proportion (52%) of CCE patients referred for polyp surveillance. This resulted in a particularly high overall polyp detection rate of 57%. Correlation with colonoscopy could be of benefit but this data was not available as most of CCE patients did not require a short-term follow up colonoscopy within the period of the study. This does not affect the validity of our data as cases and controls did not vary significantly by age, gender or CCE indication. Surprisingly, despite a smaller proportion of castor oil CCEs referred for polyp surveillance compared to the non-castor oil group (48.4% vs 53.2%) polyp detection rates were almost twice as high (44% vs 82%). One potential reason for this is the higher completion rates leading to more frequent visualisation of the entire colonic mucosa and increased detection of left sided lesions. This highlights the value of castor oil in CCE bowel preparation and its potential as an alternative tool in polyp screening or surveillance.

CONCLUSION:

In our capsule endoscopy centre, the addition of a single 15ml dose of castor oil to booster 1, as part of a simple split dose Moviprep® CCE protocol, appears safe, acceptable by patients and significantly improves completion rates and polyp detection in an unselected cohort.

5.3 Comparing Colon Capsule Endoscopy To Colonoscopy; A Symptomatic Patient's Perspective

This subchapter has been presented as a e-poster presentation at e-poster presentation at the ESGE Days 2019 meeting in Prague. This study has been published in BMC Gastroenterol. 2022 Jan 24;22(1):31. doi: 10.1186/s12876-021-02081-0 [7]. Dr M Syafiq Ismail and Dr Greg Murphy are co-first authors to this study.

We have shown the clinical efficacy for CCE in symptomatic patient assessment in Chapter 5.1. In subchapter 5.2 we describe how changes of bowel preparation and booster regimens affect CER and BC. In this subchapter we wanted to determine patient satisfaction, comfort, and preference towards the test.

Introduction:

Fibreoptic colonoscopy is a well-established modality for investigating the large bowel and offers both diagnostic and therapeutic potential for ileocolonic diseases. In Ireland, they are usually performed under conscious sedation with Midazolam and Fentanyl. Even though colonoscopies are generally well tolerated and considered safe, they do come with potential risks. General complications associated with colonoscopies are usually related to sedation, bowel perforation and a risk of haemorrhage. A recent review article by the American Society of Gastrointestinal Endoscopy (ASGE) found a pooled perforation rate of 5.8 per 10,000 colonoscopies (95% CI, 5.7- 6.0), bleeding rate of 2.4 per 1000 colonoscopies (95% CI, 2.4-2.5), and death rate of 3 in 100,000 colonoscopies [16]. Furthermore, there is a risk of causing pain and discomfort to the patient during colonoscopy. This is often worse in younger, female patients with lower Body Mass Indices (BMI) or in patients who have had previous abdominal and pelvic surgery [17].

Apart from the risks of complications, there are also patient factors to be considered. Patients can be reluctant to undergo this invasive procedure due to their perceived embarrassment, inconvenience, or discomfort associated with colonoscopy [12, 18]. In a study about anxiety related to colonoscopy in 1336 patients, Shafer et al found very high anxiety scores (>70) reported by 29% of patients relating to the procedure itself [19].

The European Society of Gastrointestinal Endoscopy (ESGE) has recommended Colon Capsule Endoscopy (CCE) as a safe alternative to colonoscopy in average risk individuals [112]. In a more recent joint guideline update, by ESGE and the European Society of Gastrointestinal and Abdominal Radiology (ESGAR) CCE may be considered as an alternative to colonoscopy in patients with non-alarm symptoms [110]. CCE is considered less invasive and does not require air insufflation or sedation. Risks of CCE are minimum and has recently been reported in a meta-analysis by Wang et al

as capsule retention (0.26%), swallowing difficulties (0.04%), technical failure (1.76%), incomplete colonic examination (19%), and discomfort (0.81%) [113].

CCE has proven efficacy to detect both neoplastic and non-neoplastic disease in selected patient cohorts including Inflammatory Bowel Disease patient assessment, average, and low risk colorectal cancer screening, after incomplete colonoscopy and polyp surveillance [114-121, 278]. As outlined in subchapter 5.1, CCE has been shown to have a sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV) of 81%, 98%, 93% and 94% respectively in a symptomatic cohort when compared to colonoscopy for detecting CSD [4]. Despite its growing popularity and proven clinical efficacy, few studies have focused on patient preference between colonoscopy and CCE.

Aims:

The aim of this study was to identify patient reported outcomes of comfort and satisfaction in relation to both CCE and colonoscopy and to establish if there was a difference in preference between both modalities. We also wanted to assess whether there was a difference in patient versus endoscopist reported comfort scores post colonoscopy.

Method:

This study has been done in accordance with STROBE (STrengthening the Reporting of OBservational studies in Epidemiology) guidelines. This is a retrospective single centre comparative study conducted in Tallaght University Hospital (TUH), Ireland of patient reported satisfaction, comfort, and preference for CCE and colonoscopy procedures.

This study has been approved as a service assessment by the quality improvement committee, Tallaght University Hospital.

Study Population and referral criteria

Identified patients between the age of 18-80 from our electronic database who had both a CCE and colonoscopy over a 12-month period (Dec 2017 – Dec 2018) was included in this study. In order to prevent selection bias, all contactable patients who had both tests over the period were recruited. We excluded patients who could not consent to the study.

Both CCE and colonoscopy tests were performed in the cohort of patients involved in the study in subchapter 5.1 [4]. As such all participants were scheduled to have both procedures.

Study Design

A summary of the study is outlined in Table 24. All CCEs were performed using PillCam™ COLON 2 (Medtronic, Minneapolis, USA). Colonoscopy reports were generated and stored on a national endoscopy database, Unisoft (HD Clinical, Hertfordshire, UK).

Table 24: Study design and patient demographics

Study Design
Step 1: Patient identification through electronic database from Dec 2017-Dec 2018.
- N=40 patients identified - 57.5% (23/40) female, - Mean age - 48 (24-78) years
Step 2: Patient contacted for interview (Questions from Table 25)
Step 3: Further data collection for CCE and colonoscopy
- CCE data - Bowel preparation and booster medications, findings, capsule completion rate - Colonoscopy data - GCS from colonoscopy, endoscopist grade, sedation used, findings, completion, other adjuncts used.

Upon recruitment, we performed over-the-phone interviews a minimum of 3 months after completion of their investigations, focusing on questions related to satisfaction, comfort, and overall preference. Interviews were performed by trained medical professionals using secure hospital phone lines. Interview questions are listed in Table 25. A 10-point Likert scale was used to assess both comfort and satisfaction ranging from 1 (negative response) to 10 (positive response) for both CCE and colonoscopy procedures. The interviewers also asked each interviewee, if further colonic investigations were required, which test if either they would prefer; a CCE or colonoscopy. If patients had answered CCE as the preferred method of investigation, based on their own personal experience, the interviewer then asked if their answer would change if the CCE found findings that warranted referral on for a colonoscopy including incomplete CCE. The interviewer then asked an open-ended question regarding any cause of dissatisfaction for either CCE or colonoscopy.

Table 25: Patient Questionnaire

Patient Questionnaire
On a scale of 1-10 (1=Negative / 10=Positive): • How satisfied were you with your CCE? • How satisfied were you with your colonoscopy? • In terms of pain, how comfortable was your CCE? • In terms of pain, how comfortable was your colonoscopy?
<u>Preference:</u> • If you required further bowel testing in the future, would you rather a CCE or Colonoscopy?
Follow on Question (if above= "CCE"): • Would your answer change if there was a likelihood/chance that you would require a colonoscopy following CCE (i.e., have both tests)?
Any particular reasons for your dissatisfaction with CCE and/or colonoscopy?

In addition to the interview, we collected further demographic, clinical and procedural data for each patient from our CCE and endoscopy databases including bowel preparation and booster regimens, and capsule completion rate. Further colonoscopy data collected included, the Modified-Gloucester-

Comfort-Scale (GCS) score, endoscopists grade and quality data (caecal intubation rate – CIR, polyp detection rate – PDR, and mean comfort score ≤ 3), amount of sedation used, and whether a scope guide was used during colonoscopy.

The GCS is used at our centre and in all endoscopy units in Ireland. This score is usually given by the endoscopy nurses after the colonoscopy and agreed by the endoscopist in order to prevent an operator bias. As detailed Table 26, a score of 1 refers to no discomfort while 5 is associated with severe discomfort. These scores are kept on a secure database and form part of the quality indicators for colonoscopy which is regularly audited as part of the National Quality Assurance Information System (NQAIS). This data is not available on endoscopy reports and is not routinely told to the patients post procedure. There was no endoscopist reported comfort score for CCE.

Table 26: Modified-Gloucester-Comfort-Scale

Score	Scale	Description
1	No	No discomfort, talking/resting comfortably throughout
2	Minimal	One or two episodes of mild discomfort (without distress)
3	Mild	More than two episodes of mild discomfort (without distress)
4	Moderate	Significant discomfort experienced several times with some distress
5	Severe	Extreme discomfort frequently during the test

Bowel preparation

The bowel preparation used in this study is similar to that used in subchapter 5.1. Bowel preparation for CCE was a split dose 4-liter (4L) Polyethylene glycol (PEG) (KleanPrep – Norgine, Middlesex, UK) with the addition of Phospho-soda, “Fleet” (Casen Recordati, Zaragoza, Spain), Gastrograffin (Bayer, Reading, UK) and rectal Bisacodyl (Dulcolax – Sanofi-Aventis, Ireland) suppository booster medications. Similarly, all patients received a further split dose 4L Polyethylene glycol (KleanPrep –

Norgine, Middlesex, UK), bowel preparation prior to colonoscopy (Table 18). In addition, standard dietary manipulation was advised for several days prior to both procedures.

All obtained data were kept on secure encrypted hospital computers. Statistical analysis was performed using MedCalc (MedCalc Software Ltd, Belgium). A Chi-squared test was used to compare categorical data and a Student t-test was used to compare means, a $p < 0.05$ was deemed significant. Pearson Correlation Coefficient was used to assess the correlation between patient and operator reported comfort scores. A r value of ≥ 0.7 was considered as a strong correlation.

Results:

Study Population

In all, 40 patients were identified at our centre who had both a CCE and colonoscopy over the 12-months period. All the patients were contacted and were willing to participate in the over-the-phone interviews; 57.5% (23/40) of these were female, with a mean age of 48 (24-78) years. All CCE tests, were performed before the colonoscopy. The interval between the two procedures was on average 6 weeks (range 2-8 weeks). The CCE report was available to the endoscopist at the time of colonoscopy. Despite the cohort of patients for this study coming from the study in subchapter 5.1, we only included all the 40 identified and contacted patients who had both tests between December 2017 to December 2018. The reason for this is to ensure unanimity in bowel preparation and booster regimen which has been changed in beginning of January 2019, as mentioned in subchapter 5.2.1 and 5.2.2.

CCE data

CCE completion rate was 78% ($n=31$) with 100% ($n=40$) reaching the left colon. Positive findings were reported in 68% ($n=27$). Bowel preparation quality for CCE were reported as good/adequate in 36 (90%) and inadequate in 4 (10%).

Colonoscopy data

All colonoscopies were performed by two senior endoscopists who met NQAIS standards with CIR of 95.5%, 95.3%, PDR of 42.4%, 49.9% and mean GCS ≤ 3 of 99%, 96% respectively. All patients received

procedural sedation with mean sedation of 4.2mg (range 2-8mg) of Midazolam and 68.1mcg (range 50mcg-100mcg) of Fentanyl. Caecal intubation was achieved in 92.5% (n=37). The scope guide was not used in any of the colonoscopy procedures. All colonoscopies were done under air insufflation only. Positive findings were reported in 65% (n=26). Bowel preparation quality for colonoscopy was reported as good/adequate in 36 (90%) and inadequate in 4 (10%). Total colonoscopy procedural times were not available.

There were no immediate or late procedural related complications for any patients for both their CCE and colonoscopy procedures. All patients were reviewed in clinic following their tests and appropriate follow up arranged.

Interview results

The mean interval between CCE to interview was 33 weeks (14 to 52 weeks) and the mean interval between colonoscopy to the interview was 30 weeks (12 to 50 weeks). Regarding satisfaction score, mean satisfaction reported was 8.3 (range 3-10) for CCE and 7.7 (range 1-10) for colonoscopy. Regarding comfort score, mean comfort was 9.2 (range 6-10) for CCE vs 6.7 (1-10) for colonoscopy.

There was a statistically significant difference in mean comfort (9.2 vs 6.7, $p<0.0001$, 95% CI -3.51 to -1.44) but not satisfaction scores (8.3 vs 7.7, $p=0.2$, 95% CI -1.48 to 0.33) between CCE and colonoscopy, respectively.

Of note the volume of bowel preparation and booster medications required was identified as the main cause of dissatisfaction with CCE (25%, n= 10/40). The main cause of dissatisfaction with colonoscopy was pain and discomfort (33%, n=13/40).

Subgroup analysis

There were no significant differences between mean satisfaction for either CCE or colonoscopy when responses were divided into gender (male and female) or age (age less than 50 and above 50).

However, when looking at comfort, there were significant differences between responses in all subgroups favouring CCE over colonoscopy. The highest significant difference was between the comfort reported in those below 50 favouring CCE over colonoscopy (9.4 vs 6.5, $p=0.0002$, 95% CI -4.21 to -1.55).

A further breakdown of subgroup analysis is listed in Table 27.

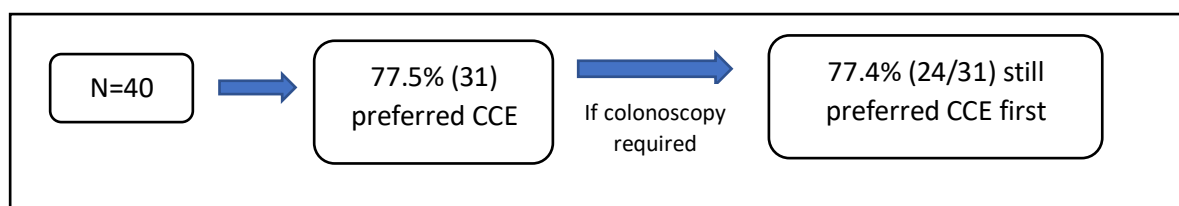
Table 27: Mean difference between patient reported scores for CCE and Colonoscopy

	CCE	Colonoscopy	P value	95% CI
Satisfaction	8.3	7.7	$p=0.20$,	-1.48 to 0.33
Male	8	8	$p=1$,	-1.06 to 1.06
Female	8.4	7.4	$p=0.16$	-2.41 to 0.41
<50	7.8	7.9	$p=0.80$	-0.83 to 1.07
>50	9	7.3	$p=0.06$	-3.56 to 0.1
Comfort	9.2	6.7	$p<0.0001$	-3.51 to -1.44
Male	9.2	6.9	$p=0.004$	-3.75 to -0.84
Female	9.2	6.6	$p=0.002$	-4.16 to -1.06
<50	9.4	6.5	$P=0.0002$	-4.21 to -1.55
>50	8.9	7.1	$p=0.05$	-3.62 to 0.02

Patient preference

Overall, 77.5% ($n=31/40$) of patients would prefer CCE if they required a further lower GI investigation in the future. Of these, 77.4% ($n=24/31$) still preferred CCE despite the potential need for a follow-up colonoscopy. 70.6% (12/17) of males and 82.6% of females prefer CCE over colonoscopy and gender does not seem to affect this preference ($p=0.37$).

Figure 4: Patient preference regarding CCE



The mean reported Modified-Gloucester-Comfort-Scale for colonoscopies were 1.4 (range 1-4). When looking at the correlation between endoscopist reported GCS mean 1.4 (range 1-4) and patient reported scores 6.7 (1-10), only a weak negative correlation was found ($r=-0.28$). If we assume that comfort was defined as a $GCS < 3$, and a 10-point scale score ≥ 7 , 73% ($n=29$) of patients reported feeling comfortable with their colonoscopy while endoscopy reported comfort was 88% ($n=35$) with a weak positive correlation reported ($r=0.44$, $p=0.004$). Table 28 summarises these findings.

Table 28: Difference and correlation between endoscopist and patient reported comfort

	CCE	Colonoscopy	R value
Comfort	6.7 (1-10) on patient reported Likert scale	1.4 (1-4) endoscopist reported GCS	$r=-0.28$
If comfort is $GCS < 3$ and Likert scale ≥ 7	88% ($n=35$) reported feeling comfortable	73% ($n=29$) reported feeling comfortable	$r=0.44$, $p=0.004$

Discussion:

Our retrospective comparative study has found that CCE was reported by patients to be a more comfortable procedure (9.2 vs 6.7, $p<0.0001$) with comparable satisfaction scores compared to colonoscopy (8.3 vs 7.7, $p=0.28$). A majority of our patients (77.5%, $n=31/40$) also preferred to have a CCE compared to colonoscopy if a repeat endoscopic procedure is required in the future. Among these, a further 77.4% (24/31) of patients still preferred a CCE over colonoscopy even if the results of the CCE would require them to have a colonoscopy for any intervention or further diagnostic work-up.

Both procedures resulted in similar satisfaction scores (CCE - 8.3 vs colonoscopy - 7.7, $p=0.28$). For CCE, high satisfaction score could be related to the minimally invasive nature of the procedure, the fact that no/minimal discomfort or pain is involved, and the lack of embarrassment associated with colonoscopy. Furthermore, in our centre, CCEs are performed in our dedicated Capsule Endoscopy Department by trained nursing staff, medical staff, and technicians as outpatient procedures. As patients are not given any sedative medications for CCE, they can go about their day as normal, with some patients opting to return to work while others seek the comfort of their own homes. For colonoscopy, the high satisfaction score could be related to the professionalism of the endoscopy

department staffs, the definitive nature of colonoscopy in most cases, and the ability to perform intervention on same procedure. The absence of complications in our cohort also could be associated with high satisfaction scores.

Of note for both procedures, patients are usually contacted prior to attending the procedure to ensure compliance with bowel preparation and diet, and to address any concerns that they may have, which could have contributed to similarly high overall satisfaction.

Despite having higher comfort and satisfaction scores, the amount of bowel preparation and booster medications (Table 18) that needed to be taken was identified as the main issue causing dissatisfaction with CCE (25% of patients). CCE relies on a high degree of bowel cleansing as it lacks the air insufflation and the ability to perform colonic cleaning and suctioning in colonoscopy. Apart from that, unlike for a Small Bowel Capsule (SBCE), booster medications are needed to propel the capsule through a patient's small bowel and colon to ensure a complete examination. This regimen, although appearing excessive, is based on the 2012 ESGE guidelines for CCE [112]. Since the completion of this study, CCE preparation in our unit has been changed to a lower volume split dose Moviprep (Norgine, Middlesex, UK) preparation pre-CCE, with Moviprep and Castor oil as boosters (Table 20). Audits of these changes have shown an 87% capsule excretion rate and also improved image quality [5, 261]. We have yet to assess patient's satisfaction and comfort following this change but due to reduction of the volume of bowel preparation, one would assume higher scores will be awarded.

This study also highlights the disconnect between the level of comfort patients experienced compared to endoscopy reported Modified-Gloucester-Comfort-Scores. The GCS, although not formally validated, is used to assess patient comfort during colonoscopy in all Irish endoscopy units, forms part of quality indicators of colonoscopy and is regularly audited by NQAIS [279-281]. Similar discordances have also been reported in other studies [282, 283]. The GCS was designed to be provided by the endoscopy nurses and agreed by the endoscopist, but it is possible that they are too intimately involved in the procedure to provide a truly objective assessment [282]. Poor comfort outcomes may cause patients to refrain from engaging with similar diagnostic tools in the future. Development and implementation of comfort scores that includes patient's perspective such as the Patient-Reported Scale for Tolerability of Endoscopic Procedures (PRO-STEP) [284] or scores that

have shown correlation with patient reported outcomes such as the St. Paul's endoscopy comfort score (SPECS) [279] should be considered. Although these scores are validated their use are not yet common. GCS itself has never been validated for patient use. To date, there isn't a validated scoring system that measures both patients reported satisfaction and comfort. This is why we chose the simpler 10-point Likert scale in our interview for better patient comprehension and understanding.

The strength of this study is that to our knowledge, it is the only study that purely focuses on patient reported outcomes following both CCE and colonoscopy procedures in a symptomatic cohort. In a mix of screening and symptomatic patients, Ojidu et al reported in different group of patients undergoing either CCE, colonoscopy and CT colonoscopy (CTC) mean GCSs of 1.3, 3.32, and 1.96 respectively [282]. Furthermore, when comparing CCE and CTC, they also found that 76.8% reported no discomfort for CCE compared to 31.9% for CTC [282]. In a CRC screening cohort, Thygesen et al reported moderate to high discomfort in 89% participants undergoing colonoscopy compared with 7% undergoing CCE [285]. It is interesting to note that despite receiving intravenous procedural sedation and analgesia for colonoscopy patient reported comfort scores are poorer, reflecting the invasive nature of this procedure.

Patient reported outcome studies may be prone to certain individual biases, however it is the only way to assess patients own perspective regarding satisfaction and comfort.

We did not report on any patient diagnosis in this study and purely focused on patient reported procedural outcomes of comfort and satisfaction. The impact of diagnosis on the overall satisfaction and perceived comfort is not known. However, it should not significantly affect the results as patients were unselected and average risk and there were no cases of cancer detected.

An advantage is that all our participants were in a comparative study and underwent both tests giving subjects the opportunity to compare both procedures directly. This could however be considered not to reflect their preferences in actual clinical practice. In particular, the need for a therapeutic colonoscopy after a positive CCE could be a disadvantage. In our cohort though, the majority who reported a preference for CCE in the future, did so accepting of that possibility. In addition, this argument supposes there is never a need for a repeat colonoscopy, for preparation quality, anticoagulant, or completion issues. As such the opportunity to directly compare tests remains a valid assessment.

Another possible limitation to this study is that interviews were conducted at most 3 months since completion of both tests. The effect of this time lag on patients recall cannot be assessed. Another factor that may not be able to assess is the effect of sedation on patient comfort and recall in our study cohort. Ball et al has previously reported that the amount of sedation given to a patient during colonoscopy does not correlate with comfort scores ($p < 0.2$) [286].

In terms of other factors that may be associated with comfort scores, it has been previously reported that symptomatic patients often experience poorer comfort scores than screening patients [282], whether or not this played a role in our cohort is difficult to determine. The use of CO₂ insufflation has been associated with better comfort scores [287]. We only used air insufflation and not CO₂ insufflation in our colonoscopies during this study period due to unavailability and hence would be a limitation to this study. Since study completion, all endoscopy rooms in our department have been installed with a CO₂ insufflation device. The correlation of its use and comfort score in our centre has yet to be reviewed. Both of our endoscopists performing the colonoscopies met and exceeded minimum NQAIS standards. The use of the scope guide has not been found to be beneficial in improving patients comfort scores in experienced endoscopists and is unlikely to have affected our results [288].

In our cohort, we did not find a difference between patients reported satisfaction and comfort when looking at age (less than and above 50) and gender as possible variables. We did not have available data to assess patients' anxiety levels pre-procedure, duration of colonoscopy, patients BMI and endoscopist reported ease of colonoscopy, all of which may be possible factors that may result in a more difficult and uncomfortable procedure [17]. This does open possibility for future prospective research.

As mentioned previously, 77.5% (31/40) of patients would prefer to have CCE over colonoscopy in the future. Interestingly of these 31 patients, 77.4% (24/31) would still choose to have CCE as first line even with the knowledge that they may have to have a colonoscopy as a second procedure if further investigation or intervention was required. As explained in the introduction, CCE has proven efficacy in a variety of clinical situations and can be used in both the symptomatic and screening cohort [114-121, 278]. As such, we would like to recommend clinicians include alternatives to colonoscopy such as CCE when discussing available investigations with patients. Providing proven

alternatives, especially ones that are associated with greater levels of comfort and less complications should form part of the process of informed consent.

Summary

CCE has a high satisfaction rating and has a higher comfort rating than colonoscopy in symptomatic patients. Studies have confirmed CCE, and colonoscopy have equivalent diagnostic yields. The majority of patients in our cohort prefer CCE to colonoscopy. CCE should be considered as an alternative to colonoscopy in selected individuals.

Chapter 6: Potential roles for CCE in response to the Covid 19 Pandemic

6.1 Colon Capsule Endoscopy to reduce waiting lists for symptomatic patients and surveillance colonoscopy patients due to the negative impact on services of the Covid-19 pandemic.

This subchapter has been submitted as a “Letter to the Editor” in Endoscopy International Open.

Dear Editor

The Covid-19 (SARS-COV 2) pandemic has had a devastating impact globally with 170,812,850 number of infections and 3,557,586 number of deaths related to the novel virus to date [289]. With the emergence of new variants, slow roll-out of vaccinations, and some countries experiencing multiple waves of infection; the effect of this pandemic is far from over. In Ireland, during the first wave of the infection a full lockdown was implemented, and multiple endoscopic procedures were deferred or cancelled. Some endoscopy centres also had to close for the third wave of the infection in Jan 2021. During these periods, most endoscopy staff had to be redeployed to other parts of the health care system to deal with the infection surge. This has undoubtedly caused a huge increase in our endoscopy waiting list nationally with a steady increase in cases from November 2019 to April 2021 [290]. An increased in number of patients on the waiting list was also noted in the month of January 2021 following the closure of some endoscopy centres (Table 1). The number of patients awaiting an endoscopy procedure longer than 18 months has also seen a rapid increase from only 302 patients in November 2019 to 2280 patients in April 2021 (7.5-fold increase) [290]. The demand for endoscopy has also seen a steady increase over this period of time (Table 29). Similar increases in wait lists and demand for endoscopy has also been seen in other countries as an effect of the pandemic [291-293].

Colon Capsule Endoscopy (CCE) has proven efficacy to detect both neoplastic and non-neoplastic disease in selected patient cohorts including symptomatic patients, Inflammatory Bowel Disease (IBD) assessment, average, and low risk colorectal cancer (CRC) screening, after incomplete colonoscopy and polyp surveillance [4, 114-121, 294]. CCE has even been shown to reduce the need for colonoscopy in a FIT-positive CRC screening cohort by 71% [115].

Unlike colonoscopy, CCE can be performed in a socially distanced manner, with the option of remote reading and reporting; potentially reducing the risk of Covid-19 transmission. At the start of the pandemic, our endoscopy capacity was severely reduced and only running at <25% capacity for several weeks. As a consequence, we opted to perform pan-intestinal endoscopy using CCE in a selected group of urgent inpatients (n=7) over a period of 2 weeks (March – April 2020). All patients managed to avoid further endoscopy and CCE assisted in their discharge from Hospital. This included an 86-year-old female who presented with Bleeding Per Rectum and anaemia. Pan-intestinal capsule had shown a fibrin clot within a sigmoid diverticulum, indicating a recent diverticular bleed but no active bleeding (Image 4). The patient did not rebleed and was discharged on oral antibiotics.

Based on a survey in our centre, CCE reading competency is achieved following reading of 50 procedures. Whereas colonoscopy competency is only achieved after close to 100 colonoscopies. CCE pre-reading can also be performed by CCE nurses or trained technicians, allowing for more procedures to be performed. CCE reading also can be performed in less than 30 minutes by fully trained readers. With the advent of Artificial Intelligence in Capsule Endoscopy, the speed and quality of CCE reading can be further improved [295, 296]. Furthermore, when looking at a cohort of symptomatic patients in our centre, CCE was associated with a higher comfort and acceptance by patients compared to colonoscopy [297].

Due to the ever-growing evidence for CCE usage, we would like to advise and urge all readers to consider the usage of CCE in order to deal with colonoscopy demand and waiting list which has been growing since the beginning of the Covid-19 pandemic.

Month	Planned Endoscopy	Total waiting list	Wait time >18 months
Nov-19	66601	22420	302
Dec-19	67003	22242	292
Jan-20	68042	22321	275
Feb-20	68269	22705	282
Mar-20	69201	28204	231
Apr-20	70320	35110	339
May-20	70885	35307	425
Jun-20	70886	35878	541

Jul-20	71238	34983	732
Aug-20	71454	34674	930
Sep-20	71887	34605	1113
Oct-20	72295	34116	1382
Nov-20	72777	33411	1538
Dec-20	73206	32539	1748
Jan-21	73991	36065	2026
Feb-21	72438	36820	2284
Mar-21	72948	35634	2331
Apr-21	73058	33832	2280

Table 29: Waiting list and planned endoscopy procedures in Ireland. Source The National Treatment Purchase Fund [290].



Image 4: Fibrin clot within a diverticulum picked up on CCE

6.2 CCE as a potential solution to impairment of colorectal cancer screening during the COVID-19 pandemic

This subchapter has been published as a correspondence in Lancet Gastroenterol Hepatol. 2021 Jun;6(6):426. Dr M Syafiq Ismail and Dr Serhiy Semenov are co-first authors of this letter.

An interesting recent article by Lucie de Jonge published in *Lancet Gastroenterology Hepatology* April 2021 [298] where the authors acknowledge a substantial concern regarding colorectal cancer screening: the short-term and long-term negative effects of disruptions in screening due to the COVID-19 pandemic. By applying microsimulation models to three countries with established screening programmes—Australia, Canada, and the Netherlands—the authors predict a worrying increase in colorectal cancer incidence (0.4–1.2%) and related deaths (0.8–2.0%) within 30 years, assuming a 12-month screening disruption. They conclude that providing immediate catchup screening can restrict colorectal cancer incidence and deaths (2020 to 2050) to less than 0.1% in all three countries. This should be the introduction. We read with great interest the Article by Lucie de Jonge and colleagues [298] and would like to suggest a role for CCE in addressing this serious issue.

Considering that catch-up screening could temporarily increase colonoscopy demand to nearly twice that of normal levels [298], we feel this solution might not be feasible in certain health-care systems. Highlighting alternative solutions is imperative for a colonoscopy service that is already under strain. In a 2020 guideline update by Spada and colleagues [110], CT colonography (CTC) is recommended when faecal immunochemical test (FIT)- based screening is unavailable, because of reported higher participation and acceptability with CTC versus colonoscopy, and a similar frequency of adverse events (0.2% vs 0.3%) to colonoscopy. As stated previously in subchapter 2.3.1, the limitations of CTC would include access to a dedicated CTC scanner, small dose of radiation exposure [103-105], and risk of colonic perforation [106].

Of interest, Vuik and colleagues [121] reported in their systematic review that colon capsule endoscopy (CCE), compared with CTC, had a higher polyp detection rate (60.0–100.0% vs 28.6–81.0%) and sensitivity (84.0–97.3% vs 32.0–90.0%), with similar specificity (87.8–97.0% vs 84.8–99.0%). Our local Irish data, published by the Trinity Academic Gastroenterology Group research centre at Tallaght University Hospital (Dublin, Ireland) confirms that CCE is effective at detecting neoplastic polyps in a FIT positive screening cohort and would reduce the number of colonoscopies by 71% [115].

In Ireland, colorectal cancer screening is only done in units certified by the Joint Advisory Group on Gastrointestinal Endoscopy (JAG), by endoscopists accredited by the National Cancer Screening Service. Owing to excess waiting lists in most Irish endoscopy units, a minority are JAG-certified. The

training time to become an accredited endoscopist is around 5–8 years. Applicants are required to meet quality indicators for colonoscopies and have done more than 300 colonoscopies within a year. By contrast, much less time is required to train competent screening CCE readers. In an unpublished survey at our CCE centre at Tallaght University Hospital, we found that CCE readers can achieve competence at 30–50 procedures, and similar reading times to colonoscopy (30–45 min). Artificial intelligence in capsule endoscopy [299] will improve CCE training and further shorten reading time, allowing CCE to be used as a viable alternative in catch-up colorectal cancer screening.

To conclude, colorectal cancer screening has required new solutions in the current climate and alternative modalities should be a serious consideration.

6.3 The pandemic and beyond

Both of these correspondence letters have highlighted the impact of the Covid-19 pandemic on endoscopy services and the possible solution offered by CCE.

Currently, there are large pilot studies based on the potential use of CCE being conducted in the UK and Ireland, the results of which will hopefully clarify and further prove its efficacy. Going forward, even after the Covid-19 pandemic is over, CCE will hopefully continue to play a vital role in patients' assessment and diagnosis. Cost benefit analysis will also need to be performed to assess the role of CCE in routine daily use beyond the pandemic.

Chapter 7: Conclusion

Lower GI symptoms albeit common, remain a diagnostic challenge for clinicians and gastroenterologists. Colonoscopy currently remains the gold standard for investigating patients with lower GI symptoms. This demand for colonoscopy far exceeds the ability to perform them, resulting in significant delays to waiting list which has been made worse with the Covid pandemic. We have outlined in Chapter 2 current and possible strategies that can be implemented to help in patient triage and prioritisation. This can be done either with symptom based triaging systems, biomarkers (serum and faecal), and/ or minimally invasive colonoscopy (CTC and CCE).

In Chapter 3 of this thesis, we have demonstrated in our retrospective study of 1116 patients, that despite having alarm symptoms, the diagnostic yield of symptoms remains poor. Clinically significant disease (CSD) occurred in only 162 (14.5%) of our cohort. Chronic diarrhoea and PR bleeding as expected, gave the highest diagnostic yield for CSD of 5.3% (OR 3.15, 95% CI 2.2 to 4.7, $p < 0.001$) and 2.9% (OR 1.9, 95% CI 1.24 to 2.9, $p = 0.003$) respectively. Using a symptom-based triaging system (NICE guideline for IBD and CRC) to classify patients as high risk and low risk in order to triage urgency of referrals, although helpful, remains non-specific with only a minimal increase in diagnostic yield; from a baseline of 14.5% to 15%. It also did not significantly improve detection of CSD cases compared to those who were NICE criteria negative 15% ($n = 133/889$) vs 13% ($n = 28/217$), (OR 1.44, 95% CI 0.919 to 2.278, $p = 0.11$). In summary, our work suggests symptoms alone are a poor predictor of CSD and alternative referral criteria need to be developed to optimise yield and reduce unnecessary diagnostic tests.

In Chapter 4, we have described the use of biomarkers in different GI diseases. We started by doing a review of current and potential biomarkers that can be used in the management of small bowel conditions. FC shows the most promise, with evidence to support its role in predicting relapse post-Inflammatory Bowel Disease surgery (at a threshold of 100–140 mg/g had a pooled sensitivity of 0.68, specificity of 0.91 and AUC was 0.77 (95% CI: 0.73–0.81 [169])). FC also shows evidence in monitoring treatment response in patients with Crohn's disease [164] [165-167] [168]. A FC less than 50mg/g may also be used as a cut-off to triage referrals for capsule endoscopy in patients with suspected small bowel Crohn's disease [155]. In addition in patients with suspected small bowel bleeding there is evidence to show a positive FIT test pre-capsule may help to prioritize referrals

[187]. We also described in this chapter the usage of serum CRP, FC, and FIT in assessing disease activity and as a surrogate marker of mucosal healing (MH) in patients with IBD. In our retrospective review of 107 IBD patients undergoing colonoscopy, MH was seen in 36% (38/107) patients and deep healing was seen in 30% (32/107). All biomarkers were significantly lower in MH cases compared to active cases, CRP (3.3 vs 8.7, $p=0.0220$), FIT (99.8 vs 1221.9, $p=0.00003$) FC (295 vs 1028.2, $p=0.016$). Using pre-defined cut offs, FIT appears to have the best data with AUC of 0.788, followed by FC (0.748) then by CRP (0.641).

In Chapter 5, we explored the use of serum and stool biomarkers (ESR, CRP, FIT, FC) combined with minimally invasive colon capsule endoscopy (CCE) in the diagnosis of symptomatic patients compared to the gold standard, optical colonoscopy. In our prospective review of 66 included patients, we found that CCE performed better than biomarkers for predicting significant disease and correlated well with colonoscopy ($r=0.83$). The sensitivity, specificity, PPV and NPV values of CCE for significant disease compared to colonoscopy were 81 %, 98 %, 93 % and 94 % respectively. Apart from that, CCE has the extra added value of able to diagnose small bowel pathology in 22 % of our cohort of which 5 % was deemed clinically significant and was subsequently diagnosed with Crohn's disease. As our study was a prospective comparative study between biomarkers, CCE and colonoscopy, all patients had undergone all tests. If we were to look at how many patients in our study that would have needed a colonoscopy following CCE, all patients with significant disease on CCE (14=21 %) would have needed a colonoscopy either for therapeutic polypectomy or tissue sampling. Apart from that, as capsule excretion rate in our study was 76% (50) but reached the left colon in 100%, all incomplete studies (16) would have needed a referral for a sigmoidoscopy for completion.

Meanwhile, the diagnostic values for FIT and FC were, sensitivity 57%, 40%, specificity 60%, 64%, PPV 32%,26% and NPV 81%, 88% respectively. Neither of the serum biomarkers (ESR and CRP) predicted CCE and/or colonoscopy detected disease.

Bowel preparation quality is a key determinant of success for both CCE and colonoscopy. In addition, CCE requires effective booster medication, to help propel the capsule through the entire colon after capsule ingestion. We presented in chapter 5 the effect of changing bowel preparation regimen for CCE from a 4L PEG (KleanPrep) based preparation to a 2L PEG + ascorbic acid (MoviPrep) preparation

on both bowel cleansing and CCE excretion rates. This change resulted in a significant improvement in capsule excretion rate (72% vs 54%, $p=0.002$) without affecting bowel cleansing.

The chapter then continues with a prospective study assessing the effect of adding 15mls of castor oil to our CCE booster regimen, which has further resulted in a significant increase in CCE excretion rate 87% (54/62) vs 73% (90/124), ($p=0.01$) again without compromising in bowel cleansing quality [adequate and/or diagnostic in 90% (56/62) vs 92% (114/124)]. The addition of castor oil also resulted in an increase in polyp detection rate 82% (51/62) vs 44% (55/124), ($p<0.0001$) and overall diagnostic yield, 84% (52/62) vs 46% (57/124), ($p<0.0001$).

We finished this chapter with our study looking at our symptomatic cohort's reported satisfaction, comfort, and preference between CCE and colonoscopy. We discovered in a cohort of 40 patients, there was a significant difference between patient reported comfort between CCE and colonoscopy (9.2 vs 6.7, $p<0.0001$, 95% CI -3.51 to -1.44) with a comparable level of satisfaction (8.3 vs 7.7, $p=0.2$, 95% CI -1.48 to 0.33). In all 77.5% (31/40) of this cohort stated, they would prefer to have a CCE instead of an optical colonoscopy if further colonic visualisation was required and 77.4% (24/31) said they would still prefer CCE even if it resulted in a need for a subsequent follow up colonoscopy for either tissue diagnosis or therapeutic purposes.

In chapter 6, we described the effect of the Covid-19 Pandemic on service activity and the resultant increase in endoscopy waiting lists in Ireland and the need for a catch-up service for CRC screening. We offered a solution to this by using CCE as a catch-up method and an alternative to colonoscopy due to its proven effectiveness and shorter training time to competency compared to colonoscopy.

In conclusion, in this thesis, we have outlined the role of biomarkers and CCE in the management of patients with lower GI symptoms and small bowel disease. Currently with the level of evidence that we have, the use of biomarkers alone does not appear sufficient as a rule-out test for clinically significant disease. Our work has shown that CCE however, is an excellent alternative to colonoscopy and its usage should be considered in reducing the colonoscopy waiting list which has unfortunately further increased due to the Covid-19 pandemic.

Future Directions

We feel that the prospective use of capsule in the symptomatic patients should be further explored with larger multi-centre studies. These larger studies will hopefully be used to update current societal guidelines which has not recommended the use of CCE in investigating symptomatic patient. With their reasonably high NPV, a negative biomarker test may also be used as a pre-screening tool for patient selection prior to CCE and this strategy should also be further explored with future prospective studies.

With the advent of Artificial Intelligence (AI) in the world of endoscopy, its usage in capsule endoscopy including CCE should also be explored with future prospective trials. The use of AI is expected to reduce capsule reading times while maintaining or improving the reading quality offered by the human eye. This will allow CCE units to increase their throughput which will further reduce the waiting time for colonoscopy and lower GI investigation.

Another interesting area to further explore is the most optimal bowel preparation and booster regimes for patients undergoing CCE that is not only acceptable and palatable but also will result in good bowel cleaning and capsule excretion. A 4L-PEG CCE regiment has been reported in chapter 5 as a reason for patient dissatisfaction. Currently as also outlined in chapter 5, the most updated regimen in our unit in TUH is the use of a split dose 2L-PEG + ascorbic acid (MoviPrep) for bowel preparation and the use of Moviprep booster + castor oil which has given a capsule excretion rate of 87% and an adequate and/or diagnostic image quality in 90% (56/62). There is not a uniformly accepted bowel preparation and booster regimen among CCE units, and this can be further studied in future prospective research. More recently, a lower volume 1L PEG based bowel preparation (Plenvu) has been licensed in Ireland. We have not trialled this in our CCE centre as of yet, but a lower volume may result in better patient tolerability and acceptance which we are keen to look at in future studies.

Ultimately with the wider introduction and adaption of CCE in gastroenterology and endoscopy departments, and its use as a possible substitution for colonoscopy, undoubtedly issues of cost and benefit will arise. In this thesis we did not look at any cost benefit analysis specifically either for CCE nor colonoscopy. This however should be further analysed and studied in future research. This analysis should not just include costs towards each unit and hospitals but should include costs

towards patients and possible days missed being off-work if getting procedural related sedation for colonoscopy. How this process effects and fits into the Sláintecare initiative described in chapter 3 would also need to be assessed.

Abbreviations (in order of appearance)

GI – Gastrointestinal
CCE – Colon Capsule Endoscopy
CT – Computed Tomography
CTC – Computed Tomography Colonography
CSD – Clinically Significant Disease
NICE – National Institute for Health and Care Excellence
CRC – Colorectal Cancer
IBD – Inflammatory Bowel Disease
UEGW – United European Gastroenterology Week
CRP – C-Reactive Protein
FIT – Faecal Immunochemical Test for Haemoglobin
FC – Faecal Calprotectin
PEG – Poly-Ethylene Glycol
AA – Ascorbic Acid
PR – Per Rectum
Hb – Haemoglobin
ESR - Erythrocyte Sedimentation Rate
ASGE – American Society of Gastrointestinal Endoscopy
BMI – Body Mass Index
HRP – High Risk Polyps
CVL – Colonic Vascular Lesions
HRA – High Risk Adenoma
SSL – Sessile Serrated Lesion
CD – Crohn’s Disease
UC – Ulcerative Colitis
IC – Indeterminant Colitis
MC – Microscopic Colitis
PPV – Positive Predictive Value
NG – NICE Guidelines

IBS – Irritable Bowel Syndrome

QS – Quality Statement

RCSI – Royal College of Surgeons Ireland

WHO – World Health Organisation

IDA – Iron Deficiency Anaemia

FBC – Full Blood Count

MCV – Mean Corpuscular Volume

MCH – Mean Corpuscular Haemoglobin

BSG – British Society of Gastroenterology

OGD – Oesophagoastroduodenoscopy

CI – Confidence Interval

TUH – Tallaght University Hospital

OR – Odds Ratio

DNA – Deoxyribonucleic acid

RR – Relative Risk

AUC – Area Under the Curve

FOB – Faecal Occult Blood

NPV – Negative Predictive Value

ELISA – Enzyme-Linked Immunosorbent Assay

ESGE – European Society of Gastrointestinal Endoscopy

ESGAR – European Society of Gastrointestinal and Abdominal Radiology

ESD – Endoscopic Submucosal Dissection

PLR – Positive Likelihood Ratio

NLR – Negative Likelihood Ratio

AA – Advanced Adenomas

AL – Any neoplastic Lesion

AGA – American Gastroenterological Association

LGS – Lower Gastrointestinal Symptoms

GP - General Practitioner

UK – United Kingdom

SBCE – Small Bowel Capsule Endoscopy

DOR – Diagnostic Odds Ratio

SESCD – Simple Endoscopic Score for Crohn’s Disease

DBE – Double Balloon Enteroscopy

DES-CD – Double Balloon Endoscopic Score for Crohn’s Disease

MRE – Magnetic Resonance Enterography

NSAIDS – Non-Steroidal Anti-Inflammatory Drugs

CDAI – Crohn’s Disease Activity Index

CESI – Capsule Endoscopy Scoring Index

gFOB – guaiac-based faecal occult blood

Hb/HPT – Haemoglobin/haptoglobin

M2-PK - M2-Pyruvate Kinase

HMGB1 – High mobility group box 1

FA – Fatty Acid

IFABP – Intestinal fatty acid (FA)-binding protein

L-FABP – liver FA-binding protein

Cr – Creatinine

EEN – Exclusive Enteral Nutrition

SIP – Small intestine Permeability

Su – sucrose

La – Lactulose

Ma – Mannitol

DIBS – Diarrhoea predominant IBS

GFD – Gluten-Free Diet

mAbs - monoclonal antibodies

GIP – Gluten Immunogenic Peptides

MH – Mucosal Healing

ECCO – European Crohn’s and Colitis Organization

2N – 2-Normal-biomarkers

ESE – Estimated Standard Error

REC – Research Ethics Committee

STROBE – STrengthening the Reporting of OBServational studies in Epidemiology

GCS – Modified-Gloucester-Comfort-Scale

CIR – caecal intubation rate

PDR – Polyp Detection Rate

NQAIS – National Quality Assurance Information System

PRO-STEP – Patient-Reported Scale for Tolerability of Endoscopic Procedures

SPECS – St. Paul's Endoscopy Comfort Score

BC – Bowel Cleansing

CE – Capsule Excretion

NNT – Number Needed to Treat

JAG – Joint Advisory Group on Gastrointestinal Endoscopy

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