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# Efficiency in Colonoscopy

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# Statement of Originality

This thesis is the original work of the author with all other material appropriately referenced. It was produced following a series of research projects carried out during a research fellowship at the Wolfson Unit for Endoscopy, St Mark's Hospital (London).

# Copyright Declaration

"If learning the truth is the scientist's goal,
then he must make himself the enemy of all that he reads."

Al-Hasan Ibn al-Haytham
'The Father of Modern Optics'
965-1040

# Abstract

Global trends, including demographic changes, are significantly increasing the demand and cost of healthcare. Endoscopy services are no exception and, even before the Covid-19 pandemic, significant pressure resulted in many units failing to meet cancer wait targets. The need to improve efficiency has never been greater and particularly so for colonoscopy which significantly reduces morbidity and mortality from colorectal cancer. Today, advances in colonoscope technologies and emergence of artificial intelligence offer the potential for improved colonoscopy practice. The aim of this thesis is to explore how efficiency in colonoscopy can be enhanced throughout the patient pathway.

Five major studies were performed evaluating bowel preparation (CLEANSE), polyp detection (AI-DETECT), optical diagnosis (DISCARD3), insertion technique (WAVE) and post-colonoscopy colorectal cancer (AI-DETECT).

CLEANSE is an evaluation of a novel low-volume same-day bowel preparation regime (Plenvu) and showed this offers a more efficient bowel cleansing option than standard regimens. AI-DETECT is a randomised study evaluating a computer-aided detection (CADe) system (GI Genius) and showed a borderline significant improvement in polyp detection is achieved amongst high performing endoscopists. DISCARD3 is a major evaluation of optical diagnosis with a "resect and discard" strategy exploring the learning curve, quality assurance process, causes of error and economic impact. This study shows such a strategy is feasible and safe and could potentially be implemented with a quality assurance process in place within the English Bowel Cancer Screening Progamme (BCSP). WAVE is a randomised study evaluating colonoscopy insertion technique. This showed a 'hybrid' insertion technique is more efficient than a water-exchange colonoscopy technique. REFLECT is a retrospective evaluation of post-colonoscopy colorectal cancer cases identified at national level and showed after local root cause analysis a significant proportion were in fact detected cancers.

These studies provide valuable insights that we hope will ultimately lead to more efficient colonoscopy whilst maintaining quality and enhancing patient care.

# Dedication

I dedicate this work to my parents
who cultivated a love for learning,
to my wife for her unwavering and
tireless support, and to my children
who gave me the perspective to
make this possible.

# Preface

It is interesting to consider how one's life course pans out and the impact of our individual circumstances and choices on this. Although I have always had a strong interest in the scientific method and academic medicine, I had not planned to take time out from clinical training to pursue research. It was a combination of my keen interest in the challenges facing the future of healthcare, my passion for performing high quality colonoscopy and my experience during an endoscopy fellowship at St Mark's Hospital (London) that propelled my decision to pursue research focussing on "efficiency in colonoscopy". Addressing the question of how we can improve efficiency in colonoscopy is important at the clinician, patient and service level. The Covid-19 pandemic has increased service pressure further and accentuated the significance of this body of research.

In retrospect, taking time out of clinical medicine to pursue research has been a major highlight of my career. It has provided the breathing space to widen my perspective and deepen my understanding of an area of genuine interest. I have relished the freedom to explore, to ask important questions and the opportunity to gain valuable insights. A real highlight for me was the in depth analysis of optical diagnosis error and the novel insights this has provided including the discovery of pseudo-adenomas; serrated polyps that are frequently misdiagnosed as adenomas. It is this and other important findings during this research fellowship that have made the dedication and commitment required worthwhile.

In each project, I have endeavoured to keep the patient perspective central to the design and I sincerely hope that this portfolio of research will translate to improvements in the practice of colonoscopy and clinical care.

Dr Ahmir Ahmad
St Mark's Hospital, London
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Being immersed in the Wolfson Unit for Endoscopy, I appreciate the contribution of the entire team including the superb endoscopy nurses, administrative and managerial support. I am particularly grateful for the support of Kowshi Thiruvilangam who worked tirelessly to facilitate this research. The late Jean Mannings was always a friendly and supportive presence. Sarah Marshall's proactive approach helped greatly with the studies.

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was administered by the St Mark's Hospital Foundation as well as the research funding and equipment loan provided by Olympus for the DISCARD3 study.

Lastly, and most importantly, I would like to acknowledge the patients for their time and sacrifice to make this research possible.

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# List of Abbreviations

### A

ACG: American College of Gastroenterology
ADR: adenoma detection rate
AGA: American Gastroenterological Association
AHRQ: Agency for Health Care Research and Quality
AI: artificial intelligence
AI-DETECT: Randomised study evaluating use of AI for polyp detection
AMR: adenoma miss rate
ANOVA: analysis of variance
APC: adenomas per colonoscopy
ASGE: American Society for Gastrointestinal Endoscopy

### B

BASIC: BLI Adenoma Serrated International Classification
BBPS: Boston Bowel Preparation Scale
BCS: bowel cancer screening
BCSP: bowel cancer screening programme
BLI: Blue Laser Imaging
BMI: body mass index
BSG: British Society of Gastroenterology

### C

CADe: computer-aided detection
CADx: computer-aided diagnosis
CLEANSE: Evaluation of a novel low-volume bowel preparation regimen
$CO_2$: carbon dioxide
COP26: 2021 United Nations climate change conference
CORECT-R: The COloRECTal cancer Repository
Covid-19: Coronavirus disease 2019
CRC: colorectal cancer
CUSUM: cumulative sum control chart

### D

DISCARD: Detect InSpect ChAracterise Resect and Discard

### E

EMR: endoscopic mucosal resection
ESGE: European Society of Gastrointestinal Endoscopy

### F

FDA: US Food and Drug Administration
FICE: Fujinon Intelligent Colour Enhancement
FIT: faecal immunochemical test

### G

GDP: gross domestic product
GI: gastrointestinal

### H

H&E: hematoxylin and eosin
HD-WL: high definition white light
HES: Hospital Episodes Statistics

### I

IBD: inflammatory bowel disease
ICV: ileocaecal valve
ITT: intention to treat

### J

JAG: Joint Advisory Group
JNET: Japan NBI Expert Team

### K

KPI: key performance indicator

### L

LBRD: location-based resect and discard strategy

### N

NBI: narrow-band imaging
NCRAS: National Cancer Registration and Analysis Service
NED: National Endoscopy Database
NHS: National Health Service
NICE: NBI International Colorectal Endoscopic

### O

OECD: Organisation for Economic Co-operation and Development
OGD: oesophagogastroduodenoscopy

### P

PCCRC: post-colonoscopy colorectal cancer
PCCRC-3yr: proportion of people diagnosed with colorectal cancer, 6 to 36 months after an apparently negative colonoscopy
PDR: polyp detection rate
PEG: polyethylene glycol
PIVI: Preservation and Incorporation of Valuable endoscopic Innovations
PP: per-protocol
PPC: polyps per colonoscopy

### R

RCT: randomised controlled trial
REFLECT: Validation of nationally reported PCCRC cases at local level

### S

SDR: sessile serrated lesion detection rate
SD-WL: standard definition white light
SIMPLE: Simplified Identification Method for Polyp Labeling during Endoscopy
SP6: number of adenomas and sessile serrated lesions detected per six-minute withdrawal time
SPC: serrated polyps per colonoscopy
SPDR: significant polyp detection rate
SSL: sessile serrated lesion
SSP: sessile serrated polyp

### T

TI: terminal ileum
TXI: Texture and Color Enhancement Imaging

### U

UC: ulcerative colitis
UK: United Kingdom
US: United States

### W

WAVE: Water-exchange versus modified water immersion colonoscopy
WASP: Workgroup serrAted polypS and Polyposis
WEO: World Endoscopy Organisation
WHO: World Health Organisation

# Chapter 1 Introduction: Efficiency in Colonoscopy

This thesis is about improving efficiency of the colonoscopy procedure. To understand the importance of this, we will first explore factors that are driving us towards a greater need for efficiency generally. We will then focus on the efficiency within a healthcare context and then take a deep dive into efficiency of the colonoscopy procedure itself.

## 1.1 The need for greater efficiency

### 1.1.1 Global trends

At a global level, several current trends are influencing the way we interact with each other and the environment. These include: demographic changes with an increasingly aging population; a shift in economic gravity towards emerging economies and globally competitive companies; changes in globalisation patterns; and an acceleration of technological progress (1).

From a demographic perspective, population growth is accelerating at an exponential rate with a 7 fold increase in the last 200 years (2). In 2011, the global population reached 7 billion and in November 2022 the 8 billion mark was exceeded (2). This is causing a huge increase in demand on limited resources. In addition, an increasingly aging population is raising the pressure on those that are economically active to be more productive.

Figure 1 World population growth, 1700-2100[1] (3)

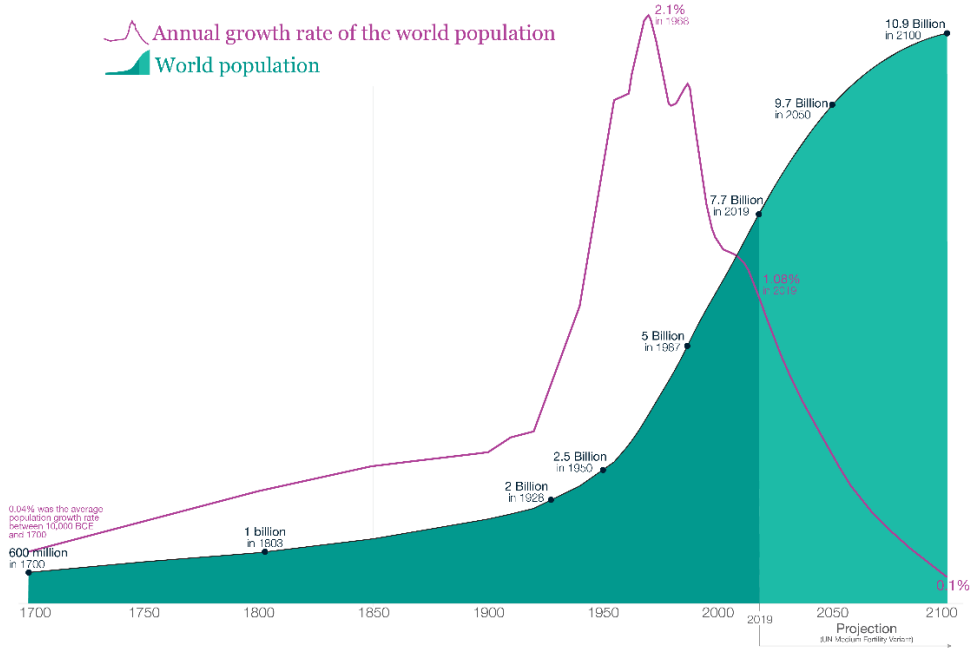
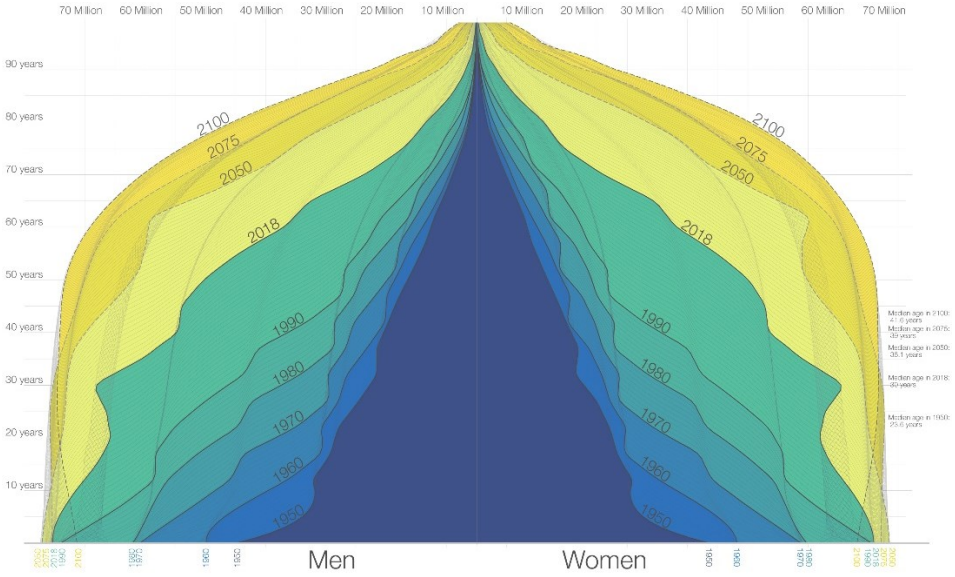



Figure 2 Demography of the World Population, 1950-2010[1] (3)




Huge technological advances have also been made in recent decades with digital technologies such as the internet, smartphones and e-commerce. The centralisation of vast volumes of data on cloud-based services has created opportunities to harness and

[1] Max Roser (2013). Future Population Growth - Our World in Data. Available from: https://ourworldindata.org/future-population-growth. Reproduced under creative commons licence 4.0 (CC BY 4.0).

analyse data more deeply and laid the foundation for artificial intelligence (AI) and machine learning. These technologies not only enhance human performance but can already perform better in several contexts.

Together these changes are fundamentally influencing employment patterns. The World Development Report 2019 and a European Commission Joint Research Centre report both examined the 'changing nature of work' (4,5). Although it is often feared that technology will replace workers, it has in fact been estimated around half of the 23 million jobs created in Europe from 1999 to 2010 were due to 'routine-replacing technological change' (6). The evidence suggests that although technology will disrupt millions of jobs, despite the loss of some roles, the demand for labour increases with new job opportunities created by technological advances.

This new way of working requires a new set of skills to be able to harness the capabilities of these technologies. The McKinsey report describes this as the "superstar" effect whereby 'disproportionately large rewards go to the winners' and those that fail to embrace change fall behind (1). This could increase inequality at a global to individual level.

These changes are occurring on a backdrop of climate change with greater awareness of the impact we are having on the environment and our potential impact on sustainability. At the 26th United Nations Climate Change Conference of the Parties (COP26) net-zero commitments were secured from 153 countries and the $100 billion climate finance goal is expected to be reached by developed countries by 2023 (7).

### 1.1.2 Healthcare trends

#### a Inefficiency in healthcare – 'healthcare inflation'

Even before Covid-19, it was estimated that each year $750 billion are wasted due to inefficient health care spending (8). More resources does not necessarily result in improved efficiency.

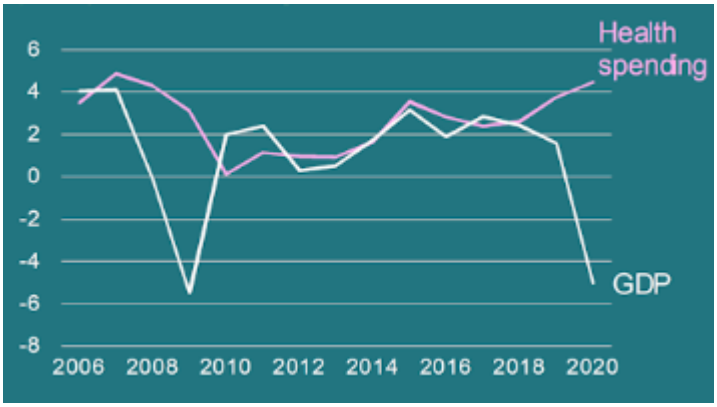
Inefficiency within healthcare has been explored previously (9) and examples of this include:

- Use of ineffective therapies
- Using effective therapies at the wrong time
- Incorrect place of treatment
- Incorrect hospital length of stay
- Incorrect order of tests
- Unnecessary testing (eg endoscopic procedures)
- Poor management of inventory and resources

### b Impact of global trends on healthcare

The global trends mentioned earlier are placing unprecedented demand on healthcare services worldwide. With 17% of the population in 2019 aged 65 years and above, who often have multiple comorbidities, the demand for healthcare services is immense. With rising demand there is rising cost and since the Covid-19 pandemic there has been rising healthcare spending despite a significant drop in gross domestic product (GDP) per capita (10).

Figure 3 Annual health expenditure growth (%) and GDP per capita (OECD average)[2] (10)




[2] OECD (2021), Health at a Glance 2021: OECD Indicators, OECD Publishing, Paris, https://doi.org/10.1787/ae3016b9-en. Reproduced with permission of OECD.

When coupled with workforce shortages of nurses and doctors in almost all Organisation for Economic Co-operation and Development (OECD) countries, despite their numbers increasing over the past decade, the scale of the challenge is immense. A recent United Kingdom (UK) Health System Review highlights that the UK has 'lower levels of doctors, nurses and health care infrastructure than most other comparable high income countries' (11).

Adoption of digital technologies within healthcare has been slow but may offer an opportunity to address the challenge. The Covid-19 pandemic has helped accelerate change due to the need for accessible healthcare. For example, the shift towards remote consultations supported by teleconferencing technologies and wider adoption of universal electronic healthcare records.

In addition, technological advances have led to huge volumes of data being generated in a short period – so called 'big data'. In the past, human capacity to acquire and analyse such data was limited. With artificial intelligence (AI), automated analysis of vast datasets can pick up trends and make predictions. This has potential to screen populations for risk factors for disease, speed up and automate diagnosis, and support optimal data-based individualised decision making.

The combination of digital technologies and AI have led to the development of new healthcare devices such as smart watches and sensors which have opened up the potential for remote monitoring of healthcare. In addition, the field of digital therapeutics is opening with the United States (US) Food and Drug Administration (FDA) and the National Institute for Health and Care Excellence (NICE) both having approved apps for treatment of healthcare conditions such as post-traumatic stress disorder and insomnia (12,13).

Such technologies could help mitigate the huge economic demands on healthcare systems and help optimise the use of limited resources.

### 1.1.3 Endoscopy trends

#### a Demand for endoscopy

The most recent national census of UK endoscopy services in 2019 showed increasing endoscopy activity and a lower proportion of services meeting national waiting time targets than the survey 2 years prior (14,15). This showed increasing pressure on endoscopy services with a 15.4% increase in per service mean GI procedures performed from 5747.7 in 2017 to 6625.9 in 2019. This rise was particularly marked in bowel cancer screening (BCS) procedures which was felt to be a reflection of the higher level of screening uptake of 61.7% in 2019 (16).

During this period total endoscopist numbers increased by 14.1% to 5578 endoscopists across all services and a comparative analysis showed a 28.1% increase in trainee numbers. There was also a 13.9% increase in nursing and allied healthcare professional staff and no difference in overall vacancy numbers across bands. Clerical staff increased by 30.1%.

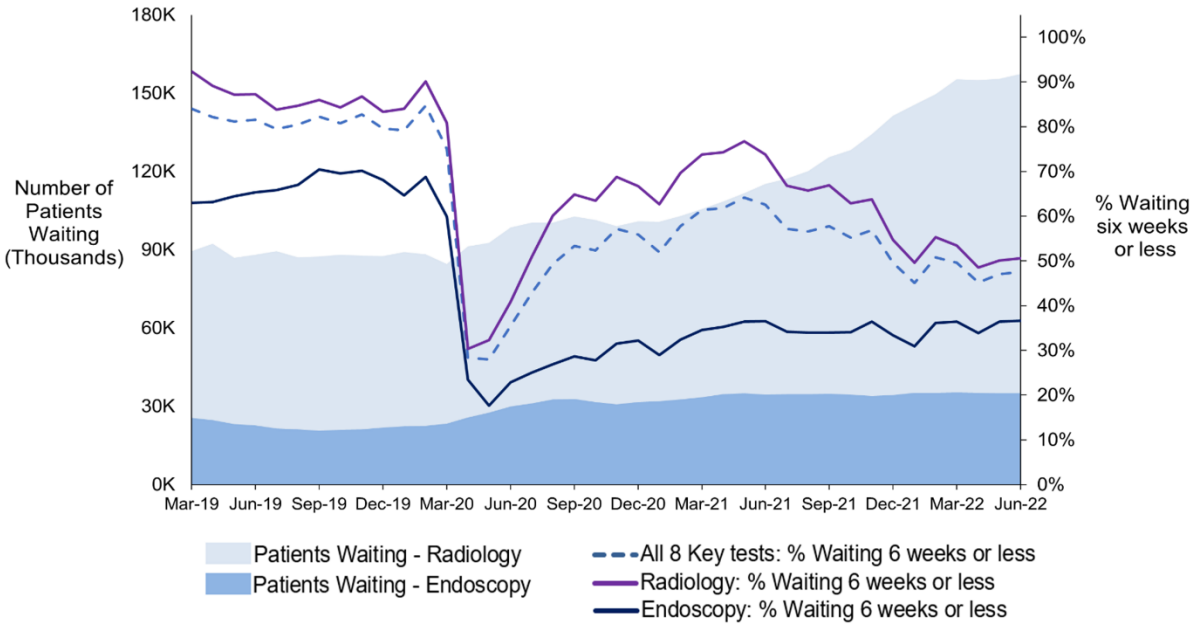
Despite this, more than a quarter of services failed to meet urgent cancer wait targets due to a combination of endoscopist, physical and nursing capacity. Staff absence due to sickness was noted to be close to 8% and may be a contributory factor. This may be attributed to stress and excessive workload which are themes of both the NHS 2018 staff survey and a national survey of consultant gastroenterologists (17,18). The failure to meet cancer wait targets suggests a significant mismatch between demand for endoscopy and the ability of the service to fulfil this.

Although Covid-19 led to a dramatic reduction in endoscopy activity (12% of pre-Covid levels), more selective vetting practices significantly increased the per-procedure cancer detection rate from 1.91% to 6.61% (19). However, weekly cancer detection rates were significantly reduced with the proportion of missed colorectal cancers as high as 72%.

As the pandemic comes to maturity, it leaves an aftermath of unprecedented waiting lists for healthcare services and a huge burden of undiagnosed or delayed detection of disease. According to a Public Health Scotland report published in 2022, as at 31 December 2021, 34224 patients were on the waiting list for endoscopy which was an increase of 8.2% from the same time in 2020 and 53.1% compared to the pre-

pandemic 12-month average (20). A concerning 13.0% of patients had waited more than a year for endoscopy compared with 3.9% on 31 December 2020 (see Figure 4).

Figure 4 Trend in patients waiting and % waiting 6 weeks or less at month-end, split by test type, in NHS Scotland, 31 March 2019 - 30 June 2022[3] (20)




## b Emphasis on quality

Endoscopy services have developed with incremental improvements over the last 50 years. In the early phase there was a period of feasibility assessment. Once proven, there was a shift towards improvements in scope technology resulting in improvements in scope optics and endoscope performance (21,22). In recent decades, several interventions have led to improvements in endoscopy quality which have been supported by accreditation bodies such as the UK's Joint Advisory Group (JAG).

Quality measures in colonoscopy were first proposed in 2002 by the US multi-society task force on colorectal cancer (23). Since then, several publications have led to refinements in quality assurance standards and key performance indicators (24,25). In addition, JAG has helped realise the national bowel cancer screening programme

[3] Health Scotland (2022). Diagnostic Waiting Times: A National Statistics release for Scotland. 2022. Available from: www.publichealthscotland.scot. Contains public sector information licensed under the Open Government Licence v3.0.

(BCSP) (26,27), developed an online e-portfolio for endoscopists (28), and established a national endoscopy database (NED) (29). To this end, there is evidence that JAG has had a positive effect on the quality of endoscopy services (30).

## 1.2 The efficiency paradox

With the current pressures facing healthcare there is a need to use resources efficiently to improve productivity. It is important, however, that any efficiency measures do not negatively impact on quality.

The relationship between quality and efficiency is important. In order to perform a highly efficient procedure it is necessary that it must be of high quality. However, a high quality procedure may not necessarily be a highly efficient procedure. The Institute of Medicine includes both timeliness and efficiency as part of the six major aims for all health care organisations (31).

Colonoscopy withdrawal times are a good example of how enhancements in quality have a limit and, if taken to an extreme, can introduce inefficiency (see Figure 5) (32). Early studies showed beneficial impact of a withdrawal time of >6 minutes compared with <6 minutes suggesting a longer colonoscopy procedure provides a better quality examination (33). However, more recent studies suggest a withdrawal time longer than 6 minutes is beneficial and that beyond a 10 minute withdrawal time there was only minimal increase in ADR (34). Therefore, performing a 15 minute withdrawal time would not add to quality but would make the procedure inefficient.

Ultimately, the goal is to achieve high quality efficiently (see Figure 5). In doing so, patient care remains optimal with maximum output achieved with minimum input. High quality can be achieved efficiently or inefficiently (see Figure 6). A low quality procedure is not efficient as it would give an inadequate or sub-optimal outcome.

Figure 5 Efficiency and Quality of colonoscopy withdrawal times

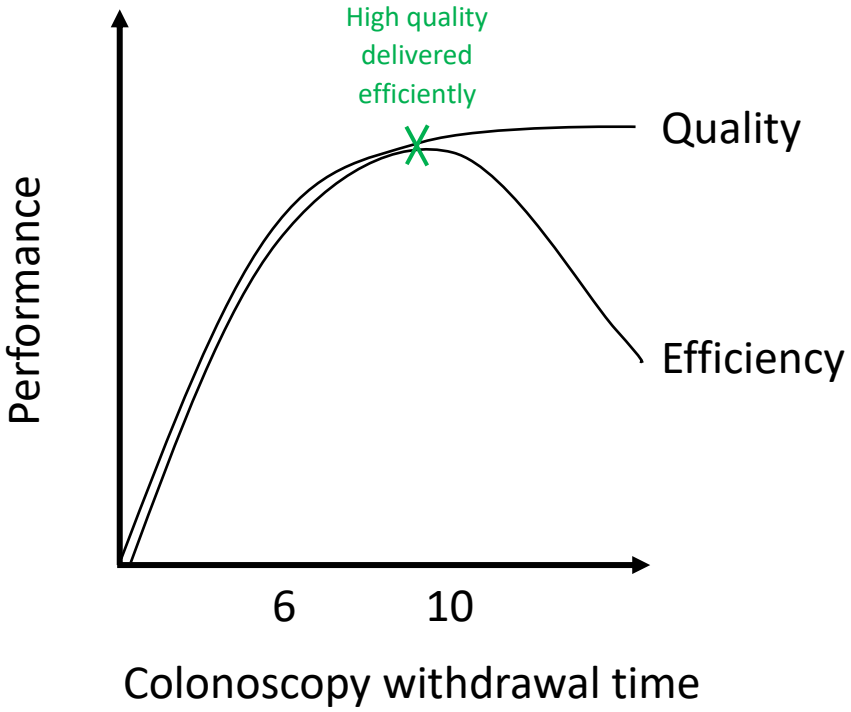
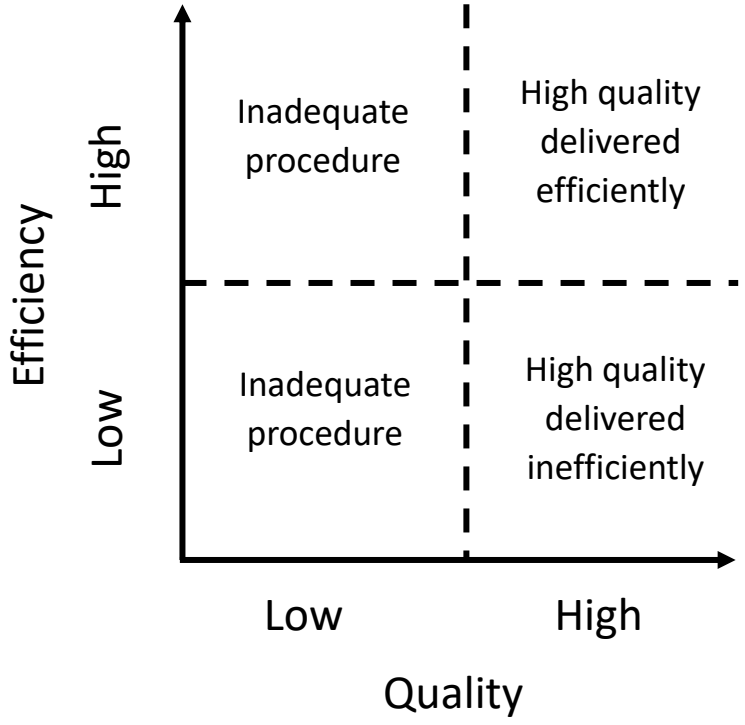



Figure 6 Relationship between Quality and Efficiency

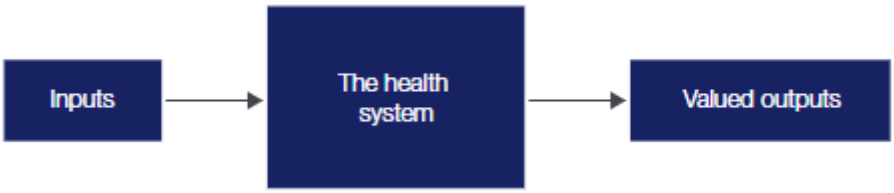


Although one may assume a faster intervention would improve efficiency, sometimes interventions that are aimed at doing so have the paradoxical effect of actually reducing efficiency (35). This so called 'efficiency paradox' highlights the need to consider the impact of any intervention in a holistic manner that takes into consideration nuances from a patient and clinician perspective. Aronson uses the results of a study evaluating telemedicine in rheumatology to explain this concept (35,36). Although it may seem obvious that telemedicine would improve efficiency, this study showed high levels of concern with this approach as 93% of clinicians and 86% of patients rated telemedicine 'worse than face-to-face for assessment accuracy'. There were also concerns about the impact on medical relationships and greater inequality with poorer access to healthcare for those that need it most (the inverse care law) (37).

### 1.2.1 What is efficiency?

Efficiency has traditionally been seen as a measure of the time and effort needed for a task to be completed. Ultimately it is about achieving maximum output with the minimum input (see Figure 7) (38).

Figure 7 'The naive view of efficiency'[4] (38)




At the simplest level, inputs may include 'hospital medical staff', 'pathology requests' and 'radiology treatments' whereas valued outputs may be 'life expectancy' as detailed in Cochrane's classic text 'Effectiveness and Efficiency' including random reflections on health services (9) (see Figure 8 and Figure 9).

[4] World Health Organisation (2016). Health System Efficiency: How to make measurement matter for policy and management. Available from: www.healthobservatory.eu. Figure reproduced with permission from the European Observatory on Health Systems and Policies.

Figure 8 Historical example of 'inputs' in the NHS[5] (9)

TABLE 3.1. *Changes in various aspects of 'input' in the NHS*

| | *1959* | *1961* | *1963* | *1965* | *1967* | *1969* |
|---|---|---|---|---|---|---|
| Hospital medical staff | 16,033 | 16,932 | 17,971 | 18,905 | 20,395 | 22,001 |
| Hospital nursing staff | 190,946 | 200,458 | 215,219 | 232,310 | 252,509 | 262,644 |
| Hospital professional and technical staff | 21,878 | 23,404 | 25,377 | 27,814 | 30,681 | 33,245 |
| General medical practitioners | 22,901 | 22,218 | 22,159 | 21,489 | 21,293 | 21,505 |
| Prescriptions (millions) | 214·0 | 205·0 | 205·5 | 244·3 | 271·2 | 264·2 |
| Pathology requests (thousands) | 17,267 | 20,603 | 24,930 | 28,562 | 33,360 | 38,792 |
| Radiology (units of treatment) (thousands) | 21,126 | 22,481 | 25,121 | 27,704 | 30,209 | 33,881 |

*Source.* Extracted from Table 3.2, *Digest of Health Statistics* (Department of Health and Social Security, 1970) and personal communication (Welsh Office).

Figure 9 Historical example of a key 'output' in the NHS[5] (9)

TABLE 3.2. *Expectation of life. Home population*

| *Age* | *Sex* | *1948–50* | *1957–9* | *1965–7* |
|---|---|---|---|---|
| 0 | M | 66·3 | 68·0 | 68·7 |
| | F | 71·0 | 73·7 | 74·9 |
| 5 | M | 64·2 | 65·0 | 65·4 |
| | F | 68·4 | 70·4 | 71·3 |
| 15 | M | 54·6 | 55·2 | 55·6 |
| | F | 58·7 | 60·6 | 61·5 |
| 25 | M | 45·3 | 45·8 | 46·1 |
| | F | 49·4 | 50·9 | 51·7 |
| 35 | M | 36·0 | 36·2 | 36·5 |
| | F | 40·1 | 41·2 | 42·0 |
| 45 | M | 27·0 | 27·0 | 27·2 |
| | F | 30·9 | 31·9 | 32·6 |
| 55 | M | 18·8 | 18·6 | 18·8 |
| | F | 22·4 | 23·1 | 23·8 |
| 65 | M | 12·2 | 12·0 | 12·0 |
| | F | 14·6 | 15·2 | 15·8 |
| 75 | M | 7·2 | 7·1 | 7·2 |
| | F | 8·5 | 8·8 | 9·3 |
| 85 | M | 4·2 | 4·2 | 3·9 |
| | F | 4·8 | 4·7 | 4·9 |

*Source.* Table 1.6, *Digest of Health Statistics for England and Wales 1970* (Department of Health and Social Security).

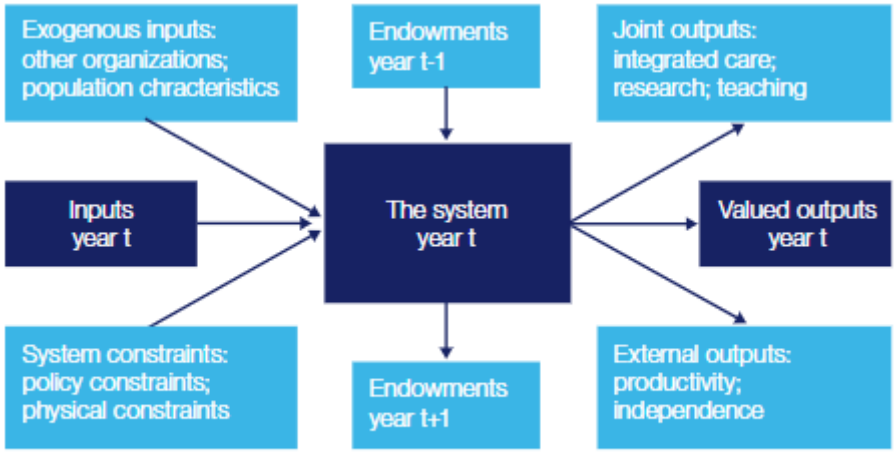
As Cochrane points out, the picture is more complex as the lack of improvement in mortality cannot be blamed on 'an increased incidence of a disease for which there is

[5] A L Cochrane (1971). Effectiveness and Efficiency: Random reflections on health services. Nuffield Trust. Reproduced with permission of Nuffield Trust.

no effective means of prevention or treatment'. Standardised mortality ratios are one approach used to take into consideration this complexity but there also needs to be a detailed understanding of 'whether effective means are available for prevention and treatment, how efficiently they have been applied, and what ineffective methods are in use for each individual disease'.

Within a healthcare context, it is therefore now recognised a more complete model is required (see Figure 10) to take into account a range of inputs (eg exogenous inputs and system constraints) and outputs (eg external factors, or joint outputs).

Figure 10 'A more complete model of efficiency'[7] (38,39)




*Source:* Smith (2009).

## 1.2.2 Measuring efficiency

### a Importance of efficiency measurement

In Cochrane's fascinating book published in 1971, he reflects on efficiency in the National Health Service (NHS) (9):

> *'If we are ever going to get the 'optimum' results from our national expenditure on the NHS we must finally be able to express the results in the form of the benefit and*

[7] World Health Organisation (2016). Health System Efficiency: How to make measurement matter for policy and management. Available from: www.healthobservatory.eu. Figure reproduced with permission from the European Observatory on Health Systems and Policies .

*the cost to the population of a particular type of activity, and the increased benefit that could be obtained if more money were made available'*

In order for such an approach to become possible he argues you must be able 'to measure the effect of a particular medical action in altering the natural history of a particular disease for the better'. This highlights the importance of measuring processes to be able to achieve efficiency. Developing efficiency metrics is therefore important as it allows the value of interventions to be tested and for benchmarking against peers.

### b The ideal efficiency measure

The Agency for Health Care Research and Quality (AHRQ) recommends efficiency measures are evaluated using the same approach as measures of quality (40):

- Important – it is worthwhile measure for at least one of the stakeholders
- Scientifically sound – the measure should be reliable and reproducible
- Feasible – data must be available or easy to obtain
- Actionable – it should be possible to implement a change.

### c Type of efficiency measures

Gellad et al describe a conceptual framework for endoscopy unit efficiency based on three measures (41):

- Structure measures – the unit setting (eg number of procedure rooms, unit layout).
- Process measures – how well the system performs using measures linked to desired outcomes with a given set of resources (eg first case start time, room turnover time, sedation time).
- Outcome measures – desired results of the system including throughput, flow time and cost (eg waiting time for discharge after medical recovery, cost per patient, patients/procedures completed per day).

### d Relationship between KPIs and efficiency measures

A key performance indicator is a way of measuring success in achieving a set objective. For example, a desirable goal of colonoscopy is to detect adenomas as endoscopists who detect more adenomas reduce the risk of interval colorectal cancer in their patients (42). As such, adenoma detection rate (ADR), 'the proportion of colonoscopies where one or more adenomas are detected' has been set as a key performance indicator (25). In the UK, the minimum adenoma detection rate of 15% is the objective (with an aspirational ADR of 20%).

Based on the AHRQ criteria, ADR is an important measure. However, it could be argued that it is also a rather crude measure of the effectiveness of an endoscopist at detecting adenomas as only one adenoma needs to be detected per colonoscopy to meet the threshold. The risk therefore is that the endoscopist finds one and is thereafter not 'incentivised' to find more adenomas during a particular case. A perhaps more sensitive measure of endoscopist quality is the total number of adenomas per colonoscopy (APC).

In terms of the second criteria, 'scientifically sound', there is a clear scientific basis for detection of adenomas due to their malignant potential. However, it must also be noted that sessile serrated lesions, which have a different often more subtle appearance, are also important to detect due to their malignant potential. The performance of an endoscopist at detecting polyps should take into account detection of both polyp types as an endoscopist might be good at detecting adenomas but not sessile serrated polyps (43).

Regarding 'feasibility' and 'actionable' a significant issue is the manual process currently required to calculate ADR as histology results must be checked before calculation. Many endoscopists, outside a research setting, are not aware of their ADR due to this barrier so may lack awareness of their performance. Automation would greatly enhance this but would require integration of endoscopy and histology reporting systems. One approach to circumvent this is to use polyp detection rate (PDR) as a surrogate marker of ADR and some studies have used an adenoma-to-polyp detection rate quotient (APDRQ) to derive ADR from PDR and shown there to be strong correlation particularly in the right colon (44,45). PDR is much easier to score as you can instantly assess

outcomes post procedure and the national endoscopy database (NED) can now calculate this automatically.

Key Performance Indicators (KPIs) such as ADR and PDR give an indication of the quality of the colonoscopy procedure but do not indicate how efficiently that was achieved. An endoscopist might spend excessive time on withdrawal resulting in an extremely high ADR which might appear to be a high quality procedure but may in fact be an inefficient use of time as: there is a limit to how much can be detected beyond a certain withdrawal time, as discussed earlier, and excessively long procedures reduce the number of procedures that can be performed on a list.

SP6, the number of significant polyps detected per six-minute withdrawal time at colonoscopy, has been proposed as a new measure of colonoscopy efficiency and quality (46). This is calculated as the number of adenomas and sessile serrated polyps divided by the total withdrawal time and then multiplied by six.

## 1.3 Colonoscopy efficiency

Colonoscopy is a valuable procedure that principally allows internal colonic examination for identification and removal of polyps with malignant potential (adenomas and sessile serrated lesions). This helps reduce the risk of colorectal cancer which is the third most commonly occurring cancer worldwide and has the second highest mortality (47).

Efficiency in colonoscopy may be examined from a service level 'top-down' perspective or a procedure level 'bottom up' perspective (see Figure 11 and Figure 12). In both approaches inputs and outputs will vary through the patient pathway over time.

Another approach is to distinguish between factors than can and cannot be modified. At the patient level non-modifiable factors include, for example, age, gender, comorbidities and a history of surgery. At a service level, the availability of endoscopists, nursing and clerical staff as well as procedure rooms are important and modifiable considerations.

In the following sections we evaluate key factors influencing colonoscopy at the service and procedure level.

Figure 11 Summary of patient and system factors influencing colonoscopy efficiency

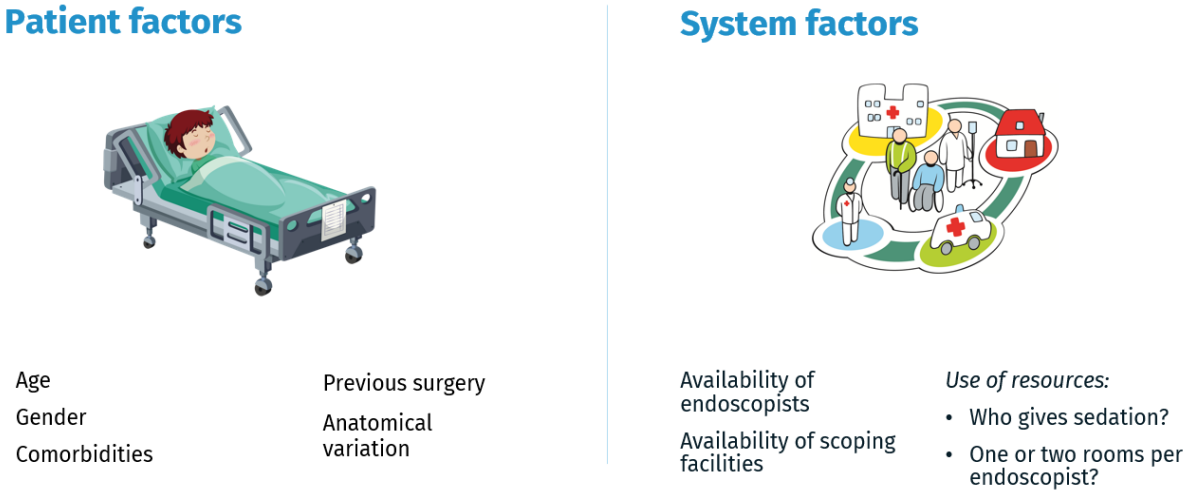
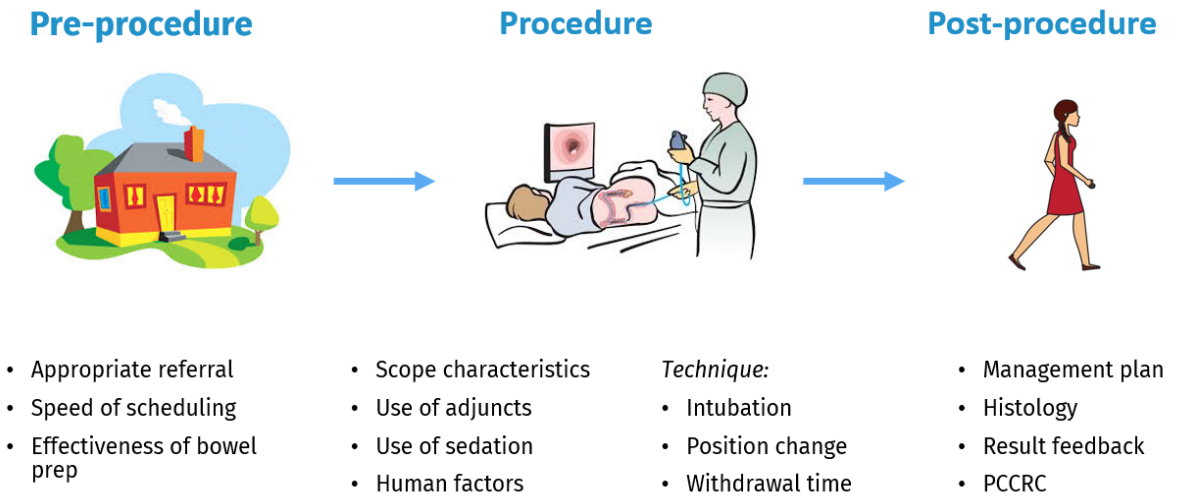



Figure 12 Summary of factors influencing efficiency in the colonoscopy pathway




# 1.4 Colonoscopy efficiency: service level

At the service level, workforce, procedure setting and use of procedure rooms may influence efficiency.

## 1.4.1 Workforce

The makeup and organisation of the workforce will have an impact on procedure efficiency. Having the appropriate staff, medical and non-medical, available will influence how smoothly the endoscopy unit runs. For example, increasing the number

of operators will not improve efficiency if there are not appropriate support staff in place to allow additional endoscopy lists to take place.

Staff that are in place also need to have appropriate training to perform their roles and responsibilities. The distribution of responsibility across roles may also influence efficiency. For example, where a non-operating professional sedates the patient before the procedure there is evidence this may improve turnover (48).

### 1.4.2 Procedure rooms

In a study where 20 experienced endoscopists were evaluated for colonoscopy efficiency there was a '3-fold variation in procedure volume score between the least efficient and most efficient endoscopists' (48). Here, procedure volume was most greatly influenced by a short turnover time in the procedure room ($p = 0.0004$). In addition, there was a trend towards improved procedure volume where two procedure rooms were used by a single endoscopist. The ability to implement such an intervention might however be limited by the availability of adequate space and resources.

### 1.4.3 Procedure setting

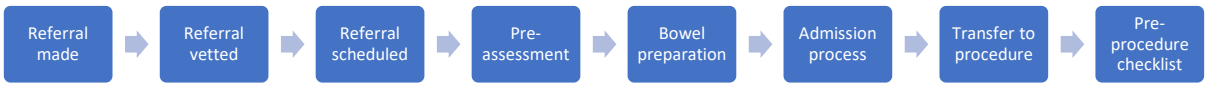
Endoscopy may be performed in a dedicated hospital endoscopy unit or in a community setting. It may also be performed in a more general non-specialised unit that has been adapted for endoscopy. The unit design will affect patient flow and therefore influence efficiency.

## 1.5 Colonoscopy efficiency: procedure level

### 1.5.1 Pre-procedure

From the point of colonoscopy referral until the patient arrives in the procedure room several events may influence efficiency of the patient pathway (see Figure 13).

Figure 13 Pre-procedure targets for improved colonoscopy efficiency




### a Referral appropriateness

Referrals for colonoscopy should be vetted to ensure indication appropriateness, patient fitness and that pre-procedure optimisation has been performed. Without vetting, there is a risk of unnecessary procedures being performed or a higher risk of procedure-related complications. Ultimately this reduces the efficiency of the service and exposes patients to unnecessary risk.

### b Scheduling speed

Scheduling is a process usually performed by the administration team. Ideally, patients will be scheduled appointments as soon as referrals have been vetted with appointment details communicated clearly to the patient. Where scheduling delays occur additional interventions from patients and referrers may be made ultimately increasing the input required to achieve the desired output and therefore reducing efficiency.

### c Pre-assessment process

A comprehensive pre-assessment process not only ensures patients are optimised medically before colonoscopy but also provides an opportunity for an explanation of the bowel preparation instructions, for language barrier/communication issues to be addressed, and for any patient concerns or fears to be relieved. Failure to pre-assess may result in, for example, a patient attending for colonoscopy without stopping anticoagulation and therefore having a colonoscopy without polypectomy being performed. They will then need to either have their procedure rescheduled or possibly have a second procedure for the same indication; clearly an inefficient use of resources.

### d Bowel preparation effectiveness

Patients often find bowel preparation the most unpleasant part of the procedure and it is the leading cause of failed colonoscopy (49). Any intervention that can help improve

compliance with bowel preparation is therefore welcome. This may include patient education materials such as information leaflets and videos provided in different languages as well as providing a contact number for queries during bowel preparation. In terms of the choice of preparation itself, new regimens offer lower volume and same-day administration which may improve efficiency and we have explored this further in the CLEANSE study (see Chapter 2).

#### e Admission process

When a patient arrives in the endoscopy unit they will usually be 'checked-in' at reception, then 'admitted' by the admission nurse who will run through pre-procedure paperwork and prepare the patient for the procedure. Once 'admitted' the patient will need to be consented, usually by the endoscopist performing the procedure. If this process does not occur smoothly, patients could still be undergoing admission when the procedure room and staff are ready to receive the patient. A smooth admission process is therefore important to help maximise procedure room output.

#### f Patient transfer to endoscopy room

Usually the endoscopist or nurse will walk the patient through to the endoscopy room. However, inpatients and some outpatients may require a hospital bed or wheelchair transfer often relying on the use of portering services. Any delay in patient transfers from the admission area to the procedure room could impact efficiency.

#### g Pre-procedure checklist

A pre-procedure checklist is a helpful means of ensuring the correct procedure is performed on the correct patient in the safest possible way. Although this might slightly delay the start of the procedure, it provides an important checkpoint to ensure procedure safety. An unsafe or inappropriate procedure is not an efficient procedure and risks wasting valuable resources.

### 1.5.2 Procedure

During the procedure itself (i.e. colonoscope intubation to extubation) several procedural factors may influence efficiency. There is an interplay between factors that could potentially improve efficiency as position change might, for example, lengthen the procedure by 44 seconds but adenoma detection rate has also been shown to increase (50,51). Use of propofol might improve adenoma detection rate but makes position change more difficult. Use of the Endocuff may improve mucosal visualisation but makes terminal ileum intubation more challenging. Therefore the endoscopist must weigh up the costs and benefits of a particular intervention and individualise the choice of intervention for each patient.

Figure 14 Procedure-related targets for improved colonoscopy efficiency


### a Scope characteristics

- *Image angle*

Colonoscopes have been developed that offer a wider angle of view potentially reducing the risk of missing lesions that are out of view (52,53) . Rex et al evaluated a prototype wide angle colonoscope (adjustable to 160-210° view) in 50 patients who underwent back-to-back same day colonoscopy by a single examiner. Wide angle colonoscopy had lower miss rate for polyps and mean examination time (6.75 min vs 7.64 mins, p = 0.0005) compared with standard colonoscopes. However, there was no significant difference in detection of adenomas between the groups. It was felt that although there is potential to reduce procedure time, resolution quality needed to be improved. In another study, a prototype colonoscope with a 144-232° lateral-backward viewing lens in addition to the standard 140° forward viewing lens was used by 4 experienced endoscopists (53). The study showed many adenomatous lesions were first detected by the lateral-backward view which could potentially increase polyp detection rate. However, it is possible that these polyps might also have been identified in the forward

view on withdrawal. Further studies are required to evaluate these novel devices and their impact on procedure efficiency.

- *Length of scope*

Some studies have assessed the impact of scope length on procedure characteristics. Dickey et al compared long (168cm) and intermediate (133cm) length colonoscopes and found no significant advantage using the shorter colonoscope (54). However, Kim et al showed a decrease in caecal intubation time with an intermediate length adult scope (133cm) versus a long length adult scope (165cm) but the long scope had a higher terminal ileal intubation rate (55).

- *Type of scope*

The use of paediatric colonoscopes, which are narrower and more flexible than adult colonoscopes, has been shown to improve successful intubation in selected patients for some time (56,57).

- *Image definition*

High definition colonoscopes improve adenoma and polyp detection in screening colonoscopy (58,59). High definition colonoscopes also enhance inflammatory bowel disease (IBD) dysplasia detection compared with standard definition colonoscopes (60).

- *Use of stiffness*

The initial evaluation of variable stiffness showed significant improvement in caecal intubation times (61). However, subsequent studies have not shown a significant reduction (62–64).

- *Image enhancing techniques*

Dye spray chromoendoscopy or virtual chromoendoscopy can be used to facilitate colonic neoplastic lesion detection. Dye spray use is time consuming and requires skill for high quality practice whereas virtual chromoendoscopy is a simple push-button technology which instantly enhances vascular structures.

A randomised non-inferiority study assessing neoplastic lesion detection in IBD patients evaluated high definition colonoscopy, dye spray chromoendoscopy, and iScan virtual

chromoendoscopy (65). This showed high definition white light (HD-WL) endoscopy and virtual chromoendoscopy were not inferior to dye spray colonoscopy for neoplastic lesion detection during surveillance colonoscopy. In this study, HD-WL endoscopy, without virtual or dye chromoendoscopy, was sufficient for dysplasia/cancer detection.

In a randomised evaluation of NBI there was also no difference in dysplasia detection with NBI versus high definition white light endoscopy (66). A more recent meta-analysis of virtual chromoendoscopy, HD-WL endoscopy and dye-spray chromoendoscopy has shown no difference in IBD dysplasia detection on a per patient analysis (67).

### b Use of scope adjuncts

- *Endocuff Vision*

Endocuff Vision is a disposable plastic tip attachment with multiple flexible prongs that hold open haustral folds on withdrawal. Several studies have shown Endocuff improves adenoma detection (68–71). The ADENOMA trial showed a 10% increase in ADR where Endocuff Vision was used in a bowel cancer screening population (70).

- *Cap*

A cap is a transparent plastic tip attachment which projects for around 4mm beyond the tip. Studies have shown variable effect of using the cap during colonoscopy (72–74). The DETECT study was a randomised tandem study comparing cuff and cap assisted colonoscopy which showed use of Endocuff Vision resulted in a higher adenoma detection rate and lower adenoma miss rate than cap-assisted colonoscopy (75). However, cuff-assisted procedures were slightly more uncomfortable and there were some occasions where it had to be removed.

- *Magnetic imaging*

ScopeGuide (Olympus) is a real-time electronic imaging device that acts like a sat-nav to aid colonoscope insertion by allowing colonoscope tip and loop visualisation, accurate loop resolution and precise placement of hand pressure.

The first clinical study showed no difference between intubation time or duration of loop formation with magnetic imaging (76). However, the imager view reduced the number

of attempts taken to straighten the colonoscope and helped provide more effective hand pressure.

A more recent randomised controlled trial showed, amongst both trainees and experts, shorter intubation times and reduced number of attempts at colonoscope straightening with the imager view (77). The effect of imager use was greater with trainees who also had a significantly reduced duration of looping.

### c Use of sedation

- *No sedation*

In cases where sedation is not used, the procedure can be started more quickly without the need for sedation to be drawn up and administered. However, there is also the possibility that these procedures might be less well tolerated or require more patient manoeuvres potentially slowing the procedure.

- *Midazolam and Fentanyl*

Midazolam is a benzodiazepine that is widely used to provide conscious sedation during colonoscopy. Often this is administered with Fentanyl, an opiate, with which it has a synergistic effect (78). Use of conscious sedation helps improve procedure tolerance whilst preserving the ability for patients to provide verbal feedback during the procedure and also allowing the patient to change position where required.

- *Propofol*

Propofol allows rapid induction with a single agent and a quick recovery compared with benzodiazepines. It also causes less nausea and vomiting than opioids.

Propofol has been shown to reduce the time taken to sedate the patient (7 to 2 minutes), recovery time (30 to 14 minutes) and discharge time (71 to 40 minutes). On just those 3 parameters, overall there is a saving of 52 minutes per patient (108 to 56 minutes) (79). It is not surprising therefore that patients were also more satisfied with their procedures.

However, unlike standard sedation, an anaesthetist is required for Propofol administration which will influence the cost-effectiveness of this approach.

- *General Anaesthetic*

In some cases, patients are unable to tolerate colonoscopy without general anaesthetic despite sedation, or a prolonged procedure may be required for complex therapy. Here general anaesthetic is an option but, like Propofol, will require additional resources such as a theatre rather than endoscopy unit setting (unless the unit is set up for general anaesthetic cases) and the anaesthetic team need to be present. Patients having general anaesthesia also have a longer post-procedure recovery time (compared with Propofol or standard sedation) and may require admission further adding to the resource required.

### d Use of antispasmodics

Antispasmodics such as glucagon and Buscopan (hyoscine butylbromide) may be used to facilitate colonoscopy.

- *Glucagon*

A randomised trial showed use of 1mg intravenous glucagon by experienced endoscopists did not improve procedure insertion/withdrawal times and resulted in no difference in spasm scores or colonoscopy yield compared with placebo (80).

- *Buscopan*

Buscopan is an anti-spasmodic which causes smooth muscle relaxation of the gastrointestinal tract. It is used by 85.6% of colonoscopists according to a UK survey (81). In the BCSP there was a 30% increase in adenoma detection with Buscopan (81). Buscopan has also been shown to improve insertion time and ileal intubation (82).

However, not all studies are conclusive of benefit in lesion detection (83–85). A meta-analysis of 7 RCTs showed no significant difference in polyp detection rate and adenoma detection rate (86). Heterogeneity is a significant issue with variation in, for example, the timing of Buscopan administration and use of sedation.

### e Procedure technique

- *Intubation technique*

Intubation technique has evolved. Originally, only air was used for insufflation. In 1953, $CO_2$ was proposed and is now widely accepted to be superior to air insufflation due to reduced bloating and pain (87,88). In 1984, water was suggested as an adjunct to gas insufflation in the context of severe diverticular disease (89).

Since the water foot pump has become widely available, use of a water-assisted colonoscopy technique more generally has become easier to implement. Two major water-assisted techniques have emerged. One where water is used to facilitate insertion with gas allowed (water immersion) and the other where water is used to facilitate insertion, with dirty water exchanged so the scope passes through clear water, and gas use is not allowed during insertion (water-exchange).

A meta-analysis comparing air insufflation, $CO_2$ insufflation, water-exchange and water immersion suggest water-exchange is the 'most efficient' for colonoscopy (90). Air insufflation had the highest pain scores and lowest adenoma and polyp detection rates. In contrast, water-exchange had the lowest pain score and highest adenoma and polyp detection rate. However, water-exchange also had the longest caecal intubation time.

We report on a survey of current water-assisted colonoscopy practice (see Chapter 3) and in the WAVE study (see Chapter 4) randomly evaluate water-exchange colonoscopy versus a modified water immersion technique (hybrid technique) which is widely used in clinical practice (predominately water insertion to splenic flexure and then $CO_2$ used predominately from splenic flexure to caecum).

- *Position change*

Position change allows colonic segments to be distended to maximise mucosal visualisation particularly in the transverse colon, splenic flexure and descending colon (91). In an audit of 100 patients undergoing colonoscopy, position change was used 144 times (average of 2 changes per patient) in 63% of participants (92). It was most frequently used at the sigmoid-descending colon (38%) where a change in position from left lateral to supine/right lateral helped advance the scope in 63% of cases. There is a significant improvement in ADR where a left lateral to supine position change is made for transverse colon and supine to right lateral position change is made for splenic flexure and descending colon (51).

The starting position for colonoscopy may also influence procedure efficiency. Where the start position is supine rather than left lateral, caecal intubation time has been shown in a randomised trial to be significantly shorter (275 seconds versus 316 seconds, p <0.001) (93). Although only a 41 second reduction this could be significant at the aggregate level. Supine position also gave a significantly lower pain score, reduced frequency of position change and need for abdominal compression.

- *Use of manual pressure*

Abdominal pressure can be used to help prevent loop formation by externally splinting the colonoscope. In an audit of looping accuracy and ancillary manoeuvres including 100 patients, abdominal pressure was used 145 times (median 2 applications per patient) in 72% of patients (92). It was used most frequently to help control the sigmoid colon when the splenic flexure is being passed. Sigmoid colon pressure was used 8 times more frequently than at the transverse colon but was successful only a third of the time. This was attributed to hand misplacement in 36% of cases and 'incorrectly appreciated or inaccessible looping' in 52% of cases. In 59% of cases abdominal pressure helped pass the hepatic flexure and was less effective at other locations.

f Diagnosis

- *Optical diagnosis*

Where findings during colonoscopy are diagnosed by the endoscopist optically rather than relying on histopathology assessment there is the potential for significant time and cost savings. This is particularly applicable for small polyps where a "resect and discard" strategy has been proposed for polyps optically diagnosed with high confidence (94,95). We have evaluated this strategy in a bowel cancer screening setting in the DISCARD3 study (see Chapter 9).

- *Use of CAD to assist in polyp detection/characterisation*

AI-based algorithms have been used to develop systems for computer-aided polyp detection (CADe) and characterisation (CADx). These may augment the endoscopist in helping identify polyps and could facilitate real-time diagnosis of polyps. We have evaluated a CADe system in the AI-DETECT study (see Chapter 5).

### g Human factors

- *Fatigue*

Studies have shown fatigue influences the quality of colonoscopy performed and may negatively impact on key performance indicators (96,97). AI may play a role in helping reduce the effect of fatigue with, for example, CADe systems designed to prompt endoscopists to the presence of a polyp.

- *Level of experience*

Colonoscopy performance requires technical skill and experience level may therefore affect achievement of key performance indicators. In a meta-analysis of annual procedure volume and colonoscopy quality, however, higher procedure volumes correlated with a higher caecal intubation rate but not ADR (98). Training also appears to play a role with differences in procedure quality previously observed between gastroenterologists and non-gastroenterologists (99).

## 1.5.3 Post-procedure

After the colonoscope is removed from the patient, several further steps are required to document and follow up the patient which present an opportunity to improve efficiency of the patient pathway.

Figure 15 Post-procedure targets for improved colonoscopy efficiency


### a Procedure documentation

Clear procedure documentation is important to provide a record for the patient notes but also to ensure good communication with colleagues who rely on the report for decision making, to check results of histology and to organise further tests.

### b Management plan formulation

The ongoing management plan for patients having colonoscopy, such as the surveillance interval assigned, is important to help ensure patients are not over or under-investigated.

### c Findings communication

Findings are traditionally communicated to the referrer with paper records that may require a postal service. Nowadays, these are more efficiently and instantly delivered by e-mail.

### d Histology results

Histology results are usually manually checked by the endoscopist or members of the endoscopy team. Automated systems for checking and acting on the histology results may improve efficiency in this area.

### e Detection of post-colonoscopy colorectal cancer (PCCRC)

There are various causes for PCCRC with a frequent cause being an inadequate procedure. This suggests that improvements in procedure quality might help reduce PCCRC occurrence. We have evaluated PCCRC causation in the REFLECT study (see Chapter 12).

## 1.6 Research question

The overarching research question is: how can efficiency in colonoscopy, at the procedure level, be improved throughout the patient pathway?

## 1.7 Thesis structure

Chapter 1 provides an overview of the definition of efficiency and how this is applied to healthcare and more specifically colonoscopy practice.

Chapter 2 evaluates the efficiency of bowel preparation with evaluation of a novel low-volume bowel preparation regimen (Plenvu) against standard regimens (CLEANSE study).

Chapters 3 and 4 explore colonoscopy insertion technique practice and efficiency. Chapter 3 provides an overview of the findings from a national survey of current practice in water-assisted colonoscopy. Chapter 4 details a randomised evaluation of water-exchange colonoscopy versus a modified water immersion colonoscopy technique (WAVE study).

Chapters 5 and 6 investigate use of AI to improve polyp detection efficiency. Chapter 5 is an early evaluation of the first available polyp detection system (GI Genius). Chapter 6 is a randomised study assessing the use of GI Genius versus standard colonoscopy (AI-DETECT study)

Chapters 7 to 11 explore optical diagnosis and potential for improving efficiency with a "resect and discard" strategy. Chapter 7 reveals the findings of a UK survey about current optical diagnosis practice. Chapter 8 is an exploration of colonoscopy photodocumentation quality; an essential requirement for optical diagnosis implementation. Chapter 9 is a study evaluating the feasibility and acceptance of optical diagnosis with a "resect and discard" strategy assessing the learning curve and proposes a quality assurance process (DISCARD3 study). Chapter 10 is a deep dive into understanding why optical diagnosis error occurs. Chapter 11 explores efficiency gains with a "resect and discard" strategy from an economic perspective.

Chapter 12 assesses post-colonoscopy colorectal cancer, a key measure of the efficiency of a colonoscopy service, through a root cause analysis of nationally reported PCCRC cases (REFLECT study).

Chapters 13 and 14 provide a discussion of the impact of this work, how it adds to existing knowledge, future directions and a final conclusion.

# Chapter 2 Bowel preparation 1: Evaluation of a novel low-volume bowel preparation regimen (CLEANSE)

This chapter is based on a published manuscript[8] (100).

## 2.1 Background and Aims

### 2.1.1 Background

#### a Why is bowel preparation important?

The effectiveness of bowel preparation before colonoscopy has a significant impact on procedure outcome, quality and efficiency. Where bowel preparation is successful, colonoscopy examination can be expedited without need for additional time to clean the mucosa. Clear mucosal visualisation enhances identification of colonic abnormalities and increases the likelihood of a complete procedure. Conversely, poor preparation has significant negative implications at the patient, endoscopist and service level and is the leading cause of failed colonoscopies (49).

Several studies have shown poor bowel preparation is associated with failure to detect adenomas in around a third of cases (101–104). Poor bowel preparation prolongs procedure time (105,106). Where preparation is inadequate, procedures are more likely to be abandoned and need repeating causing significant inconvenience for patients (107,108). In cases of sub-optimal or 'fair' bowel preparation, surveillance intervals that are inconsistent or shorter may be offered (109). Overall, poor preparation increases procedure costs by 12-22% due to prolonged procedure times and the need for repeated procedures or earlier surveillance (110).

#### b Types of bowel preparation regimen

[8] Ahmad A *et al*. Evaluation of bowel preparation regimens for colonoscopy including a novel low volume regimen (Plenvu): CLEANSE study. *BMJ Open Gastroenterology*. 2023; 10: e001070. Tables and figures reproduced in accordance with CC BY-NC 4.0.

A number of bowel preparation regimens exist with different mechanisms of action and dosing instructions (see Table 1). Polyethylene glycol (PEG) based regimens are commonly used due to their performance and safety profile but have traditionally required a high volume preparation of up to 4L (111). More recently, PEG regimens have been combined with ascorbic acid to reduce the volume required to 2L (eg Moviprep). Giving an increased ascorbic acid content, a new IL PEG regimen called Plenvu has been developed. Magnesium citrate is an alternative bowel preparation regimen which works as an osmotic agent increasing intraluminal volume and is widely used in more than a third of colonoscopies in the UK (112). When combined with the stimulant laxative senna, bowel cleansing is significantly improved so a senna and citramag regimen has emerged (113). Although the senna and citramag regimen can be ingested with low fluid volumes it is still recommended that 2- 3 litres of fluid are taken with it to avoid risk of dehydration and that it should not be used in patients with significant renal impairment.

In view of the importance of bowel preparation, societal guidelines exist to help optimise bowel preparation administration and efficacy (111,114). It is recommended at least 90% of colonoscopies have adequate bowel preparation. There are also a number of quality scales including the Boston Bowel Preparation Scale score (BBPS) and Harefield Cleansing Scale which can be used to score bowel preparation outcomes (115–117).

Table 1 Summary of bowel preparation regimens

| | **Moviprep 2 days** | **Senna & Citramag 2 days** | **Plenvu 2 days** | **Plenvu 1 day** |
|---|---|---|---|---|
| Preparation type | Polyethylene glycol (PEG) | Magnesium citrate (osmotic agent) combined with Senna (stimulant laxative) | Polyethylene glycol (PEG) | Polyethylene glycol (PEG) |
| Bowel preparation | 4 sachets (both A and B) mixed with 2L of water | 2 sachets of Citramag mixed with 0.4L water and 10 tablets of Senna | 2 doses mixed in 1L water | 2 doses mixed in 1L water |

| | Moviprep 2 days | Senna & Citramag 2 days | Plenvu 2 days | Plenvu 1 day |
|---|---|---|---|---|
| Administration – day before | *Morning appointment:*<br>2pm: 1.5 L taken with an extra 1 L of clear fluid.<br>*Afternoon appointment:*<br>4pm: 1 L taken with an extra 1 L of clear fluid. | *All appointments:*<br>2pm: Take 10 Senna tablets (2 every 10 min within an hour) with clear fluid.<br>5pm:<br>1 sachet of Citramag dissolved in 0.2 L hot water and taken when cooled.<br>Drink an extra 1.5 L clear fluids.<br>7pm:<br>0.5 sachet of Citramag dissolved in 0.1 L water and taken.<br>Drink an extra 1.5 L clear fluids. | *Morning appointment:*<br>2pm: Mix dose 1 in 0.5 L water and take with an extra 0.5 L of clear fluid.<br>6pm: Mix dose 2 in 0.5 L water and drink 0.25 L and an extra 0.5 L of clear fluid.<br>*Afternoon appointment:*<br>4pm: Mix dose 1 in 0.5 L water and take with an extra 0.5 L of clear fluid. | |
| Administration – procedure day | *Morning appointment:*<br>6am:<br>0.5 L taken on the procedure day with an extra 0.5 L of clear fluid.<br>*Afternoon appointment:*<br>7–8am:<br>1 L taken on the procedure day with an extra 0.5 L of clear fluid. | *Morning appointment:*<br>6–7am:<br>0.5 sachet of Citramag dissolved in 0.1 L water and taken.<br>*Afternoon appointment:*<br>9–10am:<br>0.5 sachet of Citramag dissolved in 0.1 L water and taken. | *Morning appointment:*<br>6am:<br>0.25 L of prep and an extra 0.5 L of clear fluid taken.<br>*Afternoon appointment:*<br>6–7am: Mix dose 2 in 0.5 L water and drink an extra 0.5 L of clear fluid. | 6am: 0.5 L of prep and an extra 0.5 L of clear fluid taken.<br>8:30am: 0.5 L of prep and an extra 0.5 L of clear fluid taken. |
| Timing (bowel preparation + water) | *Morning appointment:*<br>Day before 2pm: 1.5 L (+1 L clear fluid). | *Morning appointment:*<br>Day before 2pm: Take Senna | *Morning appointment:*<br>Day before 2pm: 0.5 L (+0.5 L)<br>Day before 6pm: 0.25 L (+0.5 L) | Procedure day 6am:<br>0.5 L (+0.5 L clear fluid).<br>Procedure day 8:30am: |

| | Moviprep 2 days | Senna & Citramag 2 days | Plenvu 2 days | Plenvu 1 day |
|---|---|---|---|---|
| | Procedure day 6am: 0.5 L (+0.5 L clear fluid).<br>*Afternoon appointment:*<br>Day before 2pm: 1 L (+1 L clear fluid).<br>Procedure day 6am: 1 L (+0.5 L clear fluid). | Day before 5pm: 0.2 L (+1.5 L clear fluid)<br>Day before 7pm: 0.1 L (+1.5 L clear fluid)<br>Procedure day 6–7am: 0.1 L<br>*Afternoon appointment:*<br>Day before 2pm: Take Senna<br>Day before 5pm: 0.2 L (+1.5 L clear fluid)<br>Day before 7pm: 0.1 L (+1.5 L clear fluid)<br>Procedure day 9–10am: 0.1 L | Procedure day 6am:<br>0.25 L (+0.5 L)<br>*Afternoon appointment:*<br>Day before 4pm: 0.5 L (+0.5 L)<br>Procedure day 6–7am:<br>0.5 L (+0.5 L) | 0.5 L (+0.5 L clear fluid). |
| Prep volume | 2L | 0.4L | 1L | 1L |
| Minimum recommended extra fluid volume | 1.5L | 3L | 1L | 1L |
| Minimum total fluid volume | 3.5L | 3.4L | 2L | 2L |
| Diet | 2 days before: low-residue diet<br><br>Day before from 12noon: no solid food | 2 days before: low-residue diet<br><br>Day before from 12noon: no solid food | 2 days before: low-residue diet<br><br>Day before from 12 noon: no solid food | 2 days before: low-residue diet<br><br>Day before from 7pm: no solid food |

### c How can bowel preparation be optimised?

Several factors influence bowel preparation quality. Patients with increasing age, comorbidity and those that are hospitalised have poorer bowel preparation cleansing quality although these are not modifiable factors (118). Patient compliance with bowel preparation and dietary instructions may be influenced by patient motivation, education (eg. language barrier), communication techniques for explanation (eg. use of video).

Product-related factors also affect ease of bowel preparation administration such as taste, preparation volume and dosing regimen as well as timing of administration.

Of these, choice of bowel preparation regimen is relatively easy to modify. For example, split-dosing has been shown to increase bowel preparation efficacy (119). As bowel preparation is frequently cited the 'worst' part of the procedure, any intervention that improves compliance is therefore welcome.

### 2.1.2 Aims

A novel low-volume bowel preparation regimen, Plenvu (Norgine), that can be administered as a 1-day or 2-day regimen has recently emerged. This could offer the potential for enhanced compliance and potentially improved bowel preparation outcomes. There is limited evaluation of Plenvu against other established preparation regimens. The aim of this study therefore is to evaluate the efficacy of Plenvu regimens versus more commonly used bowel preparation regimens in terms of bowel cleansing effectiveness and patient acceptance.

## 2.2 Methods

### 2.2.1 Study design

In this service evaluation, patients undergoing bowel cancer screening colonoscopy at St Mark's Hospital, London (Feb 2020-Dec 2021) were provided with either Plenvu (1 or 2 day regimen), Moviprep (2 day regimen), or Senna & Citramag (2 day regimen). All patients attended a pre-assessment clinic where a specialist screening practitioner allocated the bowel preparation. An information leaflet explaining the procedure and bowel preparation process was also provided. The allocation of bowel preparation took into consideration previous bowel preparation (where a previous regimen provided good cleansing this was offered), comorbidities and patient preference (fluid and tablet tolerance). Plenvu and Senna & Citramag were not given to patients with significant cardiac, liver or renal disease. The 1 day Plenvu regimen was offered only for afternoon or evening appointments (as this regimen is not suitable for morning appointments). In

patients >70 years old or those with risk factors, blood tests were checked and reviewed by a consultant to decide on the most suitable regimen with split dose Moviprep given if estimated glomerular filtration rate (eGFR) was <60 mL/min/1.73 $m^2$, as per the hospital standard operating policy.

On the day of the procedure, patients were invited to complete a bowel preparation experience questionnaire (see Table 2). The procedures were performed by bowel cancer screening accredited colonoscopists. As part of the assessment of baseline characteristics we recorded any significant comorbidities.

Table 2 Patient bowel preparation questionnaire

1. The bowel preparation was pleasant to taste[9]
2. The volume (amount of preparation) to drink was acceptable[9]
3. The instructions were easy to follow[9]
4. If you have taken bowel preparation before, did you rate if better than last time?
5. Did you manage to complete (drink) all the preparation?
6. Since starting the bowel preparation, how much other fluid did you drink?
7. Did you experience any side effects[10]

During the procedure, fluid volumes (infused, suctioned, net [infused-suctioned]) and procedure times (insertion [intubation to ileocaecal valve reached], caecum [ileocaecal valve reached to ileocaecal valve left, withdrawal [ileocaecal valve left to extubation], total [intubation to extubation]) were recorded. Any cases where bowel preparation was inadequate to the extent a repeat procedure or CT colonography was required were documented. On withdrawal, the Boston Bowel Preparation Scale was scored by the endoscopist with a pictoral reference sheet shown to endoscopists to reduce variation. (115).

[9] Assessed on a five-point Likert scale (strongly disagree to strongly agree).
[10] Nausea/vomiting, abdominal cramps, dizziness, anal soreness, and other.

We excluded any cases where a flexible sigmoidoscopy rather than a colonoscopy was performed. Patients with extended bowel preparation regimens were not invited to participate.

### 2.2.2 Outcomes

The primary outcome was Boston Bowel Preparation Scale (BBPS) score. The secondary outcomes were fluid volumes (infused and suctioned), procedure times (insertion, withdrawal and total), polyp detection (polyps per colonoscopy [PPC], polyp detection rate [PDR], adenoma detection rate [ADR], number of adenomas and sessile serrated polyps detected per six-minute withdrawal time at colonoscopy [SP6] **(46)**) and bowel preparation experience evaluated using a patient experience questionnaire including assessment of taste, volume acceptability, completion and side effects.

### 2.2.3 Statistical analysis

Comparisons of demographics measured on a continuous scale between the bowel preparation groups were made using analysis of variance (ANOVA) if found to be normally distributed, and the Kruskal-Wallis if found to have a skewed distribution. Categorical demographic variables were compared between groups using the Chi-squared tests.

Clinical outcomes were compared between the regimens with overall and pairwise comparisons. ANOVA and ANOVA post-hoc tests were used to compare normally distributed outcomes, whilst the Kruskal-Wallis and Mann-Whitney test was used for non-normally distributed continuous variables. The Chi-square test was used for categorical outcomes. Due to multiple comparisons between pairs of groups, and increased risk of finding a significant difference due to chance alone, a Bonferroni adjustment was made.

Questionnaire outcomes were mostly ordinal in nature. The Kruskal-Wallis test and Mann-Whitney test were used to compare between the groups overall and between pairs of groups, respectively.

## 2.3 Results

### 2.3.1 Overview

There were 563 patients invited to participate with 10 exclusions (flexible sigmoidoscopies). Of 553 included patients there were: 218 Moviprep 2 day, 108 Senna & Citramag 2 day, 152 Plenvu 2 days, and 75 Plenvu 1 day (see Figure 16). Overall there were 184 female and 369 male patients with no significant difference in gender, age and body mass index (BMI) between the groups (see Table 3). Those taking Moviprep had more significant comorbidities per patient compared with the other regimens as expected from the bowel preparation allocation process.

Figure 16 Flow diagram of study

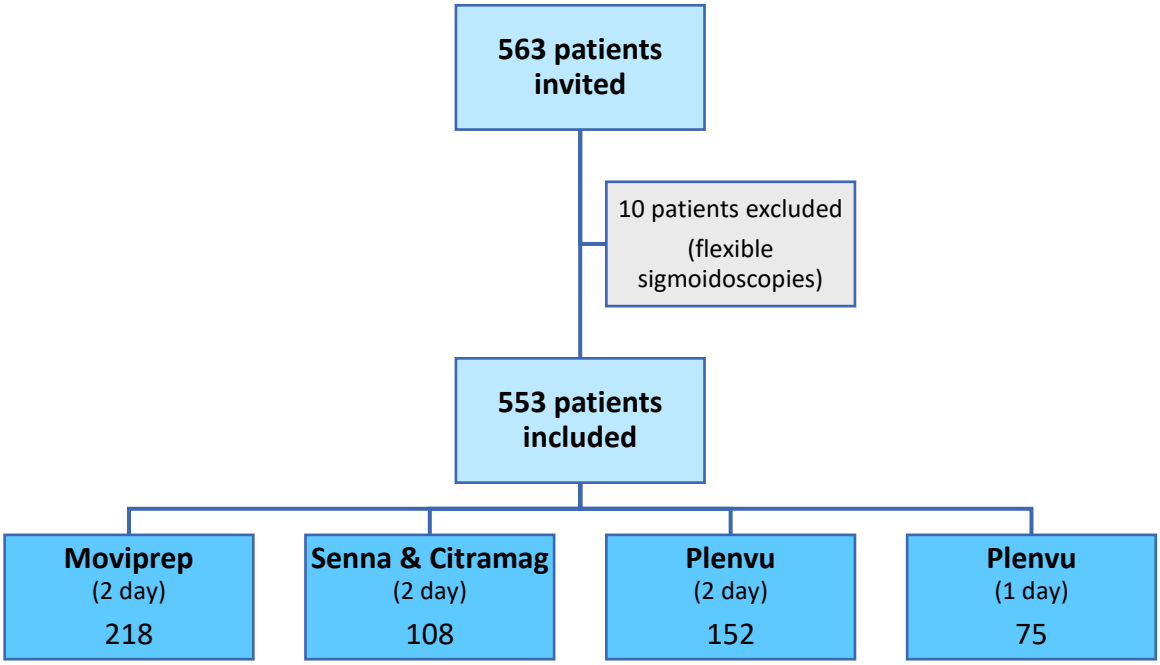


Table 3 Participant characteristics

| | Moviprep 2 day | Senna & Citramag 2 day | Plenvu 2 day | Plenvu 1 day | P-value |
|---|---|---|---|---|---|
| Patients | 218 | 108 | 152 | 75 | |
| Gender | | | | | |
| Male | 68 (31%) | 36 (33%) | 56 (37%) | 24 (32%) | 0.72 |
| Female | 150 (69%) | 72 (67%) | 96 (63%) | 51 (68%) | |
| Age (average) | 66.4 ± 11.3 | 65.1 ± 5.4 | 65.0 ± 4.3 | 63.5 ± 8.9 | 0.07 |
| BMI | 27.2 [24.3, 31.3] | 26.6 [23.3, 29.6] | 27.4 [24.2, 29.4] | 25.7 [23.2, 29.3] | 0.06 |
| Significant comorbidities | 0.83 ± 1.00 | 0.47 ± 0.68 | 0.49 ± 0.72 | 0.49 ± 0.76 | **<0.001** |

Summary statistics are: mean ± standard deviation, median [inter-quartile range] or number (percentage)

## 2.3.2 Clinical outcomes

### a BBPS score

In terms of overall differences between the four bowel preparation regimens, there was a significant difference in BBPS scores ($p<0.001$, see Table 4). When pairwise comparisons were made (see Table 5), BBPS scores were significantly higher in both 1 and 2 day Plenvu regimens (7.8 ± 1.4 and 7.7 ± 1.6) compared with Senna & Citramag (7.0 ± 1.7; $p=0.003$ and 0.002 respectively) and Moviprep (7.1 ± 1.7; $p=0.003$ and 0.001 respectively). There was no significant difference in BBPS score between Plenvu 1 and 2 day regimens, and between Moviprep and Senna & Citramag.

### b Fluid volumes

Total suctioned fluid was significantly different ($p=0.02$), when assessing overall differences between the four bowel preparation regimens, as was the net amount of fluid ($p=0.04$) but there was no difference in total fluid introduced. Plenvu 1 day had the highest volume of fluid suctioned which reached significance when compared with Moviprep ($p=0.01$). There were no other significant pairwise differences in fluid volume introduced or suctioned between the groups.

### c Procedure times

There was no overall difference in total procedure time, insertion time and caecum time between the groups. There was borderline overall difference in withdrawal time

(p=0.05). However, in pairwise comparisons, there were no significant differences in all procedure times (total, insertion, caecum and withdrawal).

### d Polyp detection

There was no difference in polyp detection between the groups.

### e Bowel preparation adequacy

There was no significant difference in proportion of cases classified as having inadequate bowel preparation between the groups (p=0.69).

Table 4 Clinical outcomes according to bowel preparation type

| | Moviprep 2 day | Senna & Citramag 2 day | Plenvu 2 day | Plenvu 1 day | P-value |
|---|---|---|---|---|---|
| **n** | 218 | 108 | 152 | 75 | |
| **Boston Bowel Preparation Scale score** | | | | | |
| Right | 2.3 ± 0.6 | 2.3 ± 0.6 | 2.5 ± 0.6 | 2.6 ± 0.5 | **<0.001** |
| Transverse | 2.4 ± 0.6 | 2.6 ± 0.5 | 2.6 ± 0.5 | 2.6 ± 0.5 | **<0.001** |
| Left | 2.4 ± 0.6 | 2.3 ± 0.6 | 2.6 ± 0.6 | 2.6 ± 0.5 | **<0.001** |
| Total | 7.1 ± 1.7 | 7.0 ± 1.7 | 7.7 ± 1.6 | 7.8 ± 1.4 | **<0.001** |
| **Fluid volumes (mL)** | | | | | |
| Total introduced | 400 [250, 550] | 400 [250, 653] | 400 [250, 600] | 450 [300, 650] | 0.59 |
| Total suctioned | 500 [400, 700] | 500 [400, 800] | 550 [400, 800] | 600 [450, 800] | **0.02** |
| Net amount | -100 [-200, 0] | -100 [-280, 0] | -150 [-300, 0] | -150 [-270, -50] | 0.04 |
| **Procedure times (minutes)** | | | | | |
| Insertion time | 7.2 [5.2, 9.9] | 6.5 [4.6, 9.0] | 7.3 [5.3, 9.6] | 7.0 [5.0, 8.5] | 0.24 |
| Caecum time | 1.8 [1.1, 2.6] | 1.5 [1.0, 2.4] | 1.7 [1.0, 2.5] | 1.9 [1.0, 2.8] | 0.55 |
| Withdrawal time | 15.0 [10.3, 20.3] | 14.5 [10.1, 21.3] | 15.6 [10.3, 23.0] | 17.1 [11.4, 24.4] | 0.05 |
| Total time | 25.1 [20.2, 31.5] | 24.3 [18.5, 30.3] | 25.4 [19.6, 33.3] | 27.4 [21.0, 35.0] | 0.10 |
| **Polyp detection** | | | | | |
| Polyps per colonoscopy | 2.5 [1, 5] | 2 [1, 5] | 3 [1, 6] | 2 [1, 5] | 0.28 |
| Polyp detection rate (%) | 83% (182/218) | 80% (86/108) | 84% (127/152) | 84% (63/75) | 0.81 |
| Adenoma detection rate (%) | 73% (159/218) | 66% (71/108) | 74% (112/152) | 64% (48/75) | 0.26 |
| SP6 | 0.94 [0.49, 1.50] | 0.86 [0.25, 1.39] | 0.94 [0.43, 1.64] | 0.64 [0.21, 1.36] | 0.13 |
| **Inadequate preparation requiring repeat colonoscopy or CTVC (%)** | | | | | |
| Inadequate prep | 5% (5/218) | 2% (2/108) | 3% (4/152) | 0% (0/75) | 0.69 |

Summary statistics are: mean ± standard deviation, median [inter-quartile range] or percentage (number/total number)

Table 5 P-values from pairwise group comparisons for clinical outcomes

| | **Moviprep 2 day vs. Senna & Citramag 2 day** | **Moviprep 2 day vs. Plenvu 2 day** | **Moviprep 2 day vs. Plenvu 1 day** | **Senna & Citramag 2 day vs. Plenvu 2 day** | **Senna & Citramag 2 day vs. Plenvu 1 day** | **Plenvu 2 day vs. Plenvu 1 day** |
|---|---|---|---|---|---|---|
| **Boston Bowel Preparation Scale score** | | | | | | |
| Right | 1.00 | **0.01** | **0.01** | **0.009** | **0.007** | 1.00 |
| Transverse | 1.00 | **0.01** | **0.02** | **0.02** | **0.02** | 1.00 |
| Left | 1.00 | **0.001** | **0.007** | **<0.001** | **0.004** | 1.00 |
| Total | 1.00 | **0.001** | **0.003** | **0.002** | **0.003** | 1.00 |
| **Fluid volumes (mL)** | | | | | | |
| Total introduced | 1.00 | 1.00 | 0.93 | 1.00 | 1.00 | 1.00 |
| Total suctioned | 1.00 | 0.28 | **0.01** | 1.00 | 0.97 | 1.00 |
| Net amount | 1.00 | 0.10 | 0.11 | 1.00 | 1.00 | 1.00 |
| **Procedure time (mins)** | | | | | | |
| Insertion time | 0.43 | 1.00 | 1.00 | 0.70 | 1.00 | 1.00 |
| Caecum time | 1.00 | 1.00 | 1.00 | 1.00 | 1.00 | 1.00 |
| Withdrawal time | 1.00 | 1.00 | 0.07 | 1.00 | 0.08 | 0.79 |
| Total time | 1.00 | 1.00 | 0.49 | 0.80 | 0.09 | 1.00 |
| **Polyp detection** | | | | | | |
| Polyps per colonoscopy | 1.00 | 1.00 | 1.00 | 0.42 | 1.00 | 1.00 |
| Polyp detection rate (%) | 1.00 | 1.00 | 1.00 | 1.00 | 1.00 | 1.00 |
| Adenoma detection rate (%) | 1.00 | 1.00 | 0.86 | 1.00 | 1.00 | 0.79 |
| SP6 | 1.00 | 1.00 | 0.32 | 0.97 | 1.00 | 0.26 |
| **Inadequate preparation requiring repeat colonoscopy or CTVC (%)** | | | | | | |
| Inadequate prep | 1.00 | 1.00 | 1.00 | 1.00 | 1.00 | 1.00 |

### 2.3.3 Patient questionnaire

Patient questionnaire outcomes are summarised in Table 6 with pairwise comparisons in Table 7.

Table 6 Patient questionnaire outcomes

| Category | Moviprep 2 day | Senna & Citramag 2 day | Plenvu 2 day | Plenvu 1 day | P-value |
|---|---|---|---|---|---|
| **1: The bowel preparation was pleasant to taste** | | | | | |
| Strongly agree | 18 (9%) | 13 (12%) | 8 (5%) | 7 (10%) | **<0.001** |
| Agree | 106 (51%) | 68 (64%) | 69 (46%) | 25 (35%) | |
| Neither agree or disagree | 27 (13%) | 6 (6%) | 9 (6%) | 10 (14%) | |
| Disagree | 26 (13%) | 11 (10%) | 33 (22%) | 16 (23%) | |
| Strongly disagree | 30 (14%) | 8 (8%) | 30 (20%) | 13 (18%) | |
| **2: The volume (amount of preparation) to drink was acceptable** | | | | | |
| Strongly agree | 15 (7%) | 17 (16%) | 11 (7%) | 14 (20%) | **<0.001** |
| Agree | 124 (60%) | 81 (76%) | 103 (70%) | 39 (55%) | |
| Neither agree or disagree | 12 (6%) | 2 (2%) | 8 (5%) | 3 (4%) | |
| Disagree | 48 (23%) | 4 (4%) | 22 (15%) | 11 (15%) | |
| Strongly disagree | 8 (4%) | 2 (2%) | 4 (3%) | 4 (6%) | |
| **3: The instructions were easy to follow** | | | | | |
| Strongly agree | 133 (64%) | 69 (65%) | 115 (77%) | 55 (77%) | **0.02** |
| Agree | 69 (33%) | 31 (29%) | 30 (20%) | 15 (21%) | |
| Neither agree or disagree | 3 (1%) | 2 (2%) | 3 (2%) | 1 (1%) | |
| Disagree | 2 (1%) | 4 (4%) | 0 (0%) | 0 (0%) | |
| Strongly disagree | 0 (0%) | 0 (0%) | 1 (1%) | 0 (0%) | |
| **4: If you have taken bowel preparation before, did you rate if better than last time?** | | | | | |
| Yes / Better | 29 (41%) | 17 (38%) | 19 (46%) | 6 (38%) | 0.94 |
| Same | 21 (30%) | 16 (36%) | 9 (22%) | 4 (25%) | |
| No / Worse | 20 (29%) | 12 (27%) | 13 (32%) | 6 (38%) | |
| **5: Did you manage to complete (drink) all the preparation?** | | | | | |
| Yes | 193 (94%) | 101 (96%) | 147 (99%) | 64 (98%) | 0.08 |
| No | 13 (6%) | 4 (4%) | 2 (1%) | 1 (2%) | |
| **6: Since starting the bowel preparation, how much other fluid did you drink?** | | | | | |
| None | 5 (2%) | 1 (1%) | 1 (1%) | 2 (3%) | **<0.001** |
| Less than 1L | 18 (9%) | 4 (4%) | 11 (7%) | 6 (8%) | |
| About 1L | 45 (22%) | 12 (11%) | 32 (21%) | 16 (23%) | |
| 1-2 L | 71 (34%) | 29 (27%) | 43 (29%) | 29 (41%) | |
| More than 2L | 68 (33%) | 60 (57%) | 62 (42%) | 18 (25%) | |
| **7: Did you experience any side effects?** | | | | | |
| Yes | 61 (29%) | 37 (35%) | 64 (43%) | 34 (48%) | **0.01** |
| No | 146 (71%) | 69 (65%) | 85 (57%) | 37 (52%) | |

Table 7 P-values from pairwise group comparisons for questionnaire outcomes

| Question | Moviprep 2 day vs. Senna & Citramag 2 day | Moviprep 2 day vs. Plenvu 2 day | Moviprep 2 day vs. Plenvu 1 day | Senna & Citramag 2 day vs. Plenvu 2 day | Senna & Citramag 2 day vs. Plenvu 1 day | Plenvu 2 day vs. Plenvu 1 day |
|---|---|---|---|---|---|---|
| 1 | **0.04** | 0.17 | 0.44 | **<0.001** | **0.002** | 1.00 |
| 2 | **<0.001** | 0.41 | 0.24 | **0.002** | 0.68 | 1.00 |
| 3 | 1.00 | 0.07 | 0.24 | 0.18 | 0.38 | 1.00 |
| 4 | 1.00 | 1.00 | 1.00 | 1.00 | 1.00 | 1.00 |
| 5 | 1.00 | 0.13 | 0.78 | 1.00 | 1.00 | 1.00 |
| 6 | **<0.001** | 0.80 | 1.00 | **0.007** | **<0.001** | 0.38 |
| 7 | 1.00 | 0.05 | **0.03** | 1.00 | 0.50 | 1.00 |

Taste was rated to be most pleasant in the Senna & Citramag group (76% agreed or strongly agreed) which achieved statistical significance when compared with Plenvu 1 day (45%, p<0.002), Plenvu 2 day (51%, p<0.001) and Moviprep 2 day (60%, p=0.04).

Patients found the volume to drink most acceptable with Senna & Citramag (92% agreed or strongly agreed) and this reached significance when compared with Moviprep 2 day (67%, p<0.001) and Plenvu 2 day (77%, p=0.002).

There was no difference between the groups in terms of experience compared with previous bowel preparation taken and in ability to drink the total amount of preparation.

The highest volume of fluid drank in addition to bowel preparation was in the Senna & Citramag group with 84% drinking >1L. This achieved significance when compared with Moviprep 2 day (67%, p<0.001), Plenvu 2 day (71%, p=0.007) and Plenvu 1 day (66%, p<0.001).

Although a greater proportion of patients drank all preparation with Plenvu 1 day and 2 day compared with other groups this did not reach statistical significance.

There was a significant difference in rate of side effects between the groups. In pairwise comparisons, Plenvu 1 day had a significantly higher number of side effects compared with Moviprep (48% and 29% respectively, p=0.03). There were no other significant pairwise differences in side effects. There was also no difference in the occurrence of

individual side effects between the groups (abdominal cramps, anal soreness, dizziness, nausea, vomiting, other).

# 2.4 Discussion

## 2.4.1 Key findings

A key test of the effectiveness of bowel preparation is whether mucosal visualisation is adequate to avoid the need for repeat colonoscopy or CT colonography. In this study, all 4 regimens showed no significant difference in the inadequate bowel preparation rate and no difference in polyp detection. In fact, for all regimens tested, including Plenvu 1 day, the rate of adequate bowel preparation surpassed the 90% threshold set by the ESGE (111). However, there were significant differences in BBPS score between the groups with 1 day and 2 day Plenvu (7.8 ± 1.4 and 7.7 ± 1.6) achieving a small but significant increase in score compared with Senna & Citramag (7.0 ± 1.7; p=0.003 and 0.002 respectively) and Moviprep (7.1 ± 1.7; p=0.003 and 0.001 respectively).

## 2.4.2 Comparison with previous studies

Several studies have evaluated Plenvu against higher volume PEG-based regimens (120–124). In a phase 3 multicentre, non-inferiority randomised trial of 849 patients, Bisschops et al. assessed efficacy of 2 day Moviprep versus 1 or 2 day Plenvu regimens in people aged 18-85 in a screening/surveillance/diagnostic colonoscopy setting. Bowel cleansing efficacy was significantly higher with 1 and 2 day Plenvu (6.6 and 6.7) compared with 2 day Moviprep (6.3, p=0.006 and p<0.001). In our study we also showed an enhanced BBPS with 1 and 2 day Plenvu versus Moviprep.

High quality right colon cleansing is particularly important to detect flat or subtle proximal lesions such as sessile serrated polyps (125). Bischopps et al. showed right colon BBPS scores were significantly higher with 1 and 2 day Plenvu versus 2 day Moviprep (2.2 and 2.2 versus 2.0; p=0.013 and p<0.001). We also found a significant improvement in right colon BBPS scores with 1 and 2 day Plenvu (2.6 and 2.5 respectively) when compared with Moviprep (2.3; p=0.01 and 0.01 respectively) and Senna & Citramag (2.3; p=0.007 and 0.009 respectively).

The first reported phase 4 multicentre randomised study of Plenvu in an Asian population (South Korea) assessed cleansing in 346 patients with either 2 day Plenvu or 2L PEG and also showed 2 day Plenvu was non-inferior, had improved high quality bowel cleansing, particularly in the right colon compared with 2L PEG (124).

In terms of polyp detection, Bisschops et al. showed the ADR and PDR in both right and overall colon was non-inferior in both 1 and 2 day Plenvu groups. In the right colon PDR group, Plenvu 2 day was superior compared with 2L PEG (23.3% vs. 16.2%; p=0.024). Hong et al. also showed improved PDR for Plenvu versus 2L PEG but there was no difference in ADR. In our study we found no significant difference in PPC, PDR, ADR and SP6 between the groups.

We also assessed fluid volumes and in pairwise comparisons found no difference in volume suctioned or introduced during colonoscopy except a higher volume suctioned with 1 day Plenvu compared with 2 day Moviprep (600mL versus 550mL, p 0.01).

The patient survey showed no difference between the regimens in the proportion of patients who completed the bowel preparation. However, a significantly higher proportion of patients reporting their bowel preparation was 'pleasant to taste' with Senna & Citramag (76%) compared with Moviprep (60%), 2 day Plenvu (51%) and 1 day Plenvu (42%). Plenvu is already available in 2 flavours (mango [dose1] and tropical punch [dose 2]) but alternative flavours may improve patient experience, although the underlying "salty" taste of all PEG-based preparations remains an issue for many patients.

Regarding safety and tolerability, Bisschops et al. showed this was comparable for 1L versus 2L PEG groups. However, both Bisschops and Hong show overall significantly higher treatment-related adverse events with Plenvu 1 day compared with 2L PEG but these were generally mild and rarely required intervention. We found, across all regimens evaluated, patients experienced side effects (such as nausea/vomiting, abdominal cramps, dizziness, and anal soreness) in 29-48% of cases. There was a borderline significant increase in side effects with 1 day Plenvu versus 2 day Moviprep (48% versus 29%, p=0.03) with no other significant difference in pairwise comparisons.

Concerns about the safety of hyper-osmotic low-volume bowel preparations with a risk of hypernatraemia and dehydration have been reported emphasizing the importance of ensuring an appropriate volume of clear fluid is taken in addition to the active ingredient (126). We did not assess changes in electrolyte balance in this service evaluation but there were no instances of severe clinical dehydration or detected cardiac arrhythmia. The patient experience survey showed the majority of patients taking Plenvu consumed >1L of clear fluid to avoid dehydration risk.

### 2.4.3 Strengths and limitations

In this study we assessed real-life experience of bowel preparation regimens, using a validated bowel cleansing score, within a bowel cancer screening setting. Apart from an earlier more limited evaluation in our unit, CLEANSE is the first substantial study to evaluate Senna & Citramag against 1 and 2 day Plenvu (121). We also provide further data on the use of Plenvu 1 day which has had limited previous evaluation.

As a non-randomised study, there is a risk of subjective allocation of bowel preparation regimens. Moviprep was given preferentially to patients with significant cardiac, liver or renal disease. Previous studies have shown an association with comorbidities such as diabetes, stroke and dementia as a risk factor for poor bowel preparation as well as polypharmacy (127–129). The Plenvu 1 day group had a lower number of patients compared with the other groups as only afternoon and evening appointments were eligible for this regimen.

### 2.4.4 Further work

Further studies are required to evaluate the economic impact of using Plenvu versus other regimens.

### 2.4.5 Conclusion

In this service evaluation, there was a significantly improved BBPS score for both one day and two day, low volume Plenvu regimens compared with Senna & Citramag and Moviprep. Plenvu may offer both enhanced cleansing and improved efficiency, particularly when administered as a same day preparation for afternoon and evening appointments by significantly reducing patient preparation time. However, the one day

Plenvu regimen was associated with more minor side effects and the taste was not rated as highly as Senna & Citramag.

# Chapter 3 Insertion technique 1: National survey of water-assisted colonoscopy practice

## 3.1 Background and Aims

### 3.1.1 Background

#### a What is water-assisted colonoscopy?

During colonoscope insertion a means of opening the collapsed bowel wall to reveal the lumen and mucosal appearance is required. Colonoscopy insertion technique has evolved over time. Originally, air insufflation was used during colonoscopy. In 1953, carbon dioxide ($CO_2$) was proposed as an alternative and it is now widely accepted to be superior to air due to reduced bloating and pain (87,88). In 1984, water was suggested as an adjunct to gas insufflation and found to be helpful in severe diverticular disease (89). Since then, the water-foot pump has become widely available in endoscopy suites making water-assisted colonoscopy easier to implement.

#### b Rationale for water use during colonoscopy

The problem with air insufflation is that it distends and elongates the colon making the insertion more lengthy. It also sharpens colon angulations which promotes loop formation. This results in more uncomfortable procedures with a greater sedation requirement. Water infusion helps avoid overdistension and allows the sigmoid to straighten thereby reducing the risk of loop formation. In theory, this results in a better tolerated procedure with a lower sedation requirement.

Studies show water-assisted colonoscopy may offer more efficient colonoscope insertion with lower pain scores and higher adenoma and polyp detection rates (90). However, procedure time may be increased. Water may also be used therapeutically for underwater endoscopic mucosal resection (EMR).

#### c Types of water-assisted colonoscopy

Water-assisted colonoscopy insertion techniques vary with some techniques involving exclusive water use on insertion and others permitting use of gas alongside water. Two water-assisted colonoscopy techniques have emerged and were defined in a recent Delphi review (130) (see Table 8):

- *Water immersion colonoscopy*

'Water is infused to facilitate scope progression and caecal intubation; gas insufflation (room air or $CO_2$) may be used as needed during insertion; most of the infused water is aspirated during withdrawal.'

- *Water-exchange colonoscopy*

'A standardized insertion technique in which infused water is removed mainly during insertion to allow progression in clear water, without any gas insufflation and removing all residual gas pockets trying to achieve the best possible degree of colon cleanliness.'

Table 8 Summary of standard water-assisted colonoscopy techniques

| | Water immersion | Water-exchange |
|---|---|---|
| **Insertion** | Water facilitates insertion.<br>Gas may be used. | Water infused and exchanged to allow progression in clear water.<br>Gas pockets removed.<br>No gas insufflation. |
| **Withdrawal** | Gas used on withdrawal.<br>Most infused water suctioned on withdrawal. | Gas used on withdrawal. |

### d Knowledge gap

Despite several studies being published advocating the use of water-assisted colonoscopy, it is unclear how widely this technique is used, how practice varies, and the level of endoscopist training.

## 3.1.2 Aims

1. Assess current water-assisted colonoscopy practice in the UK

2. Determine the degree of training and confidence in use of water-assisted colonoscopy

# 3.2 Methods

## 3.2.1 Study design

An online survey with a series of questions (multiple choice and free text) about water-assisted colonoscopy was prepared (see questionnaire in 16.2.5). The survey was approved by the British Society of Gastroenterology (BSG) Endoscopy Section who circulated this via email to section members in October and November 2021.

## 3.2.2 Outcomes

a **Colonoscopy experience**

- Procedures performed
- Setting

b **Water-assisted colonoscopy experience**

- Distention technique – rectum to splenic flexure
- Distention technique – splenic flexure to caecum
- Frequency of water-assisted colonoscopy use
- Formal training
- Type of water used
- Carbon dioxide unit usage
- Perceived impact on procedure (insertion time, patient comfort, mucosal visualisation)
- Issues using water-assisted colonoscopy (free text response)

## 3.3 Results

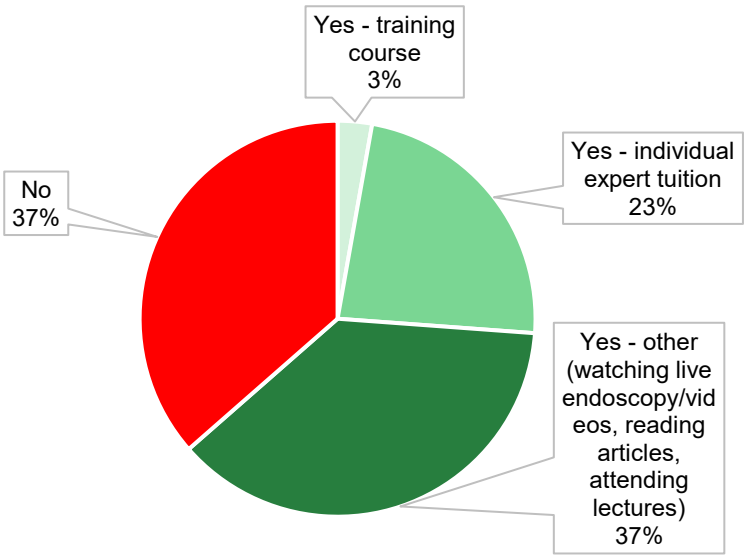
### 3.3.1 Overview

There were a total of 107 responses. The vast majority (78.5%) were experienced endoscopists (>1000 colonoscopies) and colonoscopies were performed in district general hospital (50.5%), teaching/specialist hospital setting (47.7%) or other settings (1.8%).

The majority of endoscopists (57%, 61/107) use water to assist colonoscope insertion for most colonoscopies and 31.8% (34/107) use water occasionally. Only 11.2% (12/107) rarely or never use water.

In terms of training, 63.6% (68/107) had participated in formal training. Of these, only 4.4% (3/68) had attended a course, 36.8% (25/68) had individual tuition and 58.8% (40/68) had another form of training (see Figure 17).

Figure 17 'Have you had formal training in water-assisted colonoscopy?'




Sterile water is used by 80.6% (83/103) with the remainder using tap water.

From rectum to splenic flexure (see Figure 18), 72.9% (78/107) use water (with or without $CO_2$) with 48.6% (52/107) using this in combination with $CO_2$ and 24.3% (26/107) exclusively using water.

From splenic flexure to caecum (see Figure 19), most people use $CO_2$ only (57.0%, 61/107), followed by a combination of $CO_2$ and water (36.4%, 39/107) with the remainder using alternative techniques (6.5%, 7/107).

Figure 18 Distention technique used for colonoscope insertion from rectum to splenic flexure

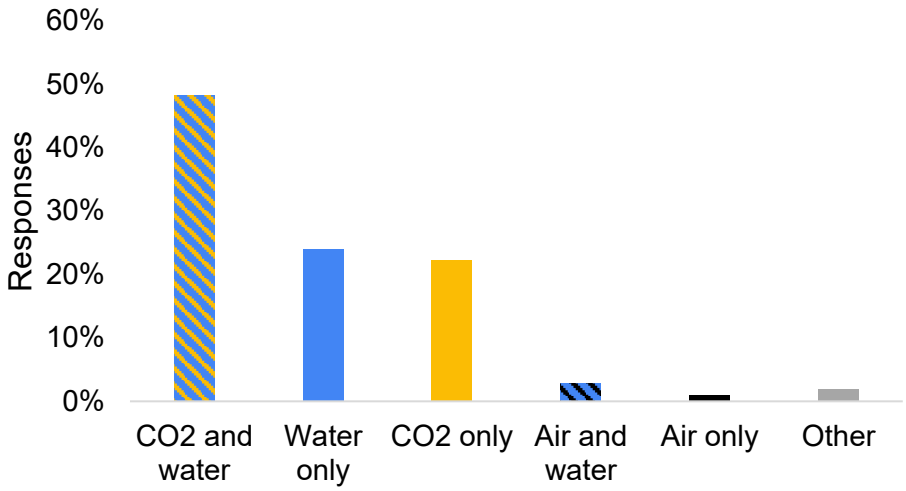
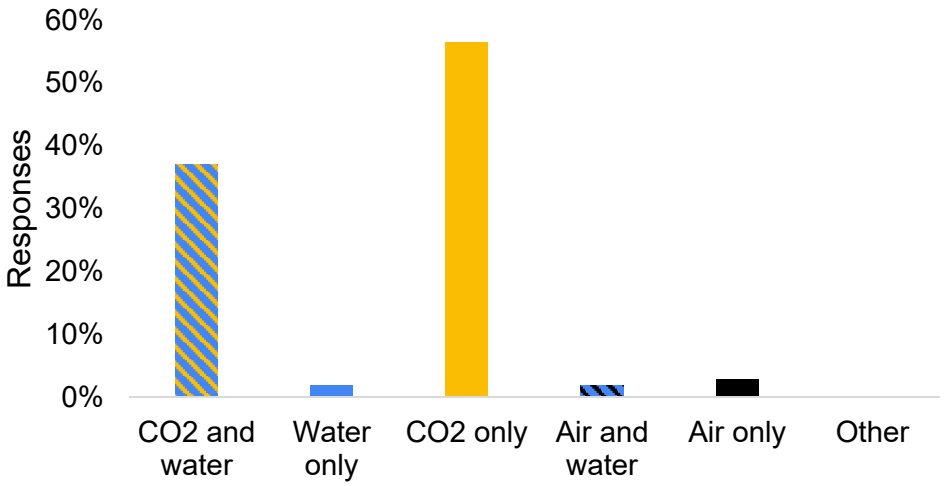
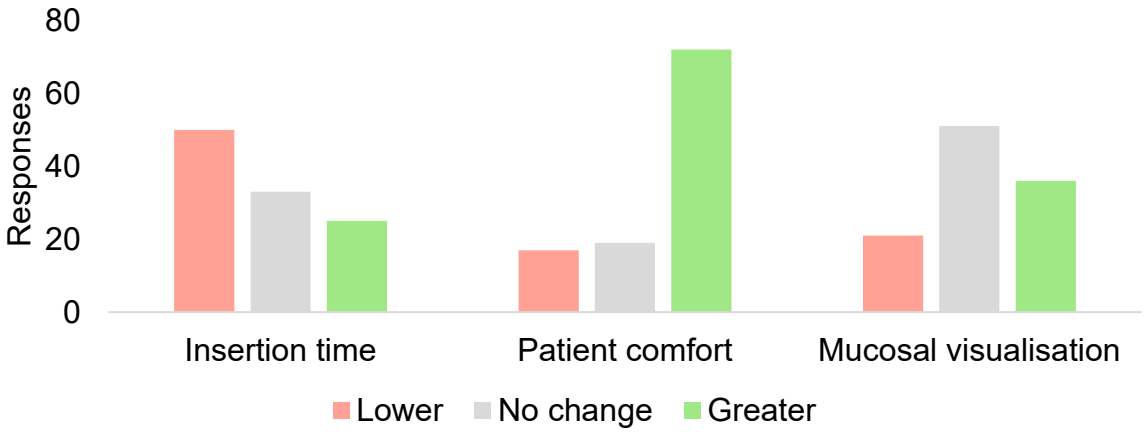



Figure 19 Distention technique used for colonoscope insertion from splenic flexure to caecum



Some 66.4% (71/107) reported greater patient comfort with water-assisted colonoscopy and 46.7% (50/107) reported a reduced insertion time (see Figure 20). 33.6% (36/107) felt there was greater mucosal visualisation with water-assisted colonoscopy.

Figure 20 Perceived impact of water-assisted colonoscopy on the procedure




Most people (69.2%, 74/107) reported experiencing issues when using water to assist colonoscope insertion including poor bowel preparation, left colon mucus and an increased withdrawal time.

# 3.4 Discussion

## 3.4.1 Key findings

a Water is used widely in clinical practice to assist colonoscope insertion.

b Most people use water and $CO_2$ to reach splenic flexure and then $CO_2$ only to reach caecum.

c There is a perceived improvement in patient comfort and reduction in insertion time with water-assisted colonoscopy.

d There are some limitations of using water-assisted colonoscopy (eg. poor bowel preparation).

### 3.4.2 Comparison with previous studies

Although several studies have compared different colonoscopy insertion techniques, there do not appear to be any publications detailing current water-assisted colonoscopy practice amongst endoscopists.

Previous studies evaluating national colonoscopy practice did not explore insertion technique (49,112). This may reflect the fact that these studies pre-dated the widespread availability of the water foot pump to the extent that water-assisted colonoscopy was not a widely practiced technique.

### 3.4.3 Strengths and limitations

Despite the national reach of this survey, there were far fewer respondents than expected even with a second survey request and reminder emails being sent. There is also a risk of selection bias as we sought the views of a group of BSG Endoscopy Section members who are experienced endoscopists. As this was a UK based survey we cannot draw conclusions on international water-assisted colonoscopy practice.

### 3.4.4 Further work

A survey evaluating water-assisted colonoscopy experience in trainees and more inexperienced endoscopists would help better understand practice in these groups. In addition, a survey conducted at international level would allow a better appreciation of variation in water-assisted colonoscopy practice globally.

The findings suggest most endoscopists use a water immersion technique to splenic flexure (both water and $CO_2$) and then use predominately $CO_2$ from splenic flexure to caecum. This 'hybrid' technique (modified water immersion) requires evaluation against the water-exchange technique and we have undertaken this in the WAVE study (see Chapter 4).

### 3.4.5 Conclusion

In this UK survey, the majority of respondents were found to use water-assisted colonoscopy, either exclusively or in combination with $CO_2$, from rectum to splenic flexure. Then from splenic flexure to caecum, $CO_2$ alone is widely used. This modified water immersion 'hybrid' technique will be explored further in the WAVE study (Chapter 4). More than a third of respondents had not had formal training. There is a perceived improvement in patient comfort with water-assisted colonoscopy. However, limitations of water use may include poor bowel preparation, left colon mucus occurrence and an increase in withdrawal time.

# Chapter 4 Insertion technique 2: Water-exchange versus modified water immersion colonoscopy (WAVE)

## 4.1 Background and Aims

### 4.1.1 Background

#### a Colonoscope insertion

A fundamental aspect of high quality colonoscopy is ensuring a comfortable and timely insertion to the caecal pole. This requires luminal distension to allow accurate colonoscope tip steering. Room air was traditionally used to insufflate the colon as it is cheap and readily available. However, it is associated with patient discomfort during and after the procedure. This led to the introduction of $CO_2$ as an alternative as it is more rapidly absorbed and excreted in the lungs. $CO_2$ has proven to be much better than room air as it reduces post procedure distension and therefore improves patient comfort. Furthermore, it also has the advantage that is does not support combustion thereby reducing the risk of explosion during diathermy use as a result of retained colonic gases (hydrogen and methane) (87,88,131,132).

In 1984, water use during colonoscopy was first suggested to help facilitate scope insertion in areas of severe diverticulosis (89). Since then, the water-driven foot pump has become widely available and water-assisted colonoscopy is frequently used during routine colonoscopy.

Theoretically, water avoids bowel distention caused by gas and also minimises loop formation as it helps weigh and straighten particularly the sigmoid colon (133,134). This helps improve procedure tolerance and reduces the need for sedation. In contrast, gas insufflation (air or $CO_2$) causes overdistention resulting in colon elongation, which sharpens angulations at the flexures and which may promote loop formation. However,

$CO_2$ allows more rapid bowel distension than water and can provide clearer forward views for accurate steering, particularly when preparation is suboptimal.

### b Current practice

In the literature, two water-assisted colonoscopy techniques have emerged which were recently described in a Delphi consensus: water-exchange and water immersion (see Table 9) (135). In water-exchange, water is infused and removed predominately during insertion to 'allow progression in clear water' with any gas pockets suctioned and no gas insufflation allowed during insertion. In water immersion, water is used to 'facilitate scope progression and caecal intubation' with gas insufflation allowed during insertion and infused water aspirated mainly during withdrawal. Previous studies have suggested water-exchange is superior to water immersion in terms of procedure pain and completion rates for unsedated colonoscopy (136–138).

In a national survey of water-assisted colonoscopy practice we found 95% of BSG Endoscopy Section members have used water to facilitate colonoscope insertion with the majority (56%) using it frequently (see Chapter 3). Water-assisted colonoscopy was perceived to provide greater patient comfort, reduced insertion time and improved mucosal visualisation. However, we found most respondents appear to use a hybrid technique with a combination of water and $CO_2$. In this modified water immersion technique, water is used predominately from rectum to splenic flexure and $CO_2$ is used predominately from splenic flexure to caecum.

Table 9 Summary of water-assisted colonoscopy techniques

| | Water-Exchange | Water Immersion | Hybrid |
|---|---|---|---|
| **Insertion** | Water infused and exchanged to allow progression in clear water.<br><br>Gas pockets removed.<br><br>No gas insufflation. | Water facilitates insertion.<br><br>Gas may be used. | Water facilitates insertion to splenic flexure (gas may be used).<br><br>$CO_2$ facilitates insertion from splenic flexure to caecum (water may be used). |
| **Withdrawal** | Gas used on withdrawal. | Gas used on withdrawal.<br><br>Most infused water suctioned on withdrawal. | Gas used on withdrawal. |

There is some evidence that water-exchange is superior to water immersion in terms of bowel cleansing, patient discomfort and polyp detection although inferior in terms of procedure times and amount of water used (135,139) . However, there is only limited evidence that water techniques are superior to $CO_2$ and no direct comparisons of water-exchange to the commonly used hybrid technique (140–142).

### 4.1.2 Aims

1. Evaluate performance of a 'hybrid' technique (predominately water from rectum to splenic flexure and predominately $CO_2$ from splenic flexure to caecum) versus a water-exchange technique (water alone used for insertion with $CO_2$ switched off until caecal intubation)
2. Assess efficiency of 'hybrid' and water-exchange colonoscopy techniques in terms of insertion time, overall procedure time, patient comfort and polyp detection.

## 4.2 Methods

### 4.2.1 Study design

This prospective randomised controlled trial ran over the period Mar 2021 to Jun 2022 with four endoscopists (2 nurse endoscopists, 1 endoscopy fellow and 1 consultant), all with experience of 1000-5000 colonoscopies, performing colonoscopy at London North West University Healthcare NHS Trust. In the parallel study design, participants were randomised to either hybrid or water-exchange colonoscopy with a 1:1 allocation ratio. Standard 2-day split dose bowel preparation regimens were used (Moviprep, Senna and Citramag, or Plenvu).

Inclusion criteria were patients aged 18 years or above attending for symptomatic colonoscopy who had capacity to consent. Exclusion criteria were patients with a history of bowel surgery, those who were pregnant, and unable to consent.

Prior to the study, all endoscopists undertook a study induction training session covering the two techniques. Newly enrolled endoscopists were overseen by the study research nurse who ensured endoscopists complied with the requirements of each arm.

In the hybrid arm, water was predominately used on insertion to the splenic flexure (with $CO_2$ use allowed if required) and $CO_2$ was predominately used from splenic flexure to caecum (with water use allowed if required). In the water-exchange arm, $CO_2$ insufflation was only allowed when rectal retroflexion was performed at the start of the procedure, after which the $CO_2$ insufflator was switched off and all gas suctioned prior to insertion to the caecum using the previously described standardised technique (8).

Olympus high definition 290 series paediatric instruments were used for the majority procedures (Table 10) with Olympus adult 290 series colonoscopes used at the discretion of the endoscopist. Antispasmodics and caps/cuffs were used at the discretion of the endoscopist.

In all procedures electromagnetic scope imaging (ScopeGuide, Olympus) was used to assess the scope shaft configuration and tip location. When a loop formed, as visualised by a loop visual aid checklist, it was recorded by a research nurse in real time (see 16.2.2). The study protocol was approved by the local review board (1/7/20; 20/LO/0258) and was reported according to CONSORT guidelines. The study was registered with ClinicalTrials.gov (NCT04710706).

### 4.2.2 Outcomes

The primary outcome measure was total procedure time with secondary outcomes of time to caecal intubation, caecal intubation rate, polyp detection (polyp detection rate [PDR], adenoma detection rate [ADR], serrated polyp detection rate [SDR], significant polyp detection rate [SPDR] and significant polyps per 6 minute withdrawal [SP6] (46)), loop formation, number of ancillary procedures (patient repositions and abdominal pressure episodes), sedation use and patient discomfort scores. There were no changes to trial outcomes after the trial commenced. The trial was stopped after the recruitment target had been achieved.

The $CO_2$ volume insufflated was recorded in a sub-group of patients using a $CO_2$ flow meter. In these cases, the standard air button on the colonoscope was replaced with a

$CO_2$ button (a sealed button with a valve that only allows gas flow when pressed unlike the air button where gas can vent/escape even when the button is not pressed). $CO_2$ volume was recorded during colonoscope insertion and withdrawal in both study arms.

### 4.2.3 Patient evaluation

Patients were invited to complete a questionnaire about their colonoscopy experience after they had fully recovered which used a visual analogue score to assess pain (score 0-10) and a Likert scale to assess procedure satisfaction (see 16.2.3). Patients were also asked if they would be happy to have the procedure performed in the same way the next time and if their procedure was different to their last experience if they had already had a colonoscopy.

### 4.2.4 Randomisation

Patients were block randomised with each list considered a block. The blocks were of size 4 or 6, depending on the size of the list. A computer-generated randomisation list was produced by the study statistician to either hybrid or water-exchange in a 1:1 ratio. Patients were enrolled by a dedicated research nurse who assigned participants to interventions based on the randomisation list which was not accessible to endoscopists. The randomisation sequence was therefore not known to endoscopists until the intervention had been assigned. There was single-blinding of participants only.

### 4.2.5 Statistical analysis

This study was powered to detect a 4 minute difference in total procedure time as this was considered a clinically significant difference. The assumed standard deviation was 10.6 based on the average standard deviation for the two study arms in a previous study (143). With a 5% significance level and a power of 80%, 112 patients in each group, 224 patients in total, were required.

Baseline characteristics of the groups were analysed descriptively. All study outcomes were compared between groups. Categorical outcomes were summarised by the number and percentage in each category, and compared between groups using the Chi-square test. Continuous variables were all found to have skewed distributions. As a result, they were summarised by the median and inter-quartile range, and were

compared between groups using the Mann-Whitney test. This test was also used to compare ordinal outcomes between groups. Corresponding confidence intervals for the group differences are also presented, along with p-values indicating the significance of the group differences.

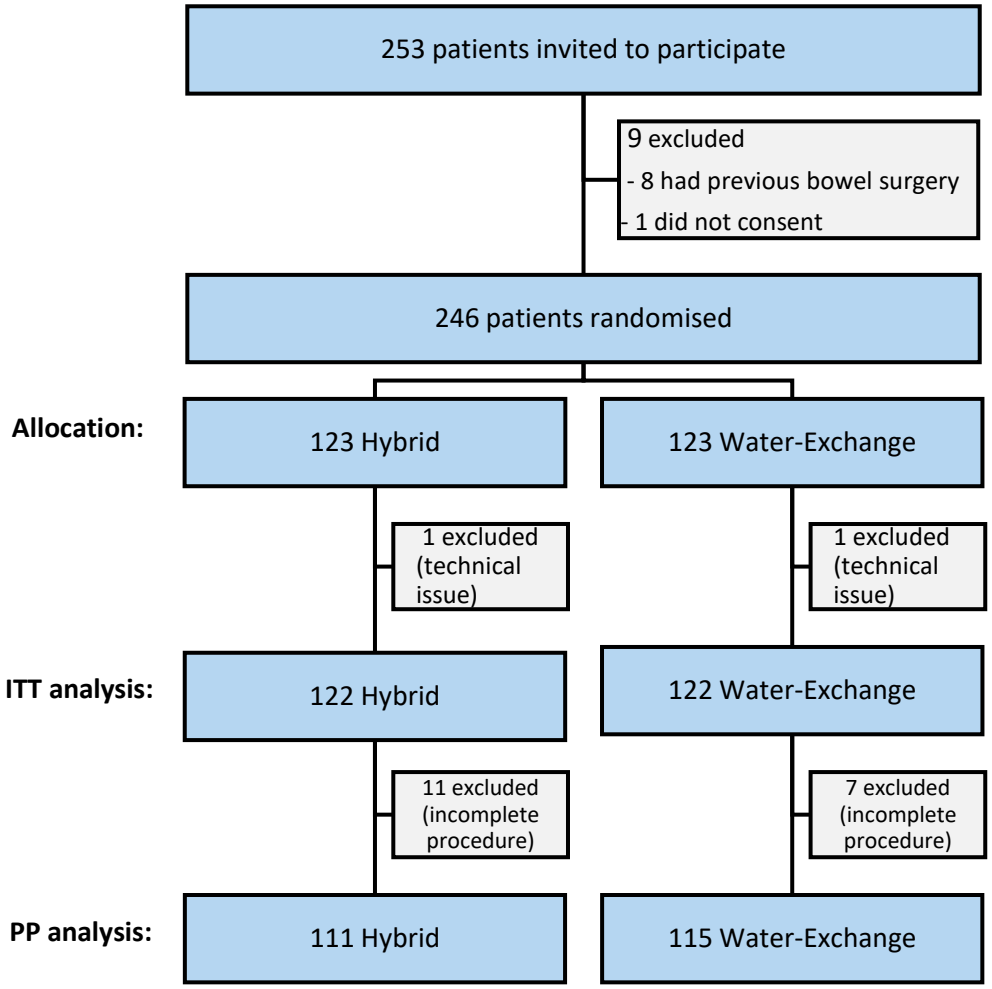
Two sets of efficacy outcomes were performed. The first set of analyses used the Intention To Treat (ITT) dataset, and then a further set of analyses was performed using the Per Protocol (PP) dataset which excluded any cases where the procedure was incomplete.

# 4.3 Results

## 4.3.1 Overview

253 patients were invited of which 9 were excluded (8 had previous bowel surgery and 1 patient did not consent). 246 patients were therefore randomised with 123 cases allocated in each arm (hybrid and water-exchange). For the primary analysis (ITT), 2 cases with technical issues were excluded (1 case in each arm where an issue with $CO_2$ insufflation resulted in air being used for part of the procedure), leaving 122 cases in each arm; see Figure 1. In the secondary analysis (PP), a further 18 cases were excluded as they were incomplete (11 in the hybrid arm [7 with poor preparation and 4 due to poor tolerance] and 7 in the water-exchange arm [4 with poor preparation and 3 due to poor tolerance]), leaving 226 patients with 111 hybrid cases and 115 water-exchange cases. There were no adverse or unintended effects in the groups.

Figure 21 Study overview




## 4.3.2 Baseline characteristics

Baseline participant and procedure characteristics were similar in the two groups with both groups well matched for sex, age, scope, Endocuff and Buscopan use (see Table 10). Bowel preparation regimens were distributed evenly between the groups. Rectal retroflexion practice was evenly distributed between the groups and was performed at the procedure start in 81% of cases, at procedure end in 14% of cases and not performed in 5% of cases.

Table 10 Baseline participant and procedure characteristics (ITT analysis)

| | Hybrid | Water-Exchange | Total |
|---|---|---|---|
| Total participants | 122 | 122 | 244 |
| Sex | | | |
| Male | 57 (47%) | 58 (48%) | 115 (47%) |
| Female | 65 (53%) | 64 (52%) | 129 (53%) |
| Age | 56.4 ± 15.4 | 54.4 ± 15.9 | 55.4 ± 15.6 |
| Scope used | | | |
| PCF 290 | 112 (92%) | 114 (93%) | 226 (93%) |
| Adult 290 | 10 (8%) | 8 (7%) | 18 (7%) |
| Endocuff used | | | |
| Yes | 15 (12%) | 18 (15%) | 33 (14%) |
| No | 107 (88%) | 104 (85%) | 211 (86%) |
| Buscopan (mg) | 10 [0, 10] | 10 [0, 20] | 10 [0, 15] |
| Yes | 83 (68%) | 81 (66%) | 164 (67%) |
| No | 39 (32%) | 41 (34%) | 80 (33%) |

Summary statistics are: mean ± standard deviation or number (percentage)

## 4.3.3 Clinical outcomes

### a Procedure time

Procedure times were evaluated in the PP analysis, as this included all completed procedures and therefore had full timing datasets (see section 16.2.1). This showed a statistically significant increase in insertion time (intubation to ileocaecal [ICV] reached), caecum time (ICV reached to ICV left) and total time (intubation to extubation) in the water-exchange group compared with hybrid group (see Table 11 and section 16.2.1). Median increase in total procedure time was 4 minutes in the water-exchange group. There was no significant difference in withdrawal times between the groups.

Table 11 Procedure times (PP analysis)

| Outcome | Hybrid | | Water-Exchange | | Difference* (95% CI) | P-value |
|---|---|---|---|---|---|---|
| | n | Summary | n | Summary | | |
| **Procedure times (minutes)** | | | | | | |
| Total time | 111 | 25 [21, 35] | 115 | 29 [23, 38] | 4 (1, 6) | **0.009** |
| *Insertion time* | 111 | 9 [7, 14] | 115 | 13 [9, 18] | 3 (2, 5) | **<0.001** |
| *Caecum time* | 111 | 3 [2, 5] | 115 | 4 [2, 5] | 1 (0, 1) | **0.04** |
| *Withdrawal time* | 111 | 11 [8, 16] | 115 | 11 [7, 16] | -1 (-2, 1) | 0.33 |

All other outcomes in the PP analysis were similar to those observed in the ITT analysis with the same outcomes showing statistical significance and all at a similar level. The outcomes reported below are from the ITT analysis (see Table 12)

### b Insertion technique

Total fluid volume infused was significantly higher in the water-exchange group compared with the hybrid group (780mL versus 500mL, $p<0.001$) and total fluid volume suctioned was also higher in the water-exchange group (780mL versus 500mL, $p<0.001$). Most fluid infusion and suction occurred during colonoscope insertion with significantly higher volumes in the water-exchange group compared with hybrid group. During colonoscope withdrawal, there was no difference in fluid volume infused or suctioned between the groups.

$CO_2$ gas insufflation use, recorded in a sub-group of cases, was significantly higher during insertion in the hybrid group versus water-exchange group (15,268 $cm^3$ versus 3,570 $cm^3$, $p=0.001$). However, there was no difference in the withdrawal $CO_2$ gas insufflation volume and the total $CO_2$ gas insufflation volume (insertion and withdrawal combined).

A change in technique from water-exchange to hybrid was required in 16% of cases and occurred most frequently due to failure to advance or impaired visualisation secondary to inadequate bowel preparation. Bowel preparation regimens were distributed evenly between the groups.

### c Ancillary procedures and loop formation

Patient reposition episodes occurred more frequently in the water-exchange group versus hybrid group (6 versus 5, $p=0.001$). There was no difference in the number of abdominal pressure episodes between the groups.

The total number of loops formed did not significantly differ between the groups. However, reverse alpha loops occurred more frequently in the hybrid group compared with water-exchange group (8 versus 1, $p=0.02$)

## d Other outcomes

Sedation use, caecal intubation rate and overall BBPS score did not differ significantly between the groups. The left colon BBPS score was significantly higher in the water-exchange group compared with hybrid (3 versus 2, p=0.04) with no significant difference in right and transverse colon scores.

Table 12 Procedural outcomes (ITT analysis)

| Outcome | Hybrid | | Water-Exchange | | Difference* (95% CI) | P-value |
|---|---|---|---|---|---|---|
| | n | Summary | n | Summary | | |
| **Sedation** | | | | | | |
| Midazolam (mg) | 122 | 1 [0, 2] | 122 | 1.5 [0, 2] | 0 (0, 0) | 0.85 |
| Fentanyl (mg) | 122 | 50 [0, 50] | 122 | 50 [0, 50] | 0 (0, 0) | 0.25 |
| Entonox used | 122 | 43 (35%) | 122 | 38 (31%) | -4% (-16%, 8%) | 0.50 |
| | | | | | | |
| **Fluid volumes (mL)** | | | | | | |
| Infused fluid | | | | | | |
| Total | 115 | 500 [270, 750] | 118 | 780 [550, 1070] | 270 (180, 360) | **<0.001** |
| *Insertion* | 118 | 300 [150, 500] | 120 | 538 [400, 925] | 250 (180, 320) | **<0.001** |
| *Withdrawal* | 115 | 150 [100, 250] | 118 | 125 [100, 300] | 0 (-50, 20) | 0.63 |
| Suctioned fluid | | | | | | |
| Total | 122 | 500 [350, 800] | 122 | 780 [550, 1100] | 250 (150, 350) | **<0.001** |
| *Insertion* | 118 | 300 [200, 400] | 118 | 500 [300, 700] | 200 (100, 300) | **<0.001** |
| *Withdrawal* | 118 | 200 [150, 350] | 118 | 300 [150, 400] | 50 (0, 100) | 0.06 |
| | | | | | | |
| **$CO_2$ insufflation ($cm^3$)** | | | | | | |
| Total | 44 | 32494 [12511, 56157] | 45 | 24087 [8530, 42028] | -8303 (-20277, 1634) | 0.12 |
| *Insertion* | 40 | 15268 [8860, 30590] | 40 | 3570 [2354, 18597] | -8082 (-13396, -3398) | **0.001** |
| *Withdrawal* | 41 | 15954 [6100, 24808] | 41 | 12576 [7123, 26938] | -503 (-6777, 5860) | 0.86 |
| | | | | | | |
| **Patient manoeuvres** | | | | | | |
| Repositions – Total | 122 | 5 [4, 6] | 122 | 5.5 [4, 7] | 1 (0, 1) | **0.003** |
| Repositions – Insertion | 118 | 2 [1, 3] | 119 | 3 [1, 4] | 1 (0, 1) | **0.004** |
| Repositions – Withdrawal | 118 | 3 [2, 4] | 118 | 3 [2, 4] | 0 (0, 1) | 0.22 |

| | | | | | | |
|---|---|---|---|---|---|---|
| Abdominal pressure episodes | 118 | 0 [0, 0] | 118 | 0 [0, 1] | 0 (0, 0) | 0.08 |
| | | | | | | |
| **Loops** | | | | | | |
| Total number | 122 | 0 [0, 1] | 122 | 0 [0, 1] | 0 (0, 0) | 0.80 |
| Sigmoid alpha loop | 122 | 12 (10%) | 122 | 18 (15%) | 5% (-3%, 13%) | 0.24 |
| Sigmoid n loop | 122 | 14 (11%) | 122 | 14 (11%) | 0% (-8%, 8%) | 1.00 |
| Reverse alpha loop | 122 | 8 (7%) | 122 | 1 (1%) | -6% (-10%, -1%) | **0.02** |
| Splenic flexure loop | 122 | 5 (4%) | 122 | 6 (5%) | 1% (-4%, 6%) | 0.76 |
| Transverse loop | 122 | 7 (6%) | 122 | 8 (7%) | 1% (-5%, 7%) | 0.79 |
| Transverse gamma loop | 122 | 2 (2%) | 122 | 3 (2%) | 1% (-3%, 4%) | 0.65 |
| Other loop | 122 | 0 (0%) | 122 | 1 (1%) | 1% (-1%, 2%) | 0.32 |
| | | | | | | |
| **BBPS score** | | | | | | |
| Right | 115 | 2 [2, 3] | 116 | 2 [2, 3] | 0 (0, 0) | 0.08 |
| Transverse | 116 | 2 [2, 3] | 116 | 3 [2, 3] | 0 (0, 0) | 0.14 |
| Left | 117 | 2 [2, 3] | 117 | 3 [2, 3] | 0 (0, 0) | **0.04** |
| Total | 122 | 6 [5, 9] | 122 | 7.5 [6, 9] | 0 (0, 1) | 0.07 |
| | | | | | | |
| **Caecal intubation rate** | 122 | 112 (92%) | 122 | 116 (95%) | 3% (-3%, 9%) | 0.30 |
| | | | | | | |
| **Polyp detection** | | | | | | |
| PDR | 122 | 62 (51%) | 122 | 65 (53%) | 2% (-10%, 15%) | 0.70 |
| ADR | 122 | 48 (39%) | 122 | 40 (33%) | -7% (-19%, 5%) | 0.29 |
| SDR | 122 | 21 (17%) | 122 | 27 (22%) | 5% (-5%, 15%) | 0.33 |
| SPDR | 122 | 54 (44%) | 122 | 57 (47%) | 2% (-10%, 15%) | 0.70 |
| SP6 | 111 | 0.0 [0.0, 0.8] | 115 | 0.0 [0.0, 0.8] | 0 (0, 0) | 0.92 |
| | | | | | | |
| **Change in technique** | | | | | | |
| Patients with technique change | 122 | 0 (0%) | 122 | 20 (16%) | 16% (10%, 23%) | **<0.001** |
| Fixed sigmoid | | 0 | | 1 | | |
| Looping | | 0 | | 9 | | |
| Poor preparation | | 0 | | 7 | | |
| Stuck at hepatic flexure | | 0 | | 2 | | |
| Polypectomy | | 0 | | 1 | | |

Summary statistics are median [inter-quartile range] or number (percentage)
*differences between groups reported as outcome for water-exchange cases minus outcome for hybrid cases. Either median difference or percentage difference reported

e Patient evaluation

There was no significant difference in reported pain score or patient satisfaction between the groups (see Table 13). There was also no difference in the proportion of patients who would be happy to have the procedure performed again in the same way and in the proportion of patients who noticed a difference in their procedure compared to their last colonoscopy.

Table 13 Patient evaluation (ITT analysis)

| Outcome | Hybrid | | Water-Exchange | | Difference* (95% CI) | P-value |
|---|---|---|---|---|---|---|
| | n | Summary | n | Summary | | |
| **Pain score+** | 118 | 2 [0, 3] | 117 | 2 [0, 3] | 0 (0, 0) | 0.58 |
| | | | | | | |
| **Satisfied with procedure** | 119 | | 117 | | - | 0.13 |
| Strongly agree | | 89 (75%) | | 76 (65%) | | |
| Agree | | 24 (20%) | | 36 (31%) | | |
| Neither agree or disagree | | 2 (2%) | | 3 (3%) | | |
| Disagree | | 1 (1%) | | 2 (2%) | | |
| Strongly disagree | | 3 (3%) | | 0 (0%) | | |
| | | | | | | |
| **Willingness to repeat procedure** | 119 | 109 (92%) | 116 | 111 (96%) | 4% (-2%, 10%) | 0.20 |
| | | | | | | |
| **Noticed difference compared with previous colonoscopy** | 87 | 40 (46%) | 90 | 30 (33%) | -13% (-27%, 2%) | 0.09 |

Summary statistics are median [inter-quartile range] or number (percentage)
+ visual analogue scale from 0 (no pain) to 10 (worst possible pain)
* differences between groups reported as outcome for water-exchange cases minus outcome for hybrid cases. Either median difference or percentage difference reported

# 4.4 Discussion

## 4.4.1 Key findings

a Water-exchange colonoscopy increases procedure time, required more patient repositions and had a significant failure rate (16% required a change in technique) compared with hybrid technique.

b Water-exchange technique provided better left colon cleansing and appears to reduce the formation of alpha loops.

c There was no difference in total BBPS score, total loop formation, sedation requirement, caecal intubation rate and polyp detection (PDR, ADR, SDR and SPDR).

This is the first randomised evaluation comparing water-exchange and hybrid techniques for colonoscope insertion. Water-exchange technique offers some advantage over hybrid technique in terms of colon cleansing and a possible reduction in alpha loop formation. However, water-exchange technique lengthened the procedure by 4 minutes, required more patient repositions and required a switch to hybrid technique in 16% of cases. For all other outcomes there was no significant difference between the groups. Hybrid technique therefore achieves similar outcomes to water-exchange in a shorter period of time and therefore appears to be a more efficient insertion technique.

## 4.4.2 Comparison with previous studies

### a Procedure time

Water-exchange increased total procedure time by 4 minutes compared with hybrid (29 mins versus 25 mins, p=0.006). This most likely reflects the increased time required to suction gas pockets and to clean water to facilitate passage through clear water. In a meta-analysis of 8371 subjects from 17 studies there was a 1.8 minute increase in mean total procedure time with water-exchange versus gas insertion (26.0 minutes versus 24.2 minutes) (144). In the consensus statements from the recently published Delphi review, most agreed with the statement 'water exchange colonoscopy increases total procedure time by a mean of 2 minutes compared with gas insufflation colonoscopy' (S5). When water-exchange is compared with water immersion, some studies have shown no difference in procedure time (136,145,146) whilst others have shown an increased procedure time with water-exchange (147).

### b Patient pain

A randomised evaluation of 576 patients compared pain scores in real-time and at discharge when using air insufflation, water immersion and water-exchange techniques (136). The real-time maximum insertion pain score and pain score at discharge was significantly lower in the water-exchange group versus water immersion (2.5 v 3.5, p=0.0006 and 1.3 v 1.8, p=0.022 respectively).

In a screening setting, Cadoni et al evaluated water-assisted colonoscopy in 1224 patients randomised to water-exchange, water immersion or air insufflation (146). This showed no difference in patient satisfaction and willingness to repeat the examination between the groups. In keeping with these findings, we found no difference in pain scores and willingness to repeat colonoscopy between the water-exchange and hybrid techniques.

### c Sedation and loop formation

There was no difference in sedation requirement and overall number of loops between the arms in our study. However, reverse alpha loops occurred less frequently in the water-exchange arm. These loops tend to occur due to variation in retroperitoneal fixation and in particular a persistent descending mesocolon. Reverse alpha loops may occur less frequently with water-exchange technique due to a reduction in the angulation caused by gas insufflation. Despite these atypical loops forming there was no adverse effect on patient comfort nor caecal intubation rate.

### d Adenoma detection

In a meta-analysis of 12 studies with 5660 patients, water-exchange has been shown to increase proximal adenoma detection rate and right adenoma detection rate compared with air/$CO_2$ insufflation (148). Water immersion did not show an improvement in proximal or right adenoma polyp detection.

In a screening setting, a double-blinded randomised trial showed water-exchange achieved a significantly higher ADR than air insufflation (49.3% vs.40.4%; p=0.03) which was not achieved with water immersion (146). In contrast with previous studies,

we found no difference in polyp detection (PDR, ADR, SDR and SPDR) between the water-exchange and hybrid groups.

e Service perspective

From a service perspective, there was an increase in procedure time and significantly higher volume of sterile water with water-exchange technique compared with hybrid technique. In addition, significantly lower volumes of sterile water were used with a hybrid technique. This may have significant cost and/or environmental implications, not specifically assessed in this study. We also assessed $CO_2$ insufflation volume which was found to be higher during hybrid insertion compared with water-exchange, but there was no significant difference in total $CO_2$ insufflation between the groups.

### 4.4.3 Strengths and limitations

This is the first randomised study evaluating a water-exchange technique versus a hybrid insertion technique. The latter technique appears to be used widely in practice which makes this study relevant and applicable to real life clinical practice. We also evaluated patient experience using both techniques. This is also, to our knowledge, the first study to measure $CO_2$ volume during water-assisted colonoscopy which may be an important parameter to consider in the context of green endoscopy.

As with other similar studies, we were unable to blind endoscopists to the insertion technique used so there is an inherent risk of observer bias. In the water-exchange arm of the study, we allowed endoscopists to use $CO_2$ only in the rectum for rectal retroflexion before turning the $CO_2$ insufflator off. This allowed those who perform early retroflexion, a practice that is becoming more widely used, to be performed with the caveat that endoscopists suctioned all gas at the rectosigmoid junction in water-exchange cases.

### 4.4.4 Further work

We would recommend future randomised studies evaluating water-assisted colonoscopy techniques include the widely used and clinically relevant hybrid technique against water immersion and water-exchange colonoscopy.

### 4.4.5 Conclusion

In this randomised evaluation, hybrid colonoscopy technique provided a faster procedure than water-exchange colonoscopy with no adverse effect on sedation requirement, caecal intubation rate and overall bowel cleansing. There was no significant difference in patient reported pain scores or satisfaction between the techniques. A hybrid technique may offer a more efficient insertion, maximising the advantages of both water and $CO_2$, and should be evaluated further in future water-assisted colonoscopy studies.

# Chapter 5 Polyp detection 1: Early evaluation of a real-time computer-aided polyp detection (CADe) system during colonoscopy

This chapter is based on a published abstract (149).

## 5.1 Background and Aims

### 5.1.1 Background

Polyp detection during colonoscopy is essential to reduce colorectal cancer associated morbidity and mortality. A number of interventions can be used to support polyp detection such as use of scope adjuncts (eg. Endocuff Vision) and use of position change. In recent years, computer-aided polyp detection (CADe) systems developed using artificial intelligence (AI) algorithms have emerged. These offer the potential for endoscopists to be provided real-time feedback during procedures. These systems have evolved over time but their effectiveness in real life clinical practice requires further evaluation.

### 5.1.2 Aims

1. To evaluate effectiveness of a CADe system during bowel cancer screening.
2. To assess clinician acceptability.

## 5.2 Methods

### 5.2.1 Study design

Prospective study running over 2 months involving all bowel cancer screening programme (BCSP) colonoscopists at the St Mark's Hospital screening unit. In the first month, standard colonoscopy without AI assistance was performed. In the second month, a CADe system (GI Genius, Medtronic Ltd) was used for all colonoscopies.

All patients meeting criteria for BCSP procedures (colonoscopy and Bowel Scope) were included. Gastroscopies and planned therapeutic procedures were excluded. GI Genius was switched on for the entire duration of the procedure (insertion and withdrawal).

A sub-group analysis was performed of all CADe-assisted polyp detections (lasting at least 1 second) to assess correlation with endoscopist interpretation. All participating endoscopists completed an evaluation form about their experience using CADe (see Section 16.2.1).

### 5.2.2 Outcomes

#### a Primary outcomes

Polyp detection rate (PDR)

Adenoma detection rate (ADR)

#### b Secondary outcomes

Analysis of all CADe-assisted polyp detections

Endoscopist acceptability

## 5.3 Results

### 5.3.1 Overview

There was no significant difference in PDR and ADR when using a CADe system in a high performing group of BCSP operators.

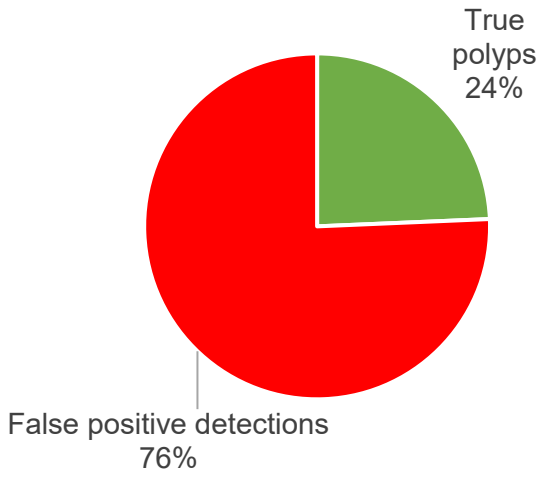
Table 1. The effect of a polyp detection system on PDR and ADR in BCSP Colonoscopy and Bowel Scope lists

| | BCSP Colonoscopy | | | BCSP Bowel Scope | | |
|---|---|---|---|---|---|---|
| | **Standard** | **CAD** | **P value** | **Standard** | **CAD** | **P value** |
| **Procedures** | 86 | 82 | | 565 | 408 | |
| **Polyps seen** | 208 | 202 | | 251 | 150 | |
| **PDR (%)** | 58.1 | 62.2 | 0.59 | 26.9 | 24.3 | 0.35 |
| **ADR (%)** | 46.5 | 48.8 | 0.77 | 12.6 | 9.8 | 0.18 |

### 5.3.2 Polyp detection

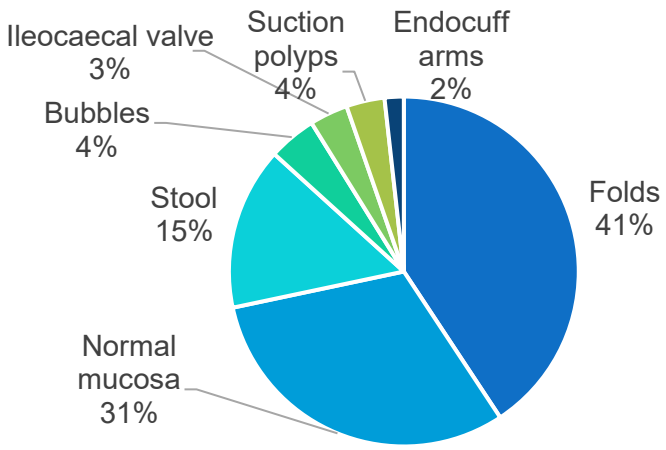
In a sub-study of 6 patients, 149 CADe-assisted 'polyp detections' were recorded of which 36/149 (24.3%) were diagnosed optically as true polyps by the endoscopist (see Figure 22).

Figure 22 Breakdown of CADe detections




The 113/149 (75.8%) false positive detections were due to folds (46), normal mucosa (35), stool (17), bubbles (5), ileocaecal valve (4), suction polyps (4) and Endocuff arms (2); see Figure 23.

Figure 23 Breakdown of false positive CADe detections




### 5.3.3 Endoscopist evaluation

Feedback was received from 11 clinicians who used the CADe system during the 1 month period. Endoscopists varied in their impression of whether CADe was helpful in identifying polyps (see Figure 24). 90% felt CADe had no adverse effect on the procedure (see Figure 25). 70% were unsure if CADe should be used in clinical practice (see Figure 26).

Figure 24 Endoscopist survey: 'CAD was helpful in identifying polyps'

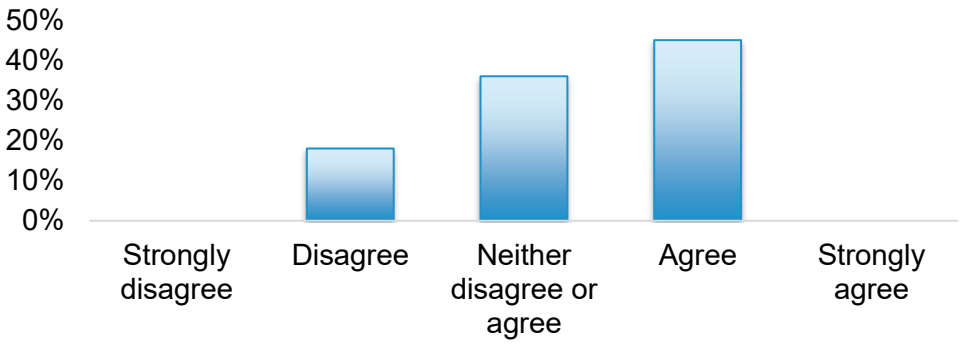


Figure 25 Endoscopist survey: 'CAD adversely affected procedure'

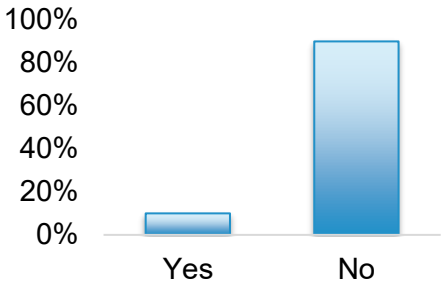
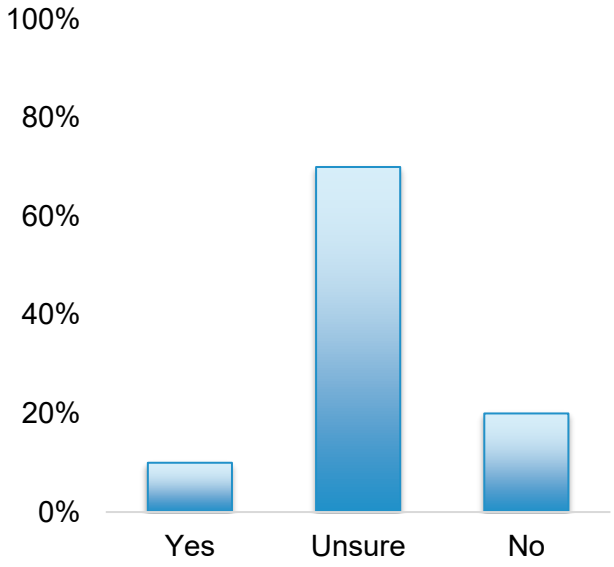



Figure 26 Endoscopist survey: 'Should CAD be used in clinical practice?'




# 5.4 Discussion

## 5.4.1 Key findings

a There was no difference in PDR and ADR with CADe in this group of high performing endoscopists

b There is a significant false positive rate with CADe

c Most endoscopists do not feel CADe adversely affects the procedure

### 5.4.2 Strengths and limitations

This was a limited evaluation of CADe which provided an early assessment of the system. A randomised evaluation would provide more robust evidence. In the AI-DETECT study (see Chapter 6) we conducted a randomised controlled trial (RCT) evaluation of CADe.

### 5.4.3 Further work

Although endoscopist opinion was sought, the patient perspective of CADe use would also be helpful to explore. In the DISCARD3 study reported in Chapter 9 a focus group was conducted which includes exploration of AI (see Section 9.3.6b)

### 5.4.4 Conclusion

No significant difference in PDR and ADR was found in this early evaluation of a CADe system in a group of high performing BCSP operators. There was a significant false positive rate. Endoscopists did not feel CADe adversely affected the procedure. Randomised evaluations of CADe systems will provide more robust data.

# Chapter 6 Polyp detection 2: Randomised evaluation of a CADe system during colonoscopy (AI-DETECT)

This chapter is based on a published manuscript[11] (150).

## 6.1 Background and Aims

### 6.1.1 Background

#### a Why is polyp detection important?

Polyp detection is a key aspect of colonoscopy to allow a reduction in colorectal cancer related morbidity and mortality. In screening programmes, high performing operators are trained to identify and remove polyps where appropriate to help effectively reduce risk. Even outside a screening programme setting, endoscopists with a high ADR have been shown to more effectively reduce the risk of post-colonoscopy colorectal cancer (PCCRC) (42).

#### b How good are we at polyp detection?

A recent systematic review and meta-analysis of tandem colonoscopy studies has shown an endoscopist polyp miss rate of 26% for adenomas and 27% for serrated lesions (151). It is therefore not surprising that there is a significant PCCRC rate within 6-36 months of an apparently 'negative' index colonoscopy (152,153). Where colonoscopy is performed within a BCSP setting there is a significant reduction in PCCRC-3yr rates from an overall unadjusted rate of 6.5% to 3.6%. This reflects the effect of enhanced technical skill and experience amongst BCSP colonoscopists.

#### c How can polyp detection be augmented?

[11] Ahmad A *et al*. Evaluation of a real-time computer-aided polyp detection system during screening colonoscopy: AI-DETECT study. *Endoscopy*. 2022; 54: 1–7. Tables and figures reproduced with permission (© Thieme).

Polyp detection during colonoscopy may be limited by a combination of patient, endoscopist and procedure related factors. At the patient level, for example, compliance with bowel preparation might alter the quality of mucosal visualisation. At the endoscopist level, operator experience may influence polyp detection. The volume of colonoscopy experience might influence the ability to maintain stable scope views throughout the withdrawal. OD experience may influence the ability to detect more subtle flat polyps. At the procedure level, the endoscopist has potential to influence polyp detection. For example, use of adjuncts such as Endocuff Vision which enhance visualisation of colonic mucosa have been shown to enhance polyp detection. In addition, patient repositioning and allowing adequate time for withdrawal can help enhance detection. However, even in highly experienced endoscopists performing optimal colonoscopy, human factors, such as distraction or fatigue may influence polyp detection rates.

#### d How might CADe help with polyp detection?

AI systems involve the use of 'algorithms that perform tasks that would usually require human intelligence' (154). Through 'machine learning', these algorithms can be 'trained to perform tasks by learning patterns from data rather than by explicit programming'.

CADe systems have been developed based on AI algorithms using polyp datasets of thousands of polyp photos. These facilitate polyp detection by automatically highlighting polyps on the endoscopist screen during colonoscopy. Theoretically, CADe can reduce the risk of human error during colonoscopy and potentially facilitate more consistent performance of high quality colonoscopy amongst operators with variable experience level.

#### e Knowledge gap

CADe systems are at an early phase of development. The first clinically available system was GI Genius (Medtronic). Prospective studies are lacking in a real life setting and are important to assess the acceptability and effectiveness of CADe before widespread adoption.

### 6.1.2 Aims

1. To assess the effectiveness of a CADe system (GI Genius) amongst a group of BCSP colonoscopists.

# 6.2 Methods

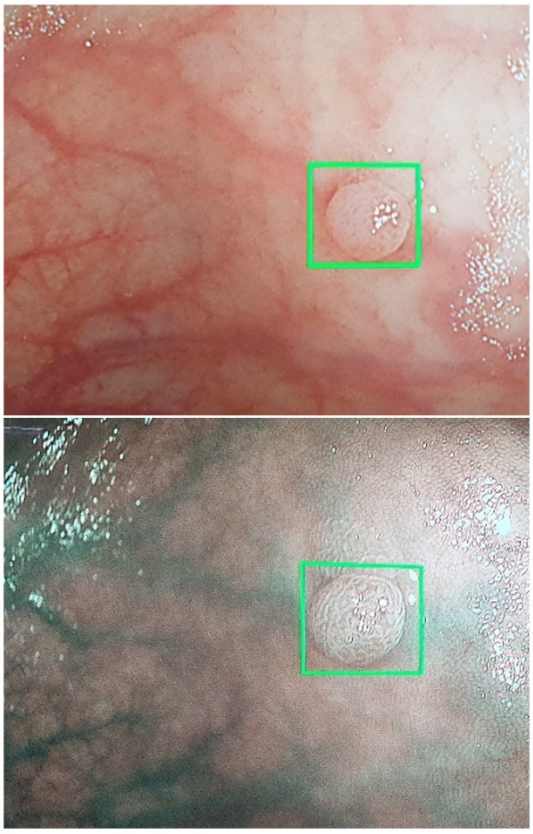
## 6.2.1 Study design

In this prospective randomised controlled trial, eight BCSP endoscopists at an NHS England BCSP centre (London North West University Healthcare NHS Trust) performed colonoscopy during the period Feb 2020 to Dec 2021. Participating patients were randomised, in the parallel design, to CADe (GI Genius, Medtronic) or standard colonoscopy (control group) with a 1:1 allocation ratio. Endoscopists used paediatric and adult high definition colonoscopes and were allowed to use colonoscope tip adjuncts; either Endocuff Vision (Olympus) or a transparent plastic cap (Olympus).

For CADe endoscopy, the GI Genius system was used (product code CB1708-EU) which is the first commercially-available CADe. Practically, the box (module) was attached to the existing endoscopy stack to integrate it within the existing set up; there were no other onsite/offsite usage requirements. The system input was the real-time video display from the standard colonoscopy video monitor. CADe was switched on before scope insertion until procedure completion. Whilst active, CADe highlighted possible polyp detections automatically and notified the endoscopist by superimposing an output of green boxes on the endoscopist's screen during the procedure (see Figure 27). Endoscopists were then able to assess 'polyp detections' and undertake polypectomy where appropriate. CADe outputs were used by the experienced endoscopists as an adjunct to their normal colonoscopy practice. Endoscopists were ultimately responsible for decision making relating to CADe detections. As the system was fully integrated with the existing set up, there were no issues with poor quality or unavailable input data.

In the control group, colonoscopy was performed as usual without CADe. For all cases polyp histology was reviewed within two weeks of the procedure.

Figure 27 Output of CADe system (GI Genius) in event of a polyp detection (white light and NBI views)



### a Inclusion and exclusion criteria

At the patient level, we included people aged 60-74 years attending for NHS BCSP screening colonoscopy due to a positive faecal immunochemical test (FIT) or a previous history of adenomas requiring post-polypectomy surveillance colonoscopy. In addition, patients aged 55 with large or multiple adenomas identified as part of the NHS bowel scope screening flexible sigmoidoscopy programme, were included. We excluded patients whose follow up was conducted outside BCSP due to their risk profile (family history or other reasons) and those that did not consent.

At the data input level, we included all cases where polyp datasets were complete and excluded cases where bowel preparation was so poor a repeat colonoscopy was required, where polyp datasets were incomplete and where the procedure was incomplete (caecum not reached).

There were no significant changes to methods after trial commencement.

### b Randomisation

Patients were block randomised with each list considered a block of 4 to 6 depending on the size of the list. Randomisation was generated using a computer-generated list produced by the study statistician to either CADe or no CADe in a 1:1 ratio. Patients were enrolled by a dedicated research nurse who assigned participants to interventions based on the randomisation list which was not accessible to endoscopists. The randomisation sequence was therefore not known to endoscopists until the intervention had been assigned. There was no operator or participant blinding.

### c Outcomes

The primary outcome is polyp detection rate (PDR); defined as number of patients with ≥ 1 polyp(s) divided by total number of colonoscopies performed. Our usual practice is to leave in situ small hyperplastic-appearing rectosigmoid polyps so these are not included in the assessment.

Secondary outcomes are:

- Adenoma detection rate (ADR)
- Sessile serrated lesion detection rate (SDR)
- 'Significant polyp' detection rate (adenoma + sessile serrated lesion [SSL])
- Polyps per colonoscopy (PPC; total polyps divided by total colonoscopies)
- Adenomas per colonoscopy (APC)
- Serrated polyps per colonoscopy (SPC)
- Procedure times: insertion (intubation to caecum), withdrawal (caecum to extubation) and total (intubation to extubation)
- SP6 (number of adenomas and sessile serrated lesions detected per six-minute withdrawal time); a measure of efficiency of polyp detection and management (46).

There were no changes to trial outcomes after the trial commenced. The trial was stopped after the recruitment target had been achieved. The technical performance of the AI system is not reported as this was not the aim of the trial.

### d Statistical analysis

The study was powered to detect a 10% rise in polyp detection from 20% in the control group to 30% with CADe. With a power of 80% and 5% significance level, 294 patients were required in each study arm (588 in total).

All analyses compared between the two groups. Demographic characteristics were compared descriptively. Continuous outcomes were found to have positively skewed distributions and were compared between groups with the Mann-Whitney test. Categorical outcomes were compared between the groups with the Chi-square test. Both an intention to treat (ITT) and a per-protocol (PP) analysis was performed.

CONSORT-AI guidelines were used to report the study which was registered with ClinicalTrials.gov (NCT04710693).

# 6.3 Results

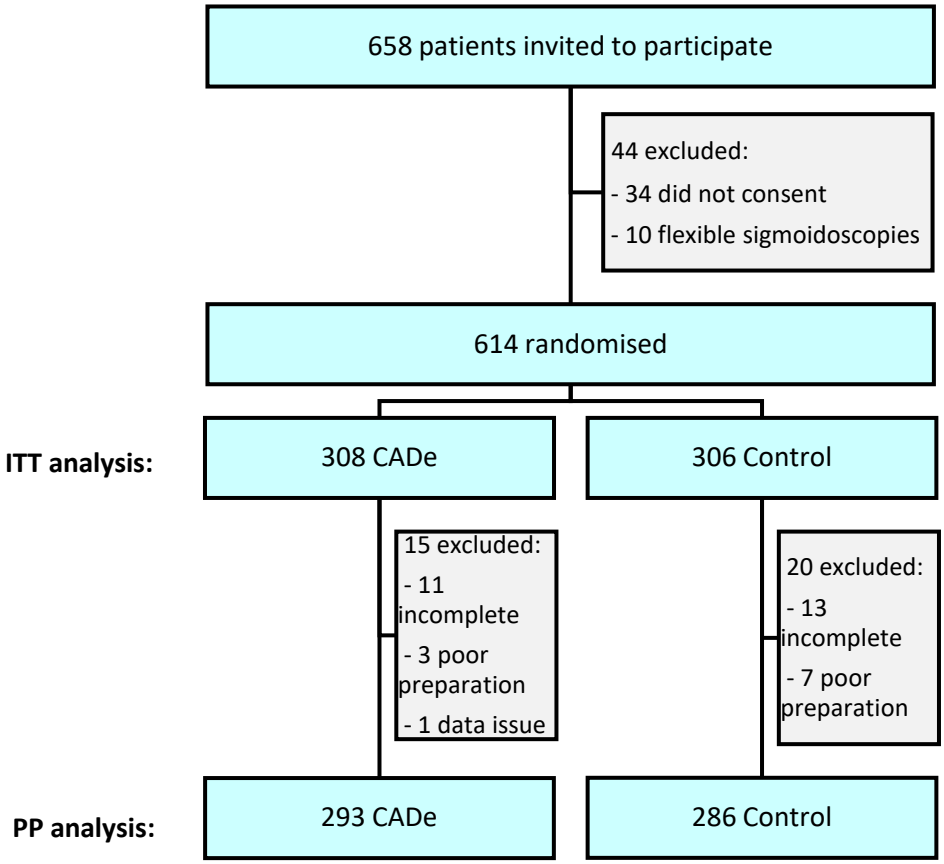
## 6.3.1 Overview

Of 658 invited patients, 614 were randomised for the ITT analysis to CADe (n=308) or control (n=306); see Figure 28 and Table 14. Post-randomisation, 35 patients were excluded (24 abandoned procedures, 10 poor preparation require a repeat procedure, 1 data issue).

In the PP analysis, there were 579 patients of which 293 were in the CADe group and 286 in the control group. Regarding scope adjunct use, Endocuff Vision was used in 71.7% (210/293) and 69.2% (198/286) for CADe and control groups respectively. A transparent cap was used in 2.0% (6/293) and 3.5% (10/286) of CADe and control cases respectively. No adjuncts were used in the remainder of cases.

There were no adverse or unintended effects in the groups.

Figure 28 Study overview




## 6.3.2 Participant characteristics

Demographic characteristics including age and gender were similar in the two groups (see Table 14).

Table 14 Baseline characteristics of participants

| | **Total** | **Control** | **CADe** |
|---|---|---|---|
| Total participants | 614 | 306 | 308 |
| Gender | | | |
| Male | 208 (33.9%) | 98 (32.0%) | 110 (35.7%) |
| Female | 406 (66.1%) | 208 (68.0%) | 198 (64.3%) |
| Age (mean ± standard deviation) | 66.3 ± 5.4 | 66.4 ± 5.4 | 66.2 ± 5.4 |

## 6.3.3 Procedure outcomes

In the ITT analysis, 2104 polyps in total were identified with a PPC of 3.6 ± 3.7 and 3.3 ± 3.3 polyps per colonoscopy in the CADe and control groups respectively (p=0.23); see

Table 15. A borderline statistically significant increase in PDR to 85.7% with CADe versus 79.7% in the control group was observed (p=0.05). There was no statistically significant difference in ADR which was 71.4% with CADe and 65.0% in the control group (p=0.09) or SSL detection rate between the groups. 'Significant polyp' (adenoma+SSL) detection rate increased with CADe compared with control (79.2% versus 71.6%; p=0.03) and this implies a small but clinically relevant benefit of CADe.

There was no difference in procedure times (total, insertion and withdrawal) as well as SP6 between the groups.

Table 15 Patient-level procedure outcomes with and without AI (ITT analysis)

| Outcome | All patients | Control | CADe | P-value |
|---|---|---|---|---|
| Total procedures | 614 | 306 | 308 | |
| | | | | |
| Total polyps | 2104 | 1001 | 1103 | |
| Adenomas | 1378 | 654 | 724 | |
| Serrated polyps | 528 | 263 | 265 | |
| *Sessile serrated lesions* | *242* | *115* | *127* | |
| *Hyperplastic polyps* | *286* | *148* | *138* | |
| Inflammatory | 24 | 10 | 14 | |
| Normal | 124 | 54 | 70 | |
| Other | 33 | 15 | 18 | |
| Left in situ | 12 | 2 | 10 | |
| Not retrieved | 5 | 3 | 2 | |
| | | | | |
| Polyps per colonoscopy | | | | |
| Total | 3.4 ± 3.5 | 3.3 ± 3.3 | 3.6 ± 3.7 | 0.23 |
| Adenomas | 2.2 ± 2.8 | 2.1 ± 2.6 | 2.4 ± 2.9 | 0.25 |
| Serrated polyps | 0.9 ± 1.4 | 0.9 ± 1.4 | 0.9 ± 1.4 | 0.93 |
| Sessile serrated lesions | 0.4 ± 0.9 | 0.4 ± 0.9 | 0.4 ± 0.9 | 0.40 |
| Hyperplastic polyps | 0.5 ± 0.9 | 0.5 ± 0.9 | 0.4 ± 0.9 | 0.45 |
| Other (inflammatory and normal mucosa) | 0.29 ± 0.66 | 0.26 ± 0.61 | 0.33 ± 0.70 | 0.06 |
| | | | | |
| Polyp detection rate (%) | 82.7 | 79.7 | 85.7 | 0.05 |
| 'Significant polyp' detection rate (%) (adenoma + SSL) | 75.4 | 71.6 | 79.2 | 0.03 |
| Adenoma detection rate (%) | 68.2 | 65.0 | 71.4 | 0.09 |
| SSL detection rate (%) | 23.1 | 21.6 | 24.7 | 0.36 |
| SP6 | 0.9 ± 0.8 | 0.8 ± 0.9 | 0.9 ± 0.8 | 0.10 |
| | | | | |
| Procedure times (minutes) | 24.7 [19.0, 32.3] | 24.3 [18.5, 32.0] | 24.9 [19.7, 32.5] | 0.18 |
| Insertion time (minutes) | 7.3 [5.5, 10.0] | 7.3 [5.4, 9.9] | 7.3 [5.7, 10.0] | 0.43 |
| Withdrawal time (minutes) | 14.5 [9.6, 21.1] | 13.9 [9.7, 20.9] | 14.9 [9.5, 21.4] | 0.34 |
| | | | | |
| Caecal intubation rate | 590 (96.1%) | 294 (96.1%) | 296 (96.1%) | 0.99 |

Summary statistics are mean ± standard deviation, median [inter-quartile range] or number (percentage)

In the PP analysis (see Section 16.2.6), 2089 polyps were evaluated and showed no statistically significant difference in polyp detection, procedure times (insertion, withdrawal, total) and SP6; see Table 35.

### 6.3.4 Polyp characteristics

In cases where polyps were detected, there was no difference in distribution, Paris classification, or polyp size (see Table 16 for ITT analysis and Table 36 for PP analysis).

Table 16 Polyp characteristics (ITT analysis)

| Outcome | All patients n (%) | No AI n (%) | AI n (%) |
|---|---|---|---|
| Total polyps | 2104 | 1001 | 1103 |
| | | | |
| Paris classification | | | |
| Is | 1107 (52.6%) | 528 (52.7%) | 579 (52.5%) |
| Isp | 83 (3.9%) | 45 (4.5%) | 38 (3.4%) |
| Ip | 139 (6.6%) | 56 (5.6%) | 83 (7.5%) |
| IIa | 729 (34.7%) | 350 (35.0%) | 379 (34.4%) |
| IIb | 32 (1.5%) | 16 (1.6%) | 16 (1.5%) |
| IIc | 5 (0.2%) | 4 (0.4%) | 1 (0.1%) |
| III | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) |
| LST-G | 5 (0.2%) | 1 (0.1%) | 4 (0.4%) |
| LST-NG | 4 (0.2%) | 1 (0.1%) | 3 (0.3%) |
| | | | |
| Site of polyps | | | |
| Caecum | 257 (12.2%) | 108 (10.8%) | 149 (13.5%) |
| Ascending Colon | 439 (20.9%) | 208 (20.8%) | 231 (20.9%) |
| Hepatic flexure | 89 (4.2%) | 38 (3.8%) | 51 (4.6%) |
| Transverse Colon | 465 (22.1%) | 233 (23.3%) | 232 (21.0%) |
| Splenic Flexure | 78 (3.7%) | 35 (3.5%) | 43 (3.9%) |
| Descending colon | 195 (9.3%) | 96 (9.6%) | 99 (9.0%) |
| Sigmoid colon | 357 (17.0%) | 177 (17.7%) | 180 (16.3%) |
| Rectosigmoid Junction | 10 (0.5%) | 6 (0.6%) | 4 (0.4%) |
| Rectum | 214 (10.2%) | 100 (10.0%) | 114 (10.3%) |
| | | | |
| Polyp size | | | |
| 1-5 mm | 1611 (76.6%) | 765 (76.4%) | 846 (76.7%) |
| 6-9 mm | 279 (13.3%) | 142 (14.2%) | 137 (12.4%) |
| 10+ mm | 214 (10.2%) | 94 (9.4%) | 120 (10.9%) |

## 6.4 Discussion

### 6.4.1 Key findings

a Amongst high performing colonoscopists using CADe within a BCSP setting the ITT analysis showed a marginal increase in PDR but no increase in ADR

b There was no improvement in detection of flat and diminutive polyps with CADe

c CADe did not adversely affect procedure time

### 6.4.2 Comparison with previous studies

A systematic review of five RCTs (4354 patients) showed a higher pooled ADR with CADe compared with control (36.6% v 25.2%, p<0.01) (155). Four of the included studies did not use GI Genius as the CADe system. Although AI systems may have similar outputs their AI-derived algorithms will vary so the results of disparate systems may not necessarily be generalisable. For example, one RCT used a 'real-time automatic quality control system' to provide feedback on polyp detection, bowel preparation and withdrawal stability (156). This system improved ADR but the individual contribution of the polyp detection aspect of this system could not be determined.

In the one included RCT that did use GI Genius (AID-1), 685 participants at 3 centres were randomised to colonoscopy with or without CADe (157). Six experienced colonoscopists (performed >2000 screening colonoscopy) were included. ADR (54.8% v 40.4%) and mean APC (1.07 ± 1.54 v 0.71 ± 1.20) were significantly higher in the CADe group than control. Adenomas up to 9mm were more frequently detected with CADe. This contrasts with our finding that there was no significant difference in ADR (71.4% and 65.0%, p=0.09) and APC (2.4 ± 2.9 and 2.1 ± 2.6, p=0.25) for CADe and control groups respectively. We also found no difference in size or morphology of polyps identified.

Recently, the only other Western randomised evaluation of GI Genius was a multicentre non-inferiority RCT (AID-2) (158). Unlike AID-1, this involved non-expert endoscopists (10 in total with <2000 colonoscopies experience). 660 colonoscopy procedures from 5 centres were included. ADR (53.3% v 44.5%) and APC (1.26±1.82 vs 1.04±1.75) increased with CADe by 22% and 21% respectively. Although AID-2 endoscopists were less experienced than in AID-1, ADR and APC findings were similar between the studies. In a post-hoc analysis, where both studies were pooled, CADe improved ADR by 29% and endoscopist experience was found to have no significant effect on ADR.

As with the AID-1 and AID-2 studies, we found no difference in withdrawal time which suggests CADe does not adversely lengthen procedures.

An alternative approach assessed in a recent multicentre tandem study is the effect of CADe on adenoma miss rate (AMR); defined as the 'number of histologically verified lesions detected at second colonoscopy divided by the total number of lesions detected at first and second colonoscopy' (159). In this study, AMR was 15.5% where CADe was the first colonoscopy versus 32.4% where standard colonoscopy was performed first. This significantly lower AMR with CADe was thought to be due to a reduction in flat and small lesions being missed. This contrasts with our study where no difference in morphology or size of detected polyps was found with or without CADe. Although the study results appear convincing of a benefit of CADe these should be interpreted with caution as tandem studies are open to bias, are unblinded and do not represent usual clinical practice.

A number of studies have evaluated the use of alternative CADe systems within a screening setting but do not specifically assess use of Endocuff Vision (160–162). Shaukat et al assessed the Skout CADe device in a randomised study with 1359 patients included in the analysis and showed a significant improvement in adenomas per colonoscopy when using CADe (0.83 v 1.05, p =0.002) for screening and surveillance colonoscopies (160). However, there was no significant difference in ADR (43.9% v 47.8%, p=0.065). In a randomised study with 800 patients, the CAD EYE (Fujifilm) CADe system was assessed within a FIT-based colorectal screening setting and significantly increased ADR (45.3% v 53.6%) and APC (0.90 v 1.13, p =0.028) (161). In another randomised study evaluating 'AI-assisted colonoscopy' a significant improvement in PDR and ADR was observed (162). CADe systems may on the surface appear to be similar in terms of their outputs, but differences in the underlying AI algorithms may to some extent explain variation in findings between studies.

Previous studies have shown ADR improvements in operators who have performed >1000 (151), >2000 (157) or >5000 (156) colonoscopies. We therefore expected a more significant difference in polyp detection with CADe than we observed.

Our study involved a group of experienced endoscopists with high baseline polyp detection which limited the potential for CADe to influence outcomes. The overall PDR was 82.7% in the ITT analysis and 86.0% in the PP analysis. With such high rates, there was a 'ceiling effect' leaving little room for the intervention to show an improvement. Also, the majority of procedures in our study were, unlike in others, performed with Endocuff vision which can improve mucosal visualisation and therefore polyp detection reducing the potential impact of additional CADe (163).

### 6.4.3 Strengths and limitations

The randomised design is a key strength of this study. In addition, evaluating performance within a homogenous group of BCSP accredited endoscopists may improve generalisability of results in a screening setting although further studies are required. Endocuff Vision is used as part of usual practice by endoscopists in this study within a bowel cancer screening setting following the ADENOMA study which showed a significant improvement in ADR (163). The CADe system therefore had a higher polyp detection threshold to exceed to show a statistically significant improvement. Had Endocuff Vision not been used, a larger improvement in polyp detection may have been observed with CADe.

The original sample size calculation was based on a mixed cohort of patients expected to have a lower PDR. The observed PDR in this study was much higher than that assumed in the sample size calculation. The power calculation was based on a 25% PDR in the two groups combined, 10% group difference, with 80% power. The observed PDR in the study was ~80% for the two groups combined. With the same sample size (n=588), the study would have a higher power of 86% to show a 10% difference (e.g. 75% vs 85%) between the groups. Therefore, although the assumptions of the original calculation were not met, this is unlikely to impact inversely on the power of the study.

In our study, as with other similar studies, endoscopists could not be blinded to use of CADe. There is therefore a risk of observer bias where, for example, endoscopists pay more attention to mucosal visualisation in cases where CADe is used.

### 6.4.4 Further work

CADe systems may have greatest potential amongst endoscopists with low PDR and in those undergoing training; in both settings further studies are required.

### 6.4.5 Conclusion

Compared to standard colonoscopy, CADe performed in a bowel cancer screening setting gave a borderline significant improvement in PDR in the ITT analysis. However, there was no increase in ADR and no significant difference in polyp detection in the PP analysis. There appears to be a limited effect of CADe in a screening setting. Such systems may be most efficacious in low polyp detectors and trainees outside screening programmes.

# Chapter 7 Optical diagnosis 1: National survey of optical diagnosis practice

## 7.1 Background and Aims

### 7.1.1 Background

#### a What is optical diagnosis?

'Optical diagnosis' (OD) refers to the process of diagnosing by sight alone without histopathological assessment. OD is widely performed in medicine and particularly during the inspection phase of a general medical physical examination. In specialties where external (dermatology) or internal (gastroenterology) surface features are assessed, OD is frequently used.

In endoscopy, mucosal assessment of the gastrointestinal tract frequently results in detection of polyps which, if appropriate, are most commonly resected and sent for histopathology assessment. Advances in scope technology, however, now allow polyps to be assessed and optically diagnosed prior to resection using validated classification systems (eg NICE). This offers the potential for an OD approach to be used for lower-risk small polyps which could then be resected and discarded, the so-called "resect and discard" strategy, if appropriate.

A "resect and discard" strategy has potential for huge cost and time savings by reducing the need for histopathology (see Chapter 11). Several gastroenterology societies have endorsed a "resect and discard" strategy for small polyps during colonoscopy but, despite this, it does not appear to have entered clinical practice (94,164,165).

#### b Image enhancing endoscopy for OD

Endoscopic images can be enhanced in real-time during colonoscopy by use of either dye-based or virtual chromoendoscopy. These have the effect of highlighting surface structures to facilitate polyp assessment and offer the potential for accurate OD. A randomised multicentre study showed no difference in OD accuracy between narrow band imaging (NBI) and high definition white light (HD-WL) (166). However, Rastogi et al showed using NBI in real-time gave the highest accuracy for predicting adenomas. Also HD-WL and NBI use resulted in a higher adenoma per subject detection rate compared with standard definition white light (SD-WL) (167).

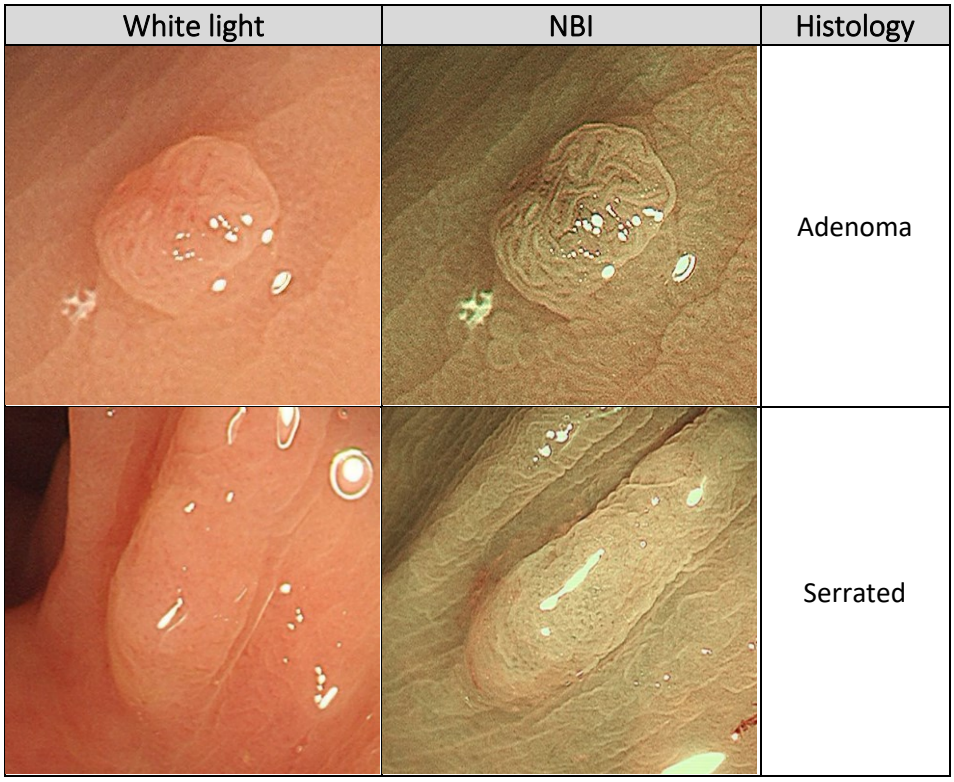
Dye-spray chromoendoscopy involves manual application of dye to stain the colonic mucosa. This pooling of dye in mucosal pits helps highlight polyp structures. Examples of dyes used include:

- Indigo carmine
- Methylene blue
- Crystal violet

Virtual chromoendoscopy has the advantage of being an instant 'push-button' technology and includes:

- NBI – narrow band imaging (Olympus Corporation)
- FICE – Fujinon Intelligent Colour Enhancement (Fujifilm)
- i-Scan – (Pentax Medical)
- BLI – blue laser imaging (Fujifilm)

Figure 29 Narrow band imaging assessment of diminutive polyps[12]




Of all the imaging modalities, the most widely studied is Narrow Band Imaging (NBI) which is currently recommended by the American Society of Gastrointestinal Endoscopy (ASGE) for OD with a resect and discard strategy (94). In a meta-analysis, NBI had a 91.0% sensitivity and 85.6% specificity (168). In addition, the learning curve for NBI is short. Although FICE and i-Scan modalities are promising, ASGE feel the data is still insufficient to recommend their use. ESGE, however, recommends NBI, i-Scan, FICE and standard chromoendoscopy for ≤5 mm polyps.

Endoscopic images can also be enhanced by increasing the resolution of the image by magnification or use of higher definition scopes. For example, magnification with near-focus scope views can offer enhanced views of vascular structures and have been shown to improve confidence of optical diagnoses compared with standard views (169,170). However, ASGE thresholds can be achieved with standard view scopes.

### c OD classification systems

[12] Ahmad A et al. Implementation of optical diagnosis with a 'resect and discard strategy' in clinical practice: DISCARD3 study. Gastrointest Endosc. 2022 Jun. Figure reproduced with permission (187).

OD polyp classification systems use criteria such as colour and vascular pattern to distinguish polyp types. These include:

- NICE (NBI international colorectal endoscopic classification, see Table 17) – this validated classification uses colour, surface and vascular pattern to distinguish adenomas from hyperplastic polyps. A key limitation is that the criteria does not allow SSPs to be diagnosed.
- WASP (Workgroup serrAted polypS and Polyposis)
- SIMPLE (Simplified Identification Method for Polyp Labelling during Endoscopy)
- Hiroshima
- JNET (Japan NBI Expert Team)
- BASIC (BLI Adenoma Serrated International Classification)
- Sano's capillary pattern classification

Table 17 Classification of polyps based on NICE criteria

| NICE criterion | Type 1 | Type 2 | Type 3 |
|---|---|---|---|
| Colour | Same or lighter than background | Brown relative to background | Brown to dark brown relative to background |
| Vessels | None or isolated lacy vessels | Brown vessels surrounding white structures | Areas of disrupted or missing vessels |
| Surface Pattern | Dark or white spots of uniform size | Oval, tubular or branched white structures surrounded by brown vessels | Amorphous or absent surface pattern |
| Histology | Serrated* | Adenoma | Cancer |

*The original NICE classification suggested most likely pathology of Type 1 polyps was hyperplastic (171).

All of the above classification systems except BASIC use NBI (SIMPLE is also validated with i-Scan). The JNET classification is the only classification system using NBI that requires the use of high magnification. Unlike the other systems, WASP and SIMPLE classification systems allow sessile serrated polyps (SSPs) to be diagnosed.

### d Adjuncts to OD

In addition to classification systems, certain characteristic features of polyps may be used to help accurately diagnose polyps optically:

- Valley sign
- Aurora rings sign
- Fibrin cap

These adjuncts could potentially enhance existing classification systems and are explored in detail in Chapter 10.

### 7.1.2 Aims

1. Assess current OD practice during colonoscopy in the United Kingdom (UK)
2. Determine the degree of training and confidence in use of OD
3. Understand which classification systems are most widely used for OD

## 7.2 Methods

### 7.2.1 Study design

An online survey with a series of questions (multiple choice and free text) about OD was prepared (see questionnaire in 16.2.5). The survey was approved by the BSG Endoscopy Section who circulated this via email to section members in October and November 2021.

### 7.2.2 Outcomes

**a Colonoscopy experience**

- Procedures performed
- Setting

**b OD experience**

- Performance of OD
- Performance of a "resect and discard" strategy
- Training in OD
- Confidence in OD
- Views on a "resect and discard" strategy

- Use of OD classification systems
- Use of adjuncts to NICE classification

# 7.3 Results

## 7.3.1 Overview

There were 107 responses and respondents had performed >1000 colonoscopies in 78.5% of cases. The setting was district general hospital (50.5%), teaching/specialist hospital (47.7%) and other (1.8%). Most respondents (91.6%, 98/107) 'send all resected diminutive colorectal polyps (≤5 mm) to histopathology where possible'. Prior to resection of polyps, 59.8% (64/107) of endoscopists always perform OD with 36.4% (39/107) 'sometimes' performing this and 3.7% (4/107) 'never' performing this.

In terms of training, only 41.1% (44/107) reported attending 'formal training in optical diagnosis of diminutive polyps'. Despite this, the majority of endoscopists (70.1%, 75/107) were 'confident' or 'very confident' in diminutive polyp OD. When asked about whether a "resect and discard" strategy is a 'desirable goal of colonoscopy' 37.4% (40/107) felt it 'desirable', 23.4% (25/107) felt it 'neither desirable nor undesirable' and 39.3% (42/107) felt it 'undesirable'.

In terms of OD classification system, the most frequently used were Kudo (78.5%, 84/107), NICE (65.4%, 70/107) and JNET (28.0%, 30/107). The 107 respondents who use the NICE classification system were asked to specify which criteria (multiple choices allowed) was the most important for OD. Surface pattern (90.2%, 92/102) was rated most important followed by vessels (53.9%, 55/102) and colour (31.4%, 32/102).

Most endoscopists who use the NICE classification also utilise adjuncts to support OD (74.8%, 80/107). Of these adjuncts, presence of a fibrin cap is used most frequently (60.0%, 48/80), followed by the WASP classification (53.8%, 43/80), valley sign (52.5%, 42/80) and the aurora rings sign (43.8%, 35/80).

# 7.4 Discussion

### 7.4.1 Key findings

a Most endoscopists perform OD and feel confident doing so

b Only a minority of endoscopists have formal training in OD

c NICE is frequently used for OD and often supplemented with adjuncts to support OD

### 7.4.2 Comparison with previous studies

To our knowledge, this is the first survey of optical diagnosis practice in the UK. Although traditionally there was greater emphasis on use of dye-chromoendoscopy, this survey suggests, virtual chromoendoscopy is now widely available and used for OD in UK practice.

In a survey exploring variation in management of diminutive colorectal polyps in the US, 167 members of the American College of Gastroenterology (ACG) participated (172). In this study, around half of participants were 'not at all' agreeable with a "resect and discard" approach with the remainder 'somewhat', 'generally' or 'very' agreeable.

This survey also assessed perceptions of a 'diagnose and leave' approach with around 70% agreeable to leaving diminutive polyps in place if 'guidelines endorsed this practice'. They found that endoscopists with greater experience and confidence in OD were predictors of those that reported leaving diminutive polyps in situ.

### 7.4.3 Strengths and limitations

This survey had national reach so was able to capture experience from a wide range of endoscopists. However, the number of respondents was far fewer than expected despite a second survey request and reminders being sent.

As with all surveys, there is a risk of selection bias. In this survey, we sought the views from a group of BSG Endoscopy Section members who clearly have a strong interest in endoscopy. This helped ensure the majority of respondents were experienced colonoscopists. A greater response rate, may have increased the power of the study

and inviting a wider group of colonoscopists would help better understand the generalisability of this data.

In addition, the study was UK based and OD practice will likely vary from country to country depending on local equipment, training and guidance.

### 7.4.4 Further work

A survey evaluating OD experience in trainees and more inexperienced endoscopists would help better understand practice in this group. An international survey would allow a better appreciation of variation in OD practice globally. The lack of formal training in OD suggests this is an important area to focus on in colonoscopy training programmes.

### 7.4.5 Conclusion

In this survey, we found OD of diminutive polyps is already performed by the majority of the endoscopists and 70.1% feel confident with this. However, less than half of respondents had formal training in OD. In addition, a "resect and discard" strategy is rarely used in clinical practice and there is a range of opinion as to whether this is a desirable goal of endoscopy.

# Chapter 8 Optical diagnosis 2: Photodocumentation quality during colonoscopy

This chapter is based on a paper which has been published[13] (173).

## 8.1 Introduction

Recommendations for photodocumentation at colonoscopy vary widely. Several societies suggest there is photographic proof of caecal intubation. For example, the British Society of Gastroenterology (BSG) quality standard recommends photodocumentation of 'ileocaecal valve, terminal ileum, anastomosis or appendix orifice [is] required in all cases' (25). Similarly, ASGE/ACG/AGA guidelines do not mandate photodocumentation of any other part of the colon (174).

Caecal photodocumentation, although important for confirmation of extent of colonoscope insertion does not provide evidence that the colonic mucosa en route has been adequately visualised.

Photodocumentation is now a relatively straightforward 'push button' process with endoscopy reporting systems designed to automatically save photos in real time and record images to the endoscopy report. In this context, should more comprehensive photodocumentation be part of routine colonoscopy practice and would this improve examination quality?

## 8.2 Background

Some argue that video-recording is preferable to static photodocumentation. Advances in data storage capability mean that video-recording the entire procedure is technically possible. Doing so has been shown to improve mucosal inspection time by 49% and quality of mucosal inspection by up to 30% (175). However, in the context of rising

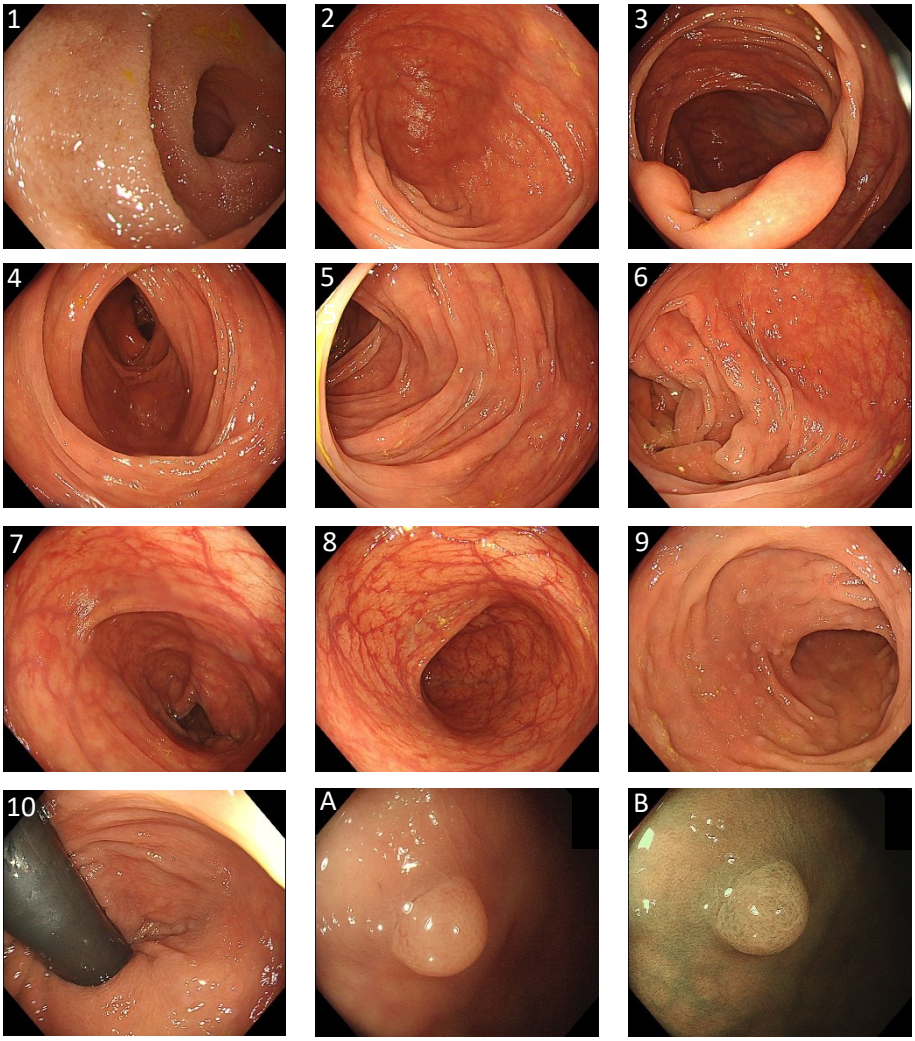
[13] Ahmad A, Saunders BP. Photodocumentation in colonoscopy: the need to do better? Frontline Gastroenterol. 2022 Jul;13(4):337–41. Tables and figures reproduced with permission.

healthcare costs, the financial implication of data storage and the challenges of sharing large data files with colleagues cannot be overlooked.

Endoscopists are already familiar with static photodocumentation which involves smaller files size outputs and this technology is fully embedded in existing systems. It may therefore be more acceptable and realistic to enhance quality with greater emphasis on enhanced photodocumentation quality, training and implementation.

In upper GI endoscopy, it is recognised there is an 11.3% failure rate in cancer diagnosis within 3 year of upper GI endoscopy (176). To help address this, enhanced photodocumentation in upper GI endoscopy, with eight anatomical landmarks is now recommended as part of the BSG standards (177). The European Society of Gastrointestinal Endoscopy (ESGE) goes further with a recommendation for at least 10 photos in total (178). In colonoscopy, ESGE has recommended 9 anatomical landmarks are photodocumented (179,180) (see Figure 30).

Figure 30 Anatomical landmarks to photodocument during colonoscopy as recommended by ESGE and examples of polyp photodocumentation




1: terminal ileum; 2: caecum and appendiceal orifice; 3: caecum and ileocaecal valve; 4: ascending colon under the hepatic flexure; 5: transverse colon just distal to the hepatic flexure; 6: transverse colon just proximal to the splenic flexure; 7: descending colon below the splenic flexure; 8: middle part of the sigmoid; 9: lower part of the rectum in forward view; 10: lower part of the rectum in retroflexed view; A: Sigmoid colon polyp photo under white light with magnification 12. Sigmoid colon polyp photo under NBI.

As optical diagnosis become more widely practiced, more comprehensive and higher quality photodocumentation will become increasingly important. For example, when implementing a "resect and discard" strategy, which has been endorsed by ESGE (181), high quality photodocumentation will serve as the sole 'polyp record' and replace histology.

Furthermore, we now recognise the phenomenon of post-colonoscopy colorectal cancer (PCCRC), an important marker of quality, which emphasises the need for optimal colonoscopy technique and photodocumenation (see Chapter 12). The PCCRC-3yr rate is a measure of the proportion of people diagnosed with colorectal cancer 6 to 36 months after an apparently negative colonoscopy. A population-based cohort study has shown in England the rate is 7.4% (152).

In order to facilitate standardisation and benchmarking, the World Endoscopy Organisation (WEO) has published consensus statements including the minimum datasets required to analyse PCCRC cases. This includes recommendation of photodocumentation of at least 2 of 3 caecal landmarks (153). Given that PCCRCs occur most frequently in the rectum and can occur throughout the colon (182), an extension of the standard photodocumentation dataset would seem logical.

Photodocumentation is therefore becoming increasing important in colonoscopy practice. The purpose of this paper is to explore current photodocumentation standards, barriers/solutions to implementation of high quality photodocumentation and future trends.

## 8.3 Current standard of photodocumentation

A national audit of UK colonoscopy practice including data from 20085 colonoscopies showed caecal intubation was photodocumented in just 50.2% of cases. In a study where 120 caecal landmark photos were assessed, reviewers classified whether they felt the caecal pole had been reached into definite, probable or uncertain categories. Definite and probable scores ranged from 44-97% (183).

Another study assessed sensitivity and specificity of photodocumentation for determination of complete colonoscopy. 80 pairs of photos were taken from complete procedures and combined with photos from non-caecal sites. Experienced endoscopists reviewed this and, where only 2 endoscopic photos were used to document colonoscopy completion, there was a 51.4% sensitivity and 89.2% specificity.

These studies show there is clearly room for improvement in current standards of photodocumentation.

## 8.4 Importance of photodocumentation

Photodocumentation provides an objective record of procedure completeness and adequacy by showing the procedure extent and quality of mucosal visualisation. It also allows significant findings to be documented and accurate recording of therapy performed. There are secondary effects from the process of photodocumentation that might improve procedure standard such as lesion detection and withdrawal time (32). Within upper GI endoscopy, for example, Park et al have shown ampulla photodocumentation is significantly associated with detection of small upper GI neoplasms (184).

The procedure account provided by photodocumentation, more broadly, serves the function of facilitating communication between clinicians and with patients. This is particularly helpful in the context of follow up site-check procedures post-polypectomy. From a medico-legal perspective, photodocumentation adds to the patient record and provides an objective account of the procedure performed.

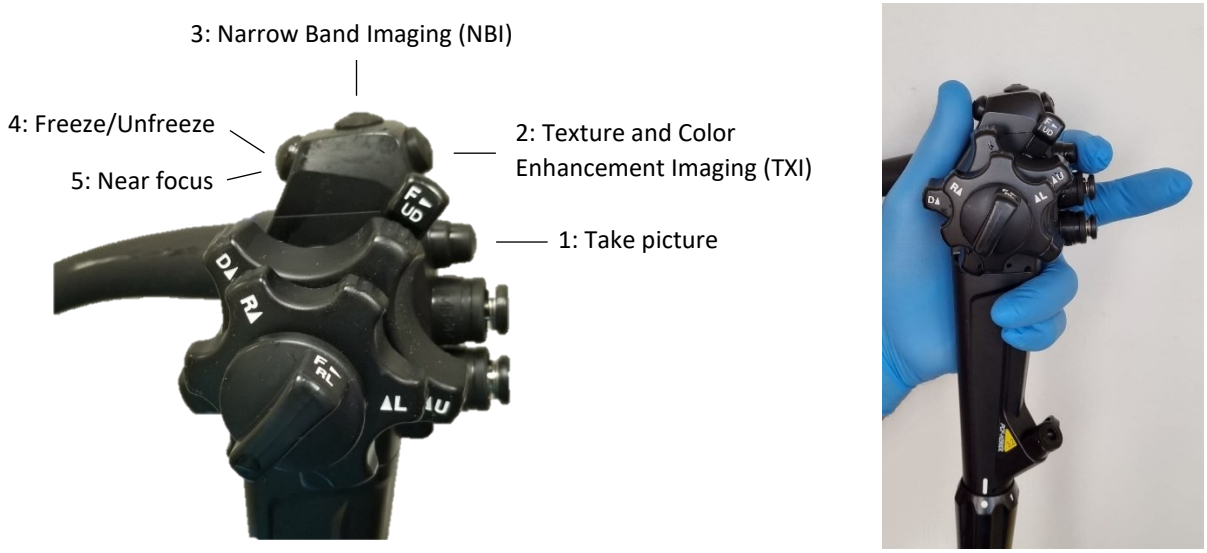
## 8.5 Overcoming barriers to photodocumentation

### 8.5.1 Scope set up/ergonomics

A poorly set up colonoscope can make photodocumentation unnecessarily challenging. From an ergonomic perspective setting up endoscope buttons 4 and 1, to freeze and take the picture respectively, is crucial to allow rapid photodocumentation during the procedure (see Figure 31).

During the course of an endoscopy list, we have found an experienced endoscopist takes on average 1.9 attempts at freezing and unfreezing the endoscopic image before a satisfactory photo has been obtained. This highlights the importance of easy access to button 4 with minimal change in left hand position.

Figure 31 Suggested scope button set up on a 290 series Olympus colonoscope and hand position relative to image capture buttons.



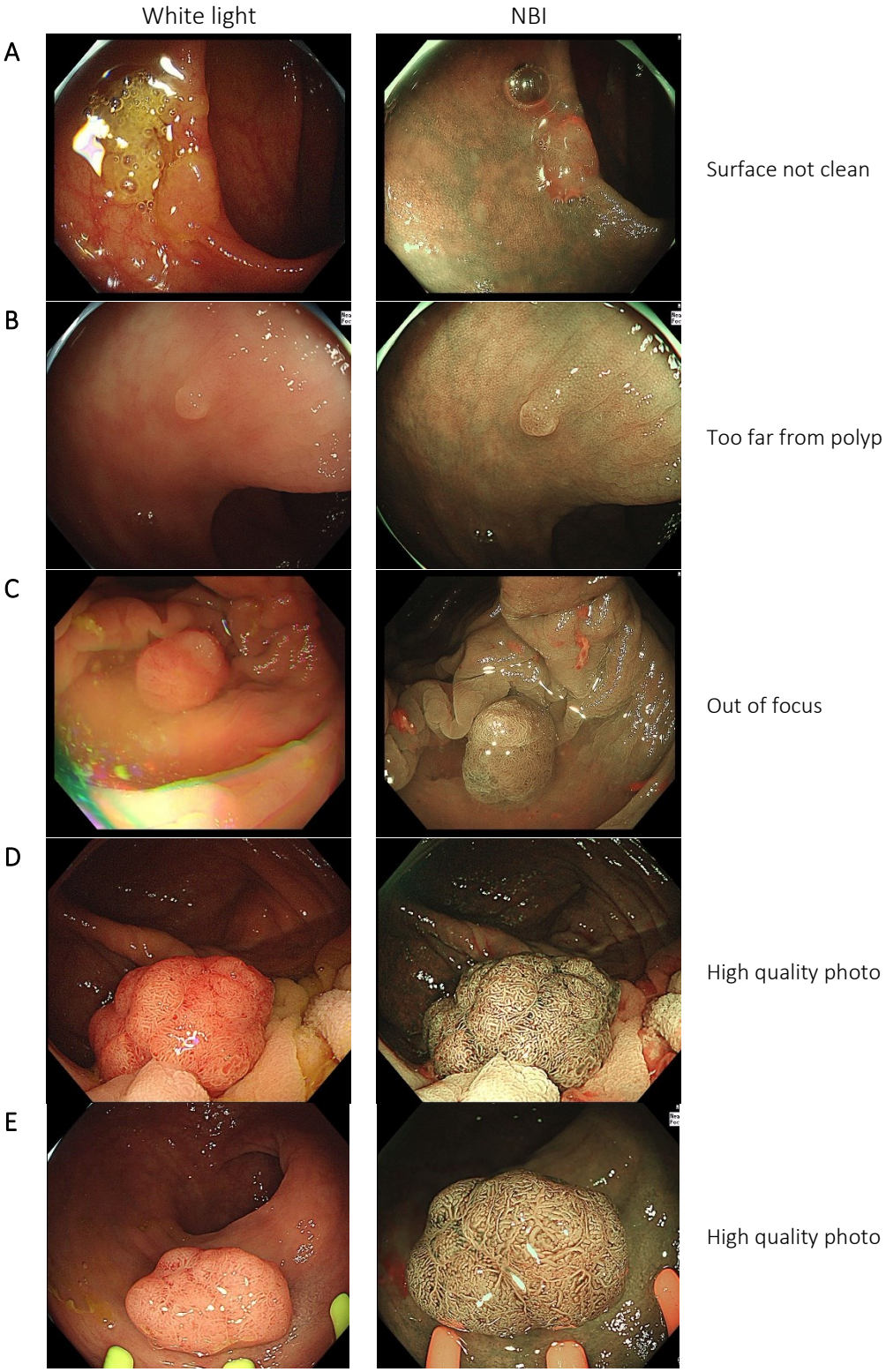

## 8.5.2 Time pressure

There is significant service pressure to maximise endoscopy list outputs with waiting lists particularly high due to the impact of Covid-19. This may reduce the time available to take and label high quality photographs. AI systems may be able to automate and therefore streamline this process so that it fits seamlessly within the colonoscopy procedure with minimal input required from the endoscopist. In addition, voice activation could remove the need for hand position change when taking and recording photos allowing the endoscopist to concentrate fully on optimising photo quality.

## 8.5.3 Poor quality photographs

Photodocumentation is important but only meaningfully adds to the patient record where this is of a high standard. Where this is not achieved, for example where a photodocumented polyp is too far away or out of focus, interpretations made using these photos by reviewing clinicians may be inaccurate (Figure 32).

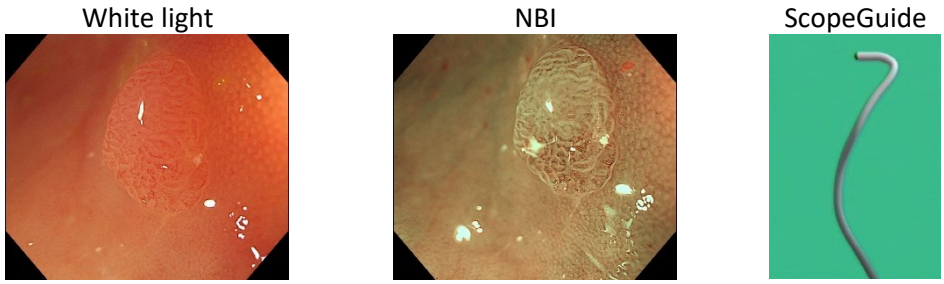
Figure 32 Common issues with photo quality (A-C) and high quality photos (D-E)




## 8.5.4 Poor photo labelling

Photo labelling by the endoscopist immediately after the procedure helps make the record useful for future reference. In some cases poor or inaccurate image labelling can create uncertainty. Use of magnetic endoscope images alongside standard photographs could provide an objective measure of photo site and avoid the need for reliance on manual labelling (see Figure 33).

Figure 33 Splenic flexure polyp with accompanying magnetic endoscope image (ScopeGuide)




## 8.5.5 Lack of training

Simple training interventions can significantly improve photodocumentation outcomes. In a study where a performance review and education session was conducted, mean appendiceal orifice photodocumentation rate improved from 55 to 91% (median change 28.5%, p=0.03) (185).

In upper GI endoscopy, we have found in a previous audit of 184 OGDs a single training session about photodocumentation standards increased anatomical site photodocumentation from 3.8 to 6.9 photos per procedure ($p<0.001$) (186). In addition, there appeared to be a trend towards increasing lesion detection, from 0.5 to 1.2 per procedure, but this did not reach significance in this small study (p=0.230).

For polyp photodocumentation, there are some specific competencies required to achieve high quality (see Figure 34).

Figure 34 How to take excellent polyp photos: basic competencies

1. Ensure a stable scope position and ensure entire polyp visible.
2. Wash and clean polyp.
3. If en face view not possible or aortic/respiratory induced wall movement: use a biopsy forceps, snare catheter or open snare: push instrument forward to flatten fold, invert and stabilise the polyp position towards the lens.
4. Ensure polyp surface is in focus.
5. Confirm that a high quality photo has been achieved. Be patient, freeze the frame, take a white light and blue light image (eg NBI/BLI/Iscan). Repetition of the process may be required to achieve a high quality image.
6. Label images clearly.
7. Audit photodocumentation as a key quality metric.

Using a standardised approach to photodocumentation, as in non-medical contexts such as passport photography, may help improve compliance. Within endoscopy, guidance on photodocumentation of colonic mucosa and polyps could help support training and research. To this end, we propose a simple checklist, the "3C endoscopy photo quality checklist", covering the three key aspects of a high quality endoscopic photo (see Table 18).

Table 18 3C Endoscopy Photo Quality Checklist to evaluate the quality of an endoscopic landmark/polyp photo

| **3C Endoscopy Photo Quality Checklist** |
|---|
| 1. Clean mucosal surface |
| 2. Complete view (en-face or panoramic view of relevant area) |
| 3. Correct focal distance (sharp) |

We also suggest that polyp photos are photodocumented with a white light and blue light image (which highlights vascular structures). This allows retrospective review of optical diagnoses to be made in the context of a root cause analysis of optical diagnosis error (see Chapter 10).

## 8.6 Future of photodocumentation

Artificial intelligence systems currently being developed are able to identify the anatomical site and degree of mucosal visualisation. It is therefore realistic that these systems will be able to automatically photodocument high quality photos for each anatomical site and provide real-time feedback for photos taken manually.

Voice recognition, might further enhance the process of photodocumentation by allowing real-time labelling and thereby reducing recall error in the context of multiple polyps. These technologies will help make endoscopy procedure reports more accurate and comprehensive for the end user.

As AI systems develop, polyp and lesion characterisation is becoming possible in real time and will influence procedural decision making. Once in clinical use, it will be important to document any assistive technologies used and the impact these had, if any, on decision making during or after the procedure.

## 8.7 Conclusion

Colonoscopic photodocumentation is now a straightforward process but is often neglected in colonoscopy practice. Enhancing current practice by taking simple measures could help reduce the risk of PCCRC and facilitate the implementation of optical diagnosis with a resect and discard strategy in clinical practice.

Gastroenterology societies could mandate a high standard of photodocumentation by supporting enhanced training and ensuring sufficient time is allocated to make this feasible during clinical practice.

Technological advances will help automate the process and may reduce variability between endoscopists, but ultimately the endoscopist is responsible for ensuring any procedure outputs are accurate and of high quality.

# Chapter 9 Optical diagnosis 3: Implementation of optical diagnosis with a "resect and discard" strategy in clinical practice (DISCARD3)

This chapter is based on a paper which has been published[14] (187).

## 9.1 Background and Aims

### 9.1.1 Background

#### a Current practice

A key goal of colonoscopy is to identify and remove pre-cursors of colorectal cancer, adenomas and sessile serrated polyps, which reduces mortality risk by 40-60% (188,189). Standard clinical practice at present is to "resect and send" polyps to histology except for small hyperplastic-appearing rectosigmoid polyps which are often left in situ (172). Surveillance intervals are determined on the basis of histological assessment.

The overwhelming majority of polyps are <10 mm in size with advanced histological features being rare in this group. For these polyps, there is therefore the potential to avoid the need for costly and time-consuming histological assessment of polyps in cases of where OD is performed with high confidence. OD is carried out using image enhancement such as NBI to highlight vascular structures (see Figure 29) which allows application of validated classification systems such as the NICE criteria (see Table 17).

#### b What is a "resect and discard" strategy?

[14] Ahmad A *et al*. Implementation of optical diagnosis with a "resect and discard" strategy in clinical practice: DISCARD3 study. *Gastrointestinal Endoscopy*. 2022; 96(6): 1021-1032.e2. Tables and figures reproduced with permission.

A “resect and discard” strategy is where a polyp, diagnosed with high confidence, is resected and discarded rather than sent to histopathology. Polyps diagnosed with low confidence are sent to histopathology as usual.

ASGE is the first body to have set a benchmark for implementation in clinical practice which requires ≥90% histology-OD surveillance interval concordance for implementation of a “resect and discard” strategy (94). Only ≤5 mm polyps diagnosed with high confidence are resected and discarded. The OD from high confidence cases is combined with pathology assessment of all other polyps to determine the OD surveillance interval.

There is a second PIVI paradigm whereby ≤5 mm rectosigmoid hyperplastic polyps diagnosed with high confidence can be left in situ where the negative predictive value for adenomas is ≥90% (‘diagnose and leave’ strategy). Many endoscopists already routinely ‘diagnose and leave’ small rectosigmoid hyperplastic polyps in situ.

### c Is it safe to “resect and discard” polyps <10 mm?

The main concern with “resect and discard” is that polyps with advanced colorectal polyp histology would be discarded and therefore potentially result in inappropriate treatment or incorrect surveillance interval assignment.

Advanced polyps include:

- adenomas at least 10 mm in size or containing high-grade dysplasia
- serrated polyps at least 10 mm in size or containing dysplasia of any grade
- some international definitions include adenomas with tubulovillous/villous histology and serrated adenomas

Studies consistently show malignant potential of polyps increases with size (190–192). Gupta et al showed advanced histology occurs in 0.8% of polyps <10 mm and 15.0% of polyps ≥10 mm (190). Lieberman et al showed the respective figures were 2.9% for polyps <10 mm and 30.6% for polyps ≥10 mm. In view of this, a resect and discard strategy is considered appropriate only for <10 mm polyps. Importantly, in these studies, the risk of cancer was 0% for ≤5 mm polyps and 0-0.2% for 6-9 mm polyps with similar findings reported in other studies (181).

Advanced diminutive polyps have been shown in a cohort study of 34221 patients not to increase the risk of metachronous advanced colon neoplasia (193). Variation in the reporting of advanced histology rates in the literature may occur due to differences in the criteria used to define advanced polyps, endoscopist sizing error and interobserver variation in pathology reporting.

Effective polypectomy eliminates the risk from advanced polyps. The first-line recommended resection technique for sessile/flat colorectal polyps <10 mm is en-bloc cold snare polypectomy (194). For diminutive polyps, a randomised controlled trial of 117 eligible polyps showed cold snare polypectomy provides improved complete resection rate versus cold biopsy forceps (93.2% v 75.9%, p=0.009). In addition, procedure time was shorter with cold snare polypectomy than cold forceps polypectomy (14.3 v 22.0 seconds, p<0.001) (195).

For some diminutive polyps, polypectomy may be difficult due to technical reasons. The guidelines recognise this and suggest cold forceps polypectomy as a second-line option only for technically difficult polyps ≤3 mm in size. Use of cold forceps for polyps >4mm increases the risk of incomplete resection.

In the scenario of an advanced polyp undergoing a "resect and discard" strategy where cold snare polypectomy is used, there is high likelihood of complete eradication of the potential risk.

### d How does a "resect and discard" strategy improve efficiency?

A "resect and discard" strategy would significantly reduce burden on pathology services with major cost and time savings (see Chapter 11). Polyps that are not retrieved would also be accurately diagnosed. In addition, a 'diagnose and leave' strategy, reduces unnecessary polypectomy and the associated risk – around a third of polypectomies are hyperplastic/non-neoplastic polyps without malignant potential.

### e What are the requirements before optical diagnosis can be implemented?

Although several gastroenterology societies have endorsed a "resect and discard" approach there are several caveats to this endorsement (94,181,196,197). ESGE, for instance advises it can be used for ≤5 mm polyps only by experienced and adequately

trained endoscopists who are audited, and should be 'reported using a validated scale', with adequate photodocumentation (164).

#### f What we already known about the learning curve for OD?

Studies have shown >90% OD accuracy can be achieved in expert hands (198,199). In addition, the learning curve for NBI appears to be short for achievement of a high level of OD accuracy (200–203).

A curriculum for OD has recently been published by ESGE including assessment of diminutive polyps (204). The suggested framework is assessment of 'at least 120 lesions prospectively with histological feedback'. The threshold for competence should be 'internationally endorsed competence thresholds' which are met in at least '60 prospectively assessed diminutive colorectal lesions'. This curriculum helps provide a framework for achievement of OD competence but the evidence for the exact figures recommended is limited.

#### g How does DISCARD3 differ from earlier studies?

The DISCARD study assessed OD in a small group of expert and non-expert endoscopists within a tertiary centre setting (2 experts, 1 trainee, 1 specialist nurse) (198). The DISCARD2 study was a wider assessment of OD within a general hospital setting involving a broad range of experience (28 colonoscopies from 5 hospitals) (205). DISCARD3 is different as all endoscopists are accredited BCSP colonoscopists and are therefore highly experienced operators performing colonoscopies in a polyp-enriched (FIT positive) patient group.

#### h Knowledge gap

Quality assurance of a "resect and discard" strategy has not previously been assessed. There are also conflicting findings from previous studies about patient acceptability. The causes of optical diagnosis error have had limited exploration in the literature (see Chapter 10). Finally, the economic and environmental impact of a "resect and discard" strategy requires further evaluation (see Chapter 11). The DISCARD3 study addresses these gaps in our understanding of OD.

### 9.1.2 Aims

1. Assess feasibility of OD, with a “resect and discard” strategy, in a bowel cancer screening setting
2. Understand OD learning curve and performance over time
3. Determine OD-histology surveillance interval concordance
4. Create an evidence-based quality assurance process for OD
5. Assess patient acceptability of OD

# 9.2 Methods

## 9.2.1 Study design

### a Overview

This prospective feasibility study involved all 8 accredited BCSP colonoscopists in a bowel cancer screening unit (screening population of 1.1 million) during Feb 2020 to Nov 2021. BCSP endoscopist accreditation is rigorous involving written and practical assessments. In addition, strict prospective monitoring of key performance indicators (KPIs) ensures standards post-accreditation remain high. Participating endoscopists had personal experience of performing >2000 colonoscopies and had used NBI during colonoscopy since March 2012 when it became available in the endoscopy unit.

During the pre-study, all endoscopists completed a validated training module (206). This involved a presentation covering the clinical significance of colorectal polyps, principles of NBI, micro-vessel visualisation and differentiation of adenomas/serrated polyps with feedback. In addition, each endoscopist completed a training test module pre and post presentation which involved review of 30 NBI polyp photos. Once training had completed, endoscopists commenced the study with supervised OD performed during colonoscopy until 120 high confidence diminutive polyp diagnoses had been made. During the supervised OD phase additional training and feedback was provided as part of a comprehensive quality assurance process (see Figure 35).

Patients eligible for the BCSP in the UK were invited to participate:

- Age 60-74 with a positive faecal immunochemical test (FIT) test (≥120 µg Hb/g faeces).
- Surveillance colonoscopy

Patients whose risk profile for follow up was outside the BCSP (eg. family history), patients with IBD, pregnancy and those unable to consent were excluded. All participating patients provided informed written consent.

### b Design

High definition colonoscopes with NBI functionality were used. All <10 mm polyps were included except ≤ 5mm rectal hyperplastic polyps which were left in situ.

For each eligible polyp identified, the following parameters were recorded in real-time prior to resection:

- Site
- Size (biopsy forceps or snare was used for reference)
- Paris classification
- OD (adenoma, serrated, inflammatory, cancer, other)
- Confidence level (high or low) – high confidence was defined based on the PIVI definition where 'clinical judgment can be used [when] deciding whether the histology of a given polyp can be assessed accurately using an endoscopic technology' (94). In practice, we advised ≥90% diagnostic confidence for a 'high confidence' OD to be made.

All eligible polyps were photodocumented with white light and NBI. All resected polyps were sent to histopathology in separate pots, were fixed in formalin and processed to paraffin wax using standard laboratory protocol. Tissue sections of 2 µm thickness were stained with haematoxylin and eosin (H&E) staining. At first, each polyp had 3 tissue sections prepared with a distance of between 10-30 µm between consecutive sections. As part of the root cause analysis (detailed below) up to three further 2 µm sections were prepared at similar intervals for some polyps.

The specimens were reported according to World Health Organisation (WHO) guidelines by histopathologists who were blinded to the original OD.

Ethics approval was obtained for the study protocol (9/10/19; 19/EE/0234).

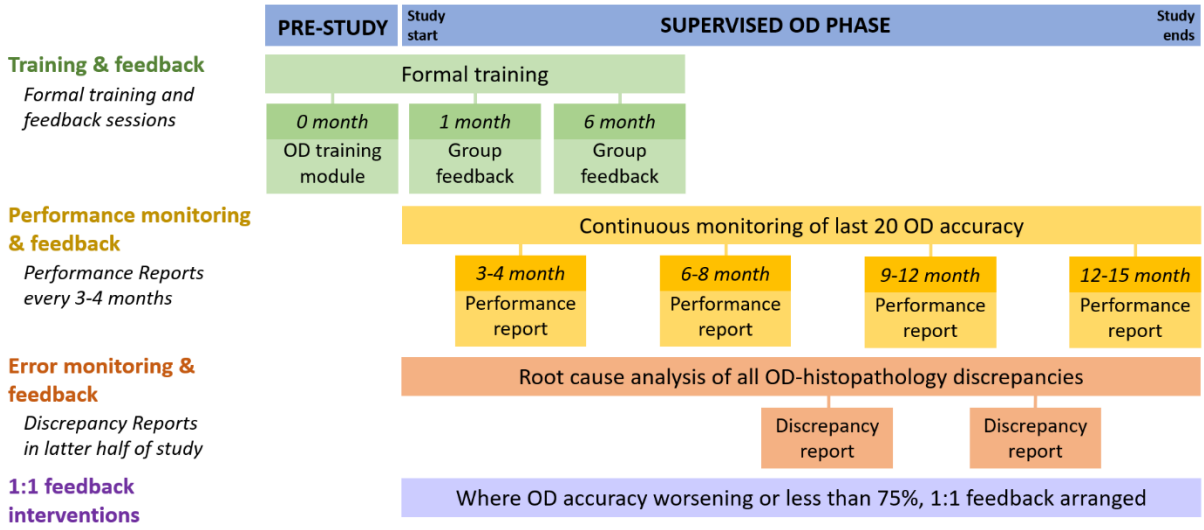
### c Learning curve

Endoscopists were provided with performance feedback (accuracy of their last 20 optical diagnoses) and OD-histopathology discrepancy reports (including detailed feedback on why error may have occurred). In addition, dedicated training sessions were provided to feedback and share key learning points to help endoscopists build on their OD competence.

### d Quality assurance

The key steps taken to quality assure OD in this study are summarised in Figure 35.

Figure 35 Study quality assurance process




In the supervised OD phase, there was continuous monitoring of OD performance for each endoscopist whereby the last 20 optical diagnoses were evaluated using a cumulative sum control chart (CUSUM) approach (207,208). Group training sessions were provided to all endoscopists after 1 and 6 months of supervised OD. These provided targeted feedback on areas where OD accuracy could be improved including photodocumentation quality, NICE criteria application, and appropriate confidence level

assignment. Endoscopists were provided with 3-4 monthly individual performance data reports showing accuracy of the last 20 high confidence diagnoses and all high confidence diagnoses to that point.

In the latter half of the study, histopathology discrepancy reports were provided detailing all cases where high confidence OD did not match the histology. These reported the individual endoscopist's errors and all other errors were provided anonymously for educational purposes. Each error was documented in the report with the white light and NBI photos as well as an explanation of the likely cause of error based on NICE criteria application and photodocumentation quality. In addition, 1:1 feedback was provided where OD accuracy was worsening or fell below 75% accuracy.

A root cause analysis of all cases of high confidence OD-histopathology diagnosis discordance was performed. Firstly, a second blinded histopathology review was undertaken. If discordance persisted, additional tissue section cuts were performed to 6 levels. If discordance still persisted, and in cases of high confidence adenoma OD, additional tissue section cuts were performed to 12 levels. If despite this, discordance remained an issue, a blinded review of white light and NBI photos by an expert endoscopist was performed with photodocumentation classified as adequate or inadequate.

The most likely cause of OD error was then categorised as:

- NICE mismatch – NICE criteria cannot be fully applied as not all polyp features fit eg. NICE type 1 colour but NICE type 2 vascular pattern.
- NICE not applied – the endoscopist does not appear to have applied the NICE criteria to the OD.
- Inadequate photodocumentation – photo quality is insufficient to give a high confidence diagnosis due to an unclean polyp surface, incomplete polyp view or out of focus polyp.
- Likely pathology error – the error is likely due to pathology as there is high confidence that the original OD was correct after review of photodocumentation.

## e Surveillance intervals

Surveillance intervals were determined using BSG, ESGE and US multi-society task force guidelines (197,209,210). The algorithms shown in Figure 36, Figure 37 and Figure 38 show where a surveillance interval can be assigned without histology, where surveillance intervals are dependent on histology and how OD surveillance intervals are determined (as well as the assumptions made in these cases).

Figure 36 Surveillance interval algorithms based on BSG guidelines

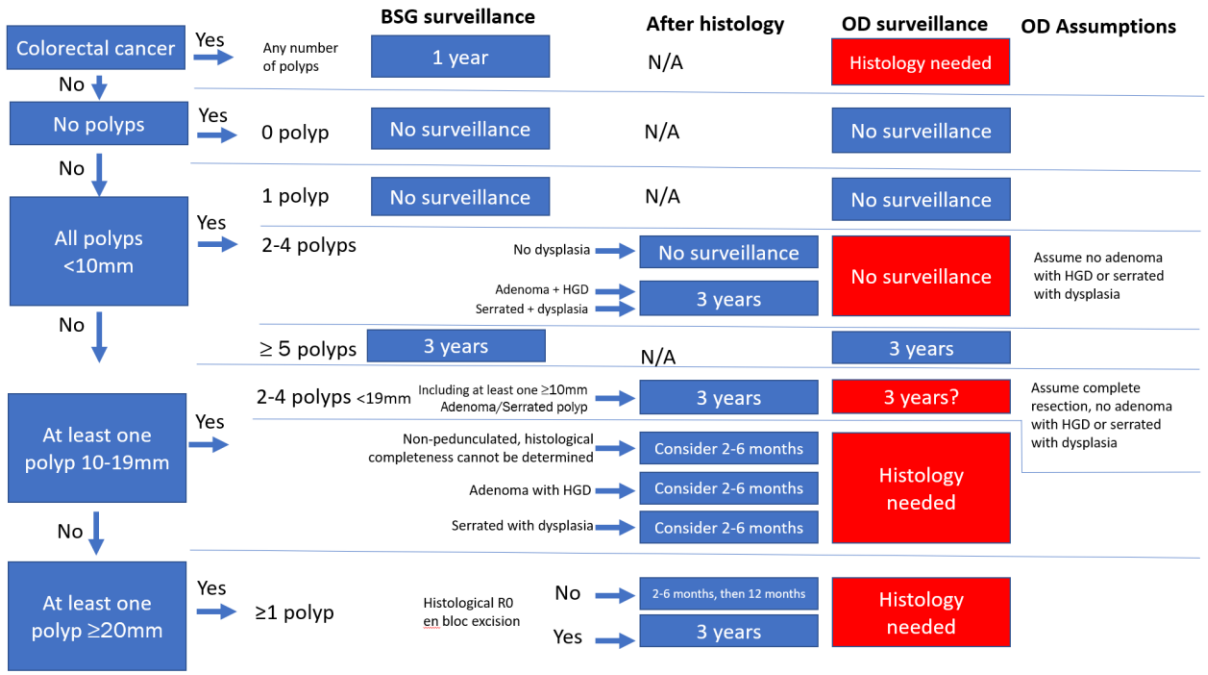



Figure 37 Surveillance interval algorithms based on ESGE guidelines

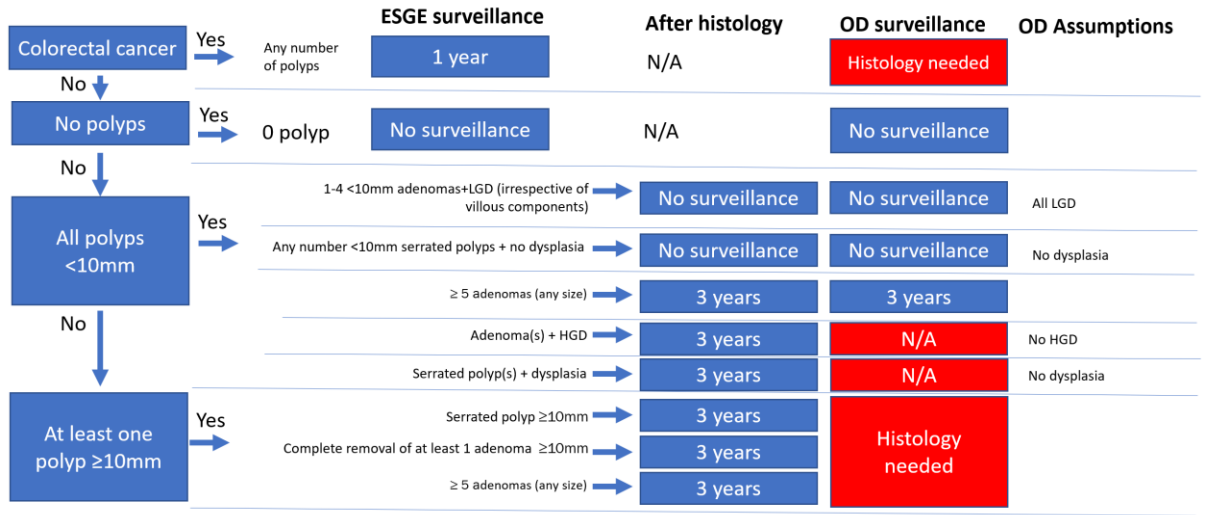
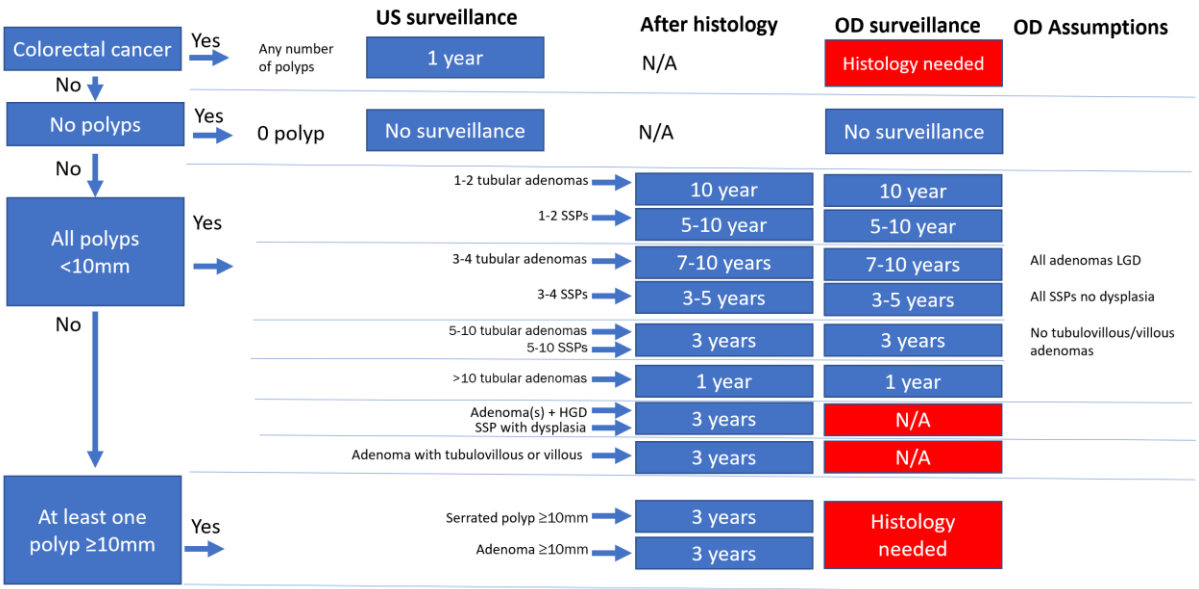


Figure 38 Surveillance interval algorithms based on US Multi-society taskforce guidelines




Histology-derived surveillance intervals were determined based on histopathology results for all polyps in each case. OD-derived surveillance intervals were determined for all cases where only polyp(s) <10 mm were found using two different OD approaches:

1. ≤5 mm OD – all high confidence ≤5 mm polyp optical diagnoses were included in the surveillance interval polyp dataset and histology results for the remaining polyps (low confidence ≤5 mm polyp optical diagnoses and all polyps 6-9 mm in size).
2. <10 mm OD – all high confidence <10 mm polyp optical diagnoses were included in the surveillance interval polyp dataset and histology results for the remaining polyps (low confidence <10 mm polyp optical diagnoses).

For the purpose of OD surveillance interval determination, serrated polyps were considered an overarching group including all subtypes. OD-histology surveillance interval discordance was defined as any case where OD-derived surveillance intervals were longer than histology-derived surveillance intervals. The remaining cases (i.e. OD-derived surveillance interval same or shorter) were classified as concordance.

#### f Patient perspective

To better understand the patient perspective of OD, we invited all patients to complete a post-colonoscopy questionnaire (see 16.2.8). A structured focus group was also held with four patients via Zoom to gain a deeper insight into patient perspectives of OD.

### 9.2.2 Outcomes

#### a Primary outcomes

- Determine OD learning curve
- OD-histology surveillance interval concordance

#### b Secondary outcomes

- Determine OD accuracy
- Analyse OD error causation
- Evaluate patient acceptability

### 9.2.3 Statistical analysis

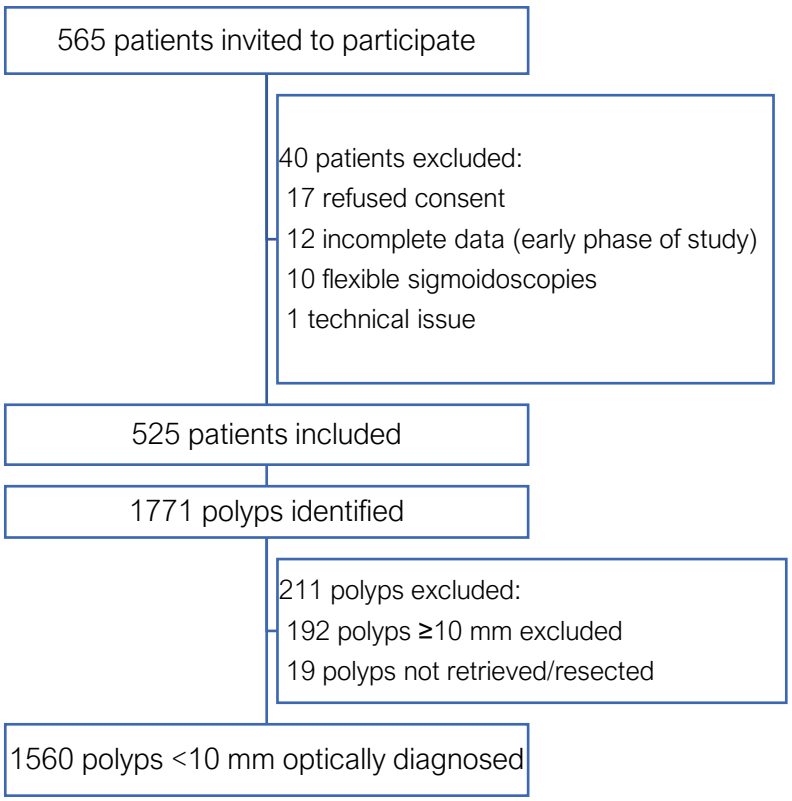
In this feasibility study, a cumulative sum control chart (CUSUM) approach was used to evaluate OD learning curve. This involved a running calculation of the last 20 high confidence ODs over time. No power calculation was required. The study was registered on ClinicalTrials.gov (NCT04710693).

## 9.3 Results

### 9.3.1 Overview

565 patients were invited to take part in this study of which 525 were included (see Figure 39). There were 1771 polyps identified (all sizes) of which 1752 were resected and retrieved. There were 1560 <10 mm polyps, 1329 ≤5 mm and 231 6-9 mm, optically diagnosed.

Figure 39 Flow diagram of patient enrolment




## 9.3.2 Optical diagnosis accuracy

Of all <10 mm polyps that were optically diagnosed, 74.9% (1169/1560) were high confidence diagnoses and 25.1% (391/1560) were low confidence diagnoses (see Table 19). A higher proportion of high confidence diagnoses were made for 6-9 mm polyps (90.5%, 209/231) compared with ≤5 mm polyps (72.2%, 960/1329).

Table 19 OD confidence level assignment and accuracy, diminutive and small polyps

| | 1-5 mm | 6-9 mm | Overall (1-9 mm) |
|---|---|---|---|
| **Optical diagnoses** | 1329 | 231 | 1560 |
| **High confidence** | 72.2% (960/1329) | 90.5% (209/231) | 74.9% (1169/1560) |
| **Low confidence** | 27.8% (369/1329) | 9.5% (22/231) | 25.1% (391/1560) |
| **Performance (correct high confidence OD)** | 86.3% (828/960) | 93.3% (195/209) | 87.5% 1023/1169 |

Overall, 87.5% of <10 mm polyp diagnoses were accurate; correct diagnoses for ≤5 mm and 6-9 mm polyps were 86.3% and 93.3% respectively (see Table 19). The sensitivity for OD of ≤5 mm adenomas was 93.0% and the PPV was 90.8% (see Table 20).

Table 20 OD performance for <10 mm adenoma and serrated polyp assessment (based on final histology result)

| Polyp type | Size | Accuracy (%) | Sensitivity (%) | Specificity (%) | PPV (%) | NPV (%) |
|---|---|---|---|---|---|---|
| **Adenoma** | ≤5 mm | 88.0 | 93.0 | 74.2 | 90.8 | 79.5 |
| | 6-9 mm | 91.7 | 91.8 | 90.9 | 98.2 | 66.7 |
| | Overall | 88.5 | 92.9 | 75.5 | 91.9 | 78.1 |
| **Serrated** | ≤5 mm | 88.9 | 80.2 | 91.4 | 73.1 | 94.1 |
| | 6-9 mm | 92.4 | 95.2 | 91.9 | 66.7 | 99.1 |
| | Overall | 89.3 | 81.5 | 91.5 | 72.4 | 94.7 |

## 9.3.3 Optical diagnosis learning curve

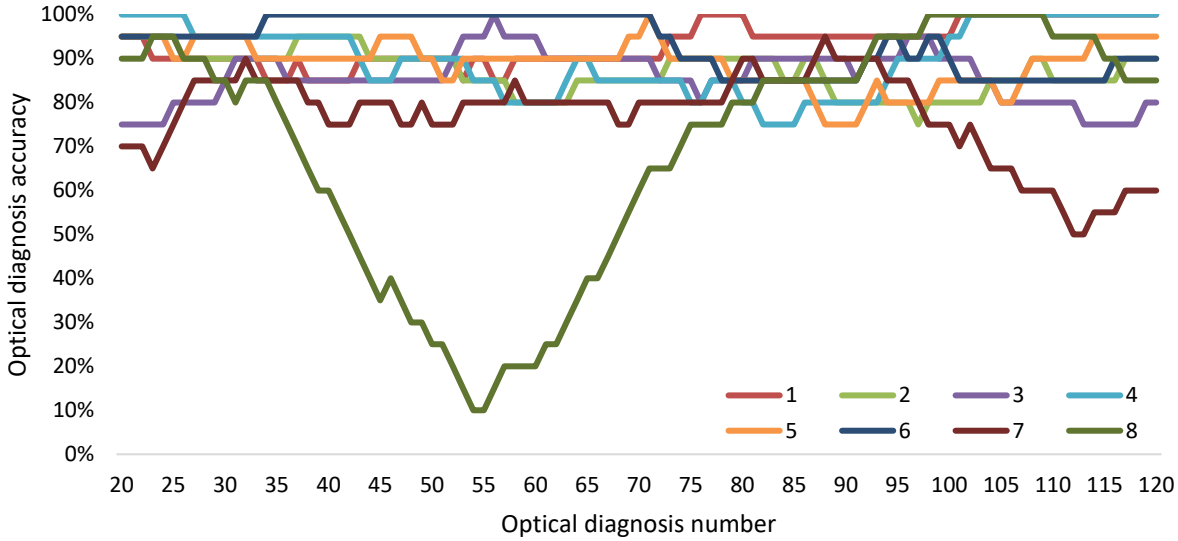
### a Performance of all endoscopists

The learning curve varied between endoscopists (see Figure 40). 6/8 endoscopists performed high confidence OD with ≥75% accuracy throughout the entire study period. In Q1, ≤5 mm OD accuracy was 85.8% (range 70-93%). There was a drop in overall accuracy in Q2, as endoscopist 8 showed falling OD accuracy performance until OD 56. Q3 and Q4 accuracies were 84.2% and 86.7% respectively.

Overall accuracy for the first 120 high confidence ≤5 mm optical diagnoses was 81.5% when assessed against the original histology result. When assessed against the final

histology, after deeper levels were performed, overall accuracy rose to 86.3%. After OD 75, 7/8 endoscopists performed OD with an accuracy ≥75%.

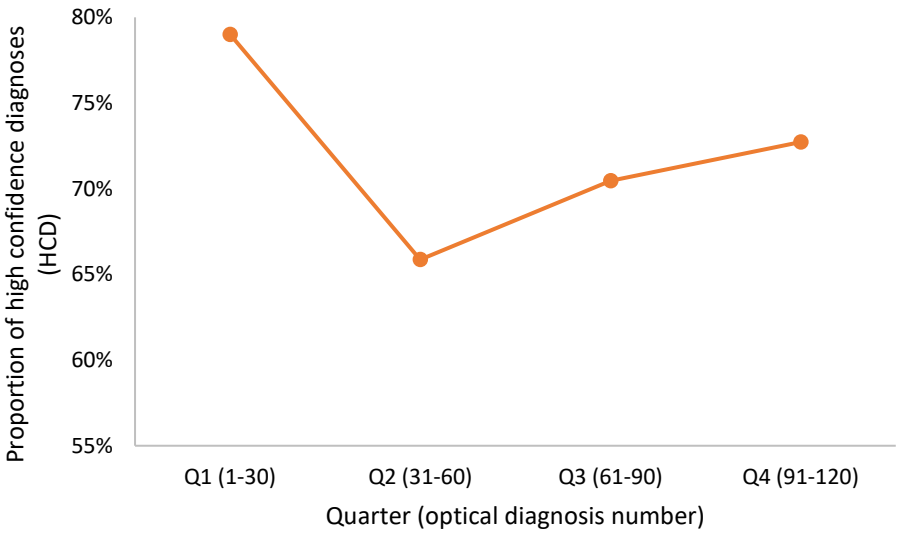
Figure 40 OD learning curve for diminutive polyps by colonoscopist




### b Change in confidence level assignment over time

Overall, the highest proportion of high confidence diagnoses was in Q1 at 80.5% (see Figure 41). In Q2, this dropped to 66.3% and subsequently rose to 74.5% (Q3) and 72.2% (Q4).

Figure 41 Mean proportion of high confidence diagnoses made for diminutive polyps across all endoscopists over time




## 9.3.4 Surveillance intervals

### a OD-histology surveillance interval concordance

Of 525 cases, surveillance intervals were determined for 354 cases (after excluding 36 cases with colorectal cancer and a further 135 cases with at least one >10 mm polyp). 85/354 (24.0%) cases had no polyps and 40/354 (11.3%) cases had only low confidence diagnoses. The remaining 229/354 (64.7%) cases had only high confidence diagnoses (116/229, 50.7%) or mixed high and low confidence diagnoses (113/229, 49.3%).

When using a ≤5 mm OD approach, OD-histology surveillance interval concordance was 98.7% (226/229), 98.3% (225/229) and 91.3% (209/227) for BSG, ESGE, and US multi-society task force guidelines respectively (see Table 21). With a <10 mm OD approach, OD-histology surveillance interval concordance exceeded the 90% PIVI threshold with BSG and ESGE guidelines but not US guidelines.

Table 21 OD-histology surveillance interval concordance on a per-patient basis

| Optical diagnosis approach | Surveillance interval concordance | | |
|---|---|---|---|
| | BSG | ESGE | US |
| ≤5 mm OD | **98.7%** (226/229) | **98.3%** (225/229) | **91.3%** (209/229) |
| <10 mm OD | **98.7%** (226/229) | **97.8%** (224/229) | **84.3%** (193/229) |

### b Occurrence of high risk lesions in small polyps

Amongst the 354 cases where surveillance intervals were evaluated there were 920 polyps identified. High risk polyps from this group are shown in Table 22.

Table 22 Occurrence of high risk lesions in diminutive and small polyps

| Polyp size | 1-5 mm | 6-9 mm | Overall (1-9 mm) |
|---|---|---|---|
| **Total polyps** | 810 | 110 | 920 |
| **Adenoma with villous components** | 3.8% (31/810) | 21.8% (24/110) | 6.0% (55/920) |
| **Adenoma with HGD** | 0.1% (1/810) | 1.8% (2/110) | 0.3% (3/920) |
| **Serrated polyp with dysplasia** | 0.5% (4/810) | 1.8% (2/110) | 0.7% (6/920) |
| **Cancer** | 0.0% (0/810) | 0.0% (0/110) | 0.0% (0/920) |

## 9.3.5 Polyp diagnosis error

### a Root cause analysis of histology-OD discrepancy

In total, 1169 <10 mm optical diagnoses were made with high confidence. Of these, discordance with histopathology occurred in 15.7% (184/1169) of cases (see Figure 42). Discordance was more common in ≤5 mm polyps occurring in 17.7% (170/960) of cases compared with 6-9 mm polyps where it occurred in 6.7% (14/209) of cases.

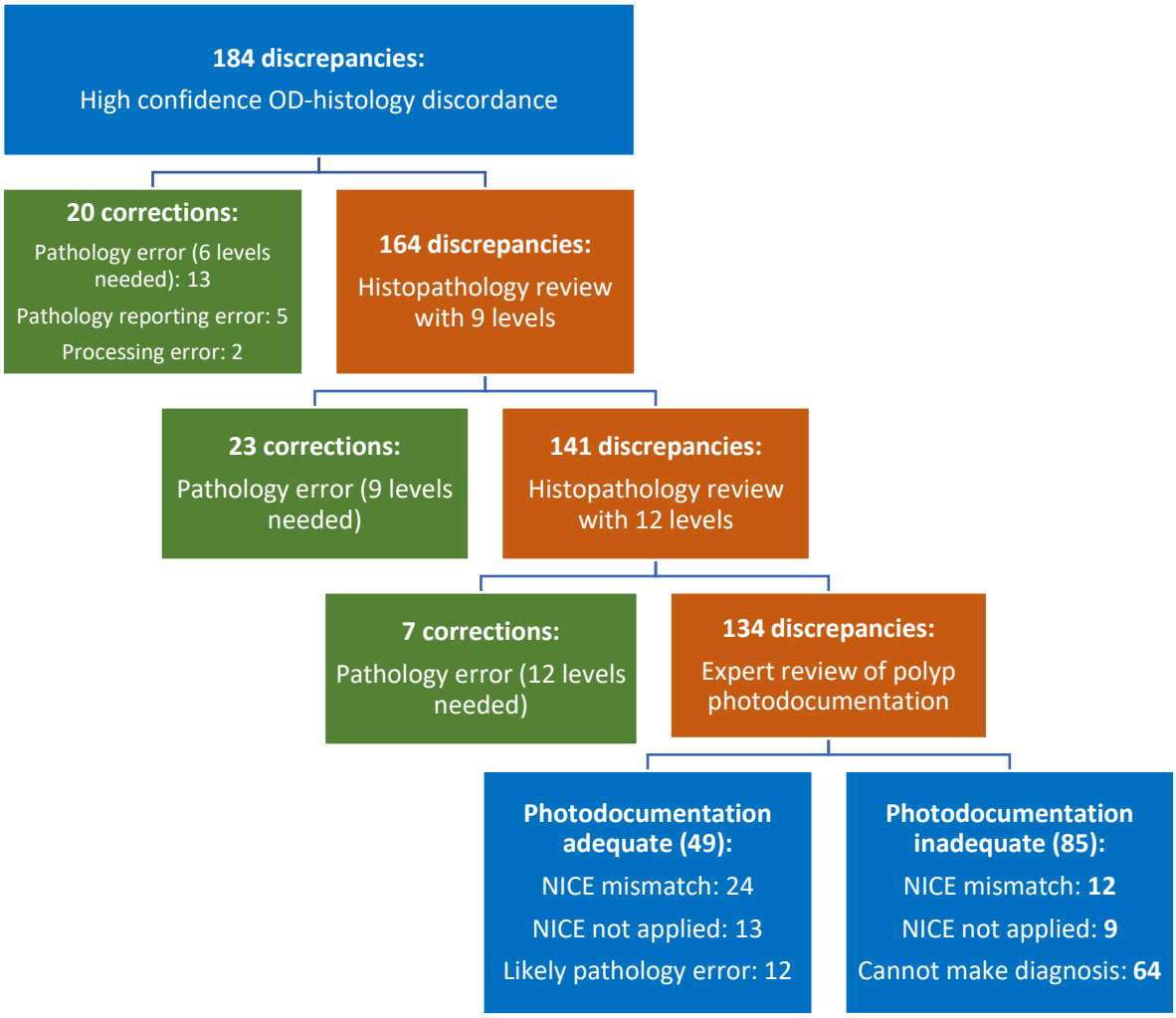
After first review of all 184 <10 mm polyp discrepancies, 20 cases were found to be due to histopathology reporting or processing error which resolved the error. In the remaining 164 discrepancies, a series of deeper histology level reviews were performed with 23 errors found at 9 levels and 7 errors at 12 levels. After analysing 12 levels,

there remained 134 discrepancies which underwent a detailed expert review of polyp photodocumentation.

Expert photodocumentation review of cases with persistent discrepancy despite histopathology reviews (72.8%, 134/184) revealed this was adequate in 36.6% (49/134) and inadequate in 63.4% (85/134) of cases. High confidence OD error was assessed to have occurred due to a NICE mismatch (26.9%, 36/134), NICE not being applied (16.4%, 22/134), or inadequate photodocumentation (47.8%, 64/134). In cases where NICE was not applied, although endoscopists had used the criteria, on retrospective review it was believed that NICE appearances were misinterpreted. Even after the photodocumentation review process 9.0% (12/134) of cases were still believed to be a result of pathology error as high quality photos showed, for example, clear NICE features of adenomas or serrated polyps, but histology reported normal mucosa.

At the end of the histology and photodocumentation review process, 33.7% (62/184) of high confidence OD-histology discordance was attributed to histopathology (20 at first review, 23 at second review, 7 at third review, and 12 at photodocumentation review). The remaining cases were endoscopy-related (66.6%, 122/184) due to a NICE mismatch (19.6%, 36/184) or endoscopist error (46.7%, 86/184).

Figure 42 Root cause analysis of high confidence OD – histopathology discordance




### b Classification of significant errors

Endoscopist error was most frequently responsible for high confidence OD-histology discrepancy (72.3%, 133/184) followed by pathology error (27.2%, 50/184). In cases of pathology error, 86.0% (43/50) corrected with deeper levels; and the remaining 14.3% (7/49) cases, due to observer/laboratory error, corrected on second review.

Table 23 Classification of significant OD errors

| Error Type | Optical Diagnosis | Histology result | Error Frequency |
|---|---|---|---|
| A | Adenoma | Serrated | 45/184 (24.4%) |
| B | Serrated | Adenoma | 55/184 (29.9%) |
| C | Adenoma | Normal | 19/184 (10.3%) |
| D | Serrated | Normal | 14/184 (7.6%) |
| E | Pathology error – observer/laboratory error | | 7/184 (3.8%) |
| F | Pathology error – deeper levels required<br>6 levels needed<br>9 levels needed<br>12 levels needed | | 43/184 (23.4%)<br>*13/184 (7.1%)*<br>*23/184 (12.5%)*<br>*7/184 (3.8%)* |
| G | Other | | 1/184 (0.5%) |

## 9.3.6 Patient perspective

### a Patient survey

445/525 (84.8%) of patients, who underwent a colonoscopy where OD was performed, completed the post-colonoscopy questionnaire (see 16.2.8). The vast majority of patients were satisfied (98.7%, 439/445) and found their procedure comfortable (86.5%, 385/445). Most patients expressed that they would be happy for polyps identified during colonoscopy to be assessed in real-time (82.5%, 367/445) and also to be given a surveillance interval immediately after the procedure (68.7%, 306/445). 88.5% (394/445) of patients felt confident in the ability of the endoscopist to diagnose polyps accurately without laboratory analysis.

### b Patient focus group

A focus group was held at St Mark's Hospital via Zoom in December 2020 involving 4 patients. The focus group was structured to allow exploration of the following questions (summarised responses are shown following each question):

1. How do you feel about the "resect and discard" approach to diagnosing and managing polyps?

- 'The diagnosis would be quicker'
- How accurate is optical diagnosis compared with histology?
- 'Where does the legal liability lie with [the cases] that are not accurate? Would it move from pathology to the endoscopist?'

- ‘I feel happy with this as it’s the same as a GP diagnosing rashes or spots on the skin’

2. Is there anything that would be important for you, as a patient to know before, during or after a colonoscopy using this approach?

- What is the international standard?
- Provide additional information to explain that polyps would not go to the histology lab and what instead happens during and after the procedure
- Ensure patients understand which polyp size the “resect and discard” approach would apply to (i.e. only diminutive polyps would be removed)

3. Do you have any concerns about the “resect and discard” approach?

- Would a professional statistician be involved?
- No concerns at all apart from advising the patient what you are doing during and after the procedure
- Could the approach be used by people that it is not intended to be used by?
- What is the experience level of endoscopists performing the colonoscopies?

4. What do you think would be the benefits of the “resect and discard” approach?

- Speed
- Provides another level of assurance
- Good training process for endoscopists

5. Would you be happy for the “resect and discard” approach to be used in clinical practice?

- Yes (all participants)
- A comment about how giving the results immediately reduces anxiety
- ‘I think it’s positive all round’

6. What are your thoughts on the role of emerging technologies (such as artificial intelligence) for diagnosis of polyps during colonoscopy?

- ‘No-brainer, use it’
- ‘If it’s beneficial for medical staff and the patient then go ahead’
- Useful add on which does not fatigue
- False positives may be an issue

- 'AI is good at helping the driver but the driver has to make the decision ultimately. Anything that helps the driver make better decisions is welcome.'
- It's about the algorithm – depends on how good the algorithm is

The key recommendation from the focus group was that patients should be informed about the "resect and discard" strategy and what to expect before the procedure as it is a different approach. However, there was unanimous support from all participants that they would be happy for the approach to be used in clinical practice.

# 9.4 Discussion

## 9.4.1 Key findings

### a Variable but mostly consistent OD learning curve

In this study, OD was performed by 8 accredited BCSP endoscopists with excellent KPIs who had also undertaken OD training. There was no significant disruption to the routine of the procedure with all endoscopists able to provide real-time optical diagnoses. OD accuracy after the first 20 optical diagnoses was 70-100% reflecting the skill level and education provided. The learning curve for consistently performing at ≥75% OD accuracy was short with 7/8 endoscopists maintaining this after 75 high confidence optical diagnoses.

OD accuracy monitoring is particularly useful to monitor OD performance and to assess when training interventions are required. Although there is not currently an OD accuracy threshold required for OD implementation, we found at 75% accuracy the PIVI-1 criteria (≥90% surveillance interval agreement) are met for US, ESGE and BSG guidelines. This threshold is supported by modelling studies which show, in FIT-positive patients, that PIVI-1 criteria can be achieved with ≥ 40% accuracy when using ESGE guidelines and ≥77% accuracy with US guidelines (211).

### b High confidence OD is possible in ~75% of cases using NICE criteria

High confidence OD assignment was greatest in Q1 and plateaued to a lower level in later quarters. This may reflect over-confidence in OD after the pre-study training which then adjusted after feedback and training provided at the 1 month training session. In

addition, the plateau level of around 75% may reflect that the NICE criteria has limitations and cannot always give a high confidence diagnosis.

### c Even operators with high initial OD performance required a period of supervised OD

The supervised OD period allows familiarity for all endoscopists in how to perform OD and provides an opportunity for high quality photodocumentation competence to be demonstrated. This is important as in a "resect and discard" strategy the sole record of the polyp is the photodocumentation.

Two endoscopists in particular showed worsening performance during the supervised OD phase. Endoscopist 8 had worsening performance in the initial phase of the study which improved with training. Endoscopist 7 had a fall in OD performance in the final 20 optical diagnoses. This fluctuation in performance most likely reflects the impact of human and environmental factors; to our knowledge, there were no clinical/equipment issues (212). This highlights the importance of a continuous quality assurance process for all endoscopists regardless of their initial performance level.

Based on this study, we would recommend 120 high confidence diagnoses are performed during supervised OD which exceeds the requirement of the ESGE OD curriculum which specifies 'at least 120 diminutive colorectal lesions' of any confidence level be assessed 'prospectively with histological feedback' (204).

We found 145-201 diminutive polyp diagnoses were required to make 120 high confidence diminutive polyp diagnoses. This was achievable, on average in 351 days (range 224-531 days) even in the context of the Covid-19 pandemic. In the post-pandemic period we expect it would take a significantly shorter period and that OD with a "resect and discard" strategy could be fully implemented within a year. This is consistent with the ESGE suggestion that 'at least 120 diminutive colorectal lesions' should be assessed 'within 1 year' to maintain competence.

### d Photodocumentation is a fundamental aspect of OD training

We identified photodocumentation as an area of performance weakness in the early phase of the study. Additional training was provided using the '3C Photo Quality

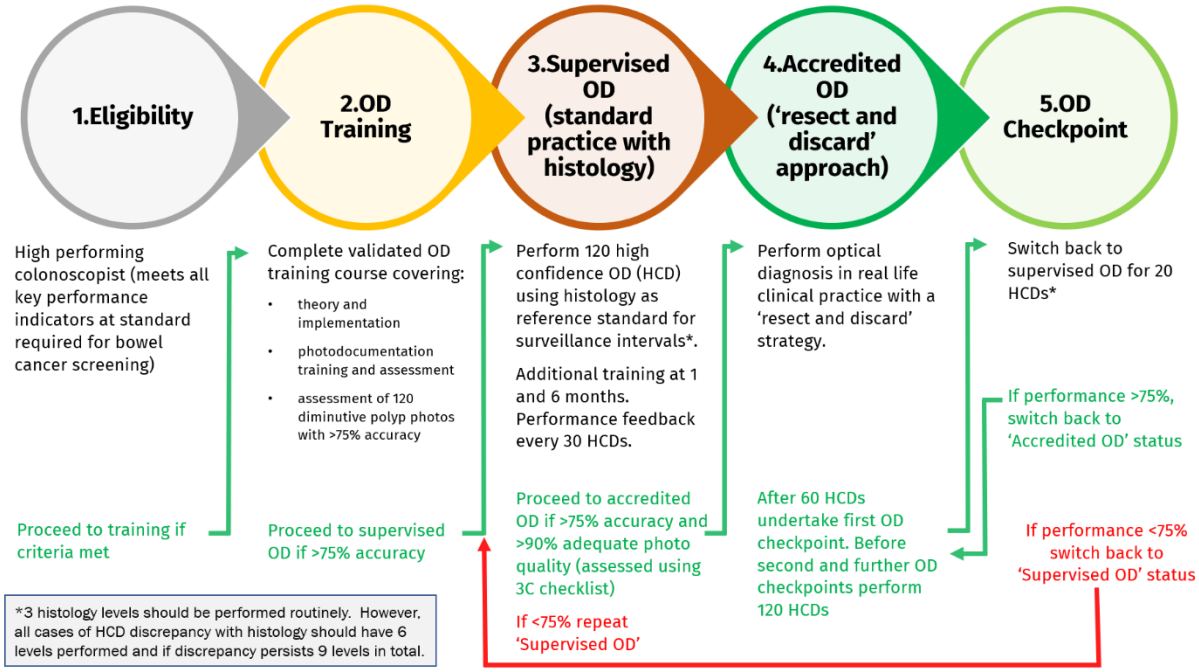
Checklist' (see Table 18) to provide guidance on high quality photodocumentation of polyps which we suggest should be achieved in >90% of all polyps (173).

### e Proposed quality assurance process

We believe a quality assurance process will help provide the reassurance that OD with a "resect and discard" strategy for small polyps can be implemented safely (see Figure 43).

This process should be overseen by a new role of 'Optical Diagnosis Champion' which could be assigned to one or more members of the clinical team to oversee and monitor the quality assurance process.

Figure 43 Continuous quality assurance process for OD with "resect and discard" strategy for <10 mm colonic polyps




The quality assurance process for OD is as follows:

- **Phase 1 (Eligibility):** colonoscopists enrolling meet KPIs required for high quality colonoscopy (25).
- **Phase 2 (OD training):** completion of a validated OD training module.

- **Phase 3 (Supervised OD):** 120 high confidence optical diagnoses are supervised with additional training sessions at 1 and 6 months as well as performance reports after every 30 high confidence diagnoses. In addition, histopathology discrepancy reports analysing all cases of high confidence OD-histology discordance should be provided where discordance is >16% as we found discordance occurred in 15.7% of high confidence diagnoses.
- **Phase 4 (Accredited OD):** 60 high confidence diagnoses are suggested on an arbitrary basis prior to the first OD checkpoint and then 120 high confidence diagnoses prior to subsequent checkpoints.
- **Phase 5 (OD Checkpoint):** 20 supervised ODs are performed as we feel this figure balances the level of uncertainty with a need for poor performance to be identified and is also sustainable over the long term.

We recommend the quality assurance process if applied flexibly across units taking into consideration individual experience and performance. A unit with less OD experience, for example, may wish to perform OD checkpoints after every 60 polyps for more than one occasion before extending this interval to 120.

### f Histopathology error is a significant cause of 'OD' error

Histology is traditionally seen as the 'gold standard' for diagnosis of polyp specimens. Our data show as many as 15.7% (184/1169) of high confidence optical diagnoses did not match the original histology result. In 23.4% (43/184) of cases discordance corrected when additional deeper levels of specimens were analysed suggesting that a proportion of OD error is in fact due to systemic limitations of histopathology processing.

After analysing 12 levels, discordance persisted in 72.8% (134/184) of cases which then underwent expert endoscopist review of photodocumentation. High confidence OD error was most commonly attributed to inadequate photodocumentation (47.8%, 64/134), NICE mismatch (26.9%, 36/134), or NICE not being correctly applied (16.4%, 22/134). In the latter group, endoscopists had used the criteria but appeared to have misinterpreted the appearances on retrospective review.

Although photodocumentation was inadequate in 63.4% (85/134) of cases, OD was still possible in 21/134 of cases. Upon completion of the review process, in 9.0% (12/134) of cases it was still felt pathology error was responsible for the incorrect OD as endoscopic photos, for example, showed a classic adenoma that met all three NICE criteria. Overall, histopathology was responsible for 33.7% (62/184) of 'OD' errors.

Other studies have also highlighted limitations of histology for diminutive polyp assessment and challenged its position as the gold standard (213,214). Histopathology protocol between units might influence the level of OD accuracy determined for endoscopists. Standardisation of process between units would help ensure accurate and comparable determination of OD accuracy between centres. We would therefore recommend 3 levels are performed as standard during the supervised OD and OD checkpoint phases. However, where after 3 levels there is high confidence OD-histology discordance, a total of 6 levels should be performed and where discordance persists a total of 9 levels is recommended.

### g OD derived surveillance intervals meet the PIVI criteria

Although a level of OD accuracy is clearly desirable for a "resect and discard" strategy, the critical endpoint is OD-histology surveillance interval concordance to reduce the long term risk of cancer. When using a ≤5 mm polyp OD approach, high confidence OD accuracy was 86.3% compared with final histology (81.5% with original histology) and surveillance interval concordance was ≥90% when US, ESGE and BSG guidelines were applied (197,209,215). When using a <10 mm polyp OD approach, surveillance interval concordance was ≥90% only for ESGE and BSG but not US guidelines.

This finding highlights the major difference in the US guidelines which place greater emphasis on histology. It is therefore not unexpected that OD becomes less accurate with the US guidelines where 6-9 mm polyps are included as the rate of villous change and high grade dysplasia increases. In contrast, when using the ≤5 mm polyp OD approach, advanced histology occurs so infrequently that the PIVI threshold is achieved for all three guidelines.

In this study we considered an OD surveillance interval that was the same or shorter than the histology-derived surveillance interval as concordance as this level of

surveillance is at least as intensive as a traditional histology approach. A risk of using an OD approach is that it might result in shorter surveillance intervals than necessary. However, OD surveillance intervals, for a <10 mm OD approach, were shorter in only 3/229, 3/229, and 9/229 cases for BSG, ESGE and US guidelines respectively. When using a ≤5 mm polyp OD approach, the respective figures are 3/229, 2/229 and 9/229. Overall, only 0.9-3.9% of surveillance intervals were shorter than histology derived surveillance intervals.

h Patients are mostly supportive of optical diagnosis approach

All patients were invited to participate in a post-procedure questionnaire and a small group took part in a focus group. 98.7% (439/445) were satisfied with their procedure and supported an OD approach. 82.5% (367/445) accepted immediate OD for small polyps during the procedure. Patient focus group feedback was consistent with this. In addition, patients reported that they would like additional information about a "resect and discard" strategy to be provided in the information leaflet. This would explain that OD would be the primary diagnostic strategy for small polyps where the endoscopist had completed the required training and accreditation.

## 9.4.2 Comparison with previous studies

Although the original DISCARD study showed OD performed by experts and non-experts could achieve a high level of surveillance interval concordance, accuracy was highest among experts (198). The later DISCARD2 study, showed in a non-academic setting where OD was performed by endoscopists with a range of experience OD accuracy was not at a level where a "resect and discard" strategy could be recommended in routine practice (205,216).

In DISCARD3, we focussed on OD performance by a group of accredited BCSP endoscopists in a polyp-enriched patient group. We also ensured quality assurance was central to the learning process including regular feedback and root cause analysis of all cases of histology-OD error.

It has been suggested in some studies that near focus of magnifying endoscopes improve rates of high confidence OD (169,170). In DISCARD3 all procedures were

performed with standard high definition colonoscopes with near focus available in some cases. Endoscopists diagnosed 72% of ≤5 mm polyps with high confidence (range 63-83%) which was sufficient for PIVI criteria to be met.

An alternative approach recently evaluated is a location-based resect and discard strategy (LBRD). Taghiakbari et al used this approach where, 'all rectosigmoid diminutive polyps were considered hyperplastic and all polyps located proximal to the sigmoid colon were considered neoplastic' (217). In this approach OD is not required and a high surveillance interval concordance is achieved. We would suggest caution with an LBRD approach as making polyp characterisation assumptions based on location without OD and photodocumentation could result in important errors for high risk polyps such as in the rectosigmoid which is a common site for early colorectal cancer (218).

Some have suggested AI could replace the need for competence in OD as CADx systems can provide automated polyp diagnosis during colonoscopy. We feel this technology increases the need for OD competence to ensure endoscopists are not deskilled and are in a position to assess AI outputs for errors and to perform high quality colonoscopy where such systems are unavailable or fail.

### 9.4.3 Strengths and limitations

A major strength of DISCARD3 is the focus on quality assurance for the first time creating a framework that could make implementation of a "resect and discard" strategy possible. The insights this has provided have helped develop a new quality assurance framework that addresses previous concerns about a resect and discard strategy and puts safety at its core. In addition, as only accredited screening colonoscopists were included, whose KPIs are monitored closely, the findings of this study are transferable to other expert colonoscopy centres. We have also sought the opinion of patients with a survey and focus group showing the majority of patients find this approach acceptable.

We did not report on differences in OD performance with/without magnification, however, standard high definition scopes were used for the vast majority of cases and this supports the generalisability of our findings.

### 9.4.4 Further work

AI systems that allow polyp characterisation (CADx) are now at an advanced stage of development. These could help expedite implementation of a "resect and discard" strategy. Our findings are based on a single bowel cancer screening unit and we would recommend a larger evaluation of OD with a "resect and discard" strategy within the setting of a national BCSP. A detailed analysis of the economic impact is provided in Chapter 11.

### 9.4.5 Conclusion

OD learning curve varies between operators and most can perform with an accuracy consistently ≥75%. A "resect and discard" strategy for ≤5 mm polyps diagnosed with high confidence, in a group of bowel cancer screening colonoscopists, exceeded the 90% surveillance interval concordance (BSG, ESGE, US guidelines) required for implementation in real life clinical practice. A "resect and discard" strategy for polyps <10 mm diagnosed with high confidence exceeds the 90% threshold for BSG and ESGE guidelines but not US guidelines.

# Chapter 10 Optical diagnosis 4: Understanding optical diagnosis error (DISCARD3)

The contents of this chapter are based on a published manuscript[15] (219).

## 10.1 Background and Aims

### 10.1.1 Background

#### a What is optical diagnosis error?

'OD error' is where a high confidence OD does not match with the final histology result for a particular polyp. This term should refer only to diagnoses made with 'high confidence' as it is accepted there are a proportion of polyps were, even after application of validated OD classification systems, accurate OD is not possible. A high confidence diagnosis is made where the endoscopist feels ≥90% confident in the diagnosis to the extent that a "resect and discard" strategy can be employed.

When defining an OD error, the reference standard should be the final histology result. Although histopathology is the 'gold standard', there is a degree of uncertainty in pathology diagnosis of polyps. On some occasions the correct pathological diagnosis is obtained with a second pathology review or when additional deeper levels of the specimen are cut and analysed. Therefore, to ensure OD error truly reflects endoscopist performance, rather than limitations of histopathology or processing, it is important that final histology result is used as the reference standard.

#### b What factors are responsible for optical diagnosis error?

- *Endoscopist*

Knowledge – a lack of OD training may result in error.

[15] Ahmad A *et al*. NBI International Colorectal Endoscopic–derived high-confidence optical diagnosis of small polyps compared with histology: understanding errors to improve diagnostic accuracy. *Gastrointestinal Endoscopy*. 2023; 97: 78-88. Tables and figures reproduced with permission.

Human factors – personal factors might influence accuracy. Eg. over-assignment of high confidence diagnoses where the endoscopist lacks insight into personal competence in OD.

- *Classification system*

Classification systems are guides to OD but have limitations. At present there are at least seven OD classification systems used in clinical practice (see Section 7.1.1c). Although the principles between systems are similar there are variations in applicability. For example, in the NICE classification system all three criteria are not always met by polyps (see Table 17 and Figure 44). In these cases where there is greater uncertainty a low confidence diagnosis should be made or adjuncts to optical diagnosis may be used.

- *Polyp*

Variations in polyp OD criteria and in descriptions of OD features within these suggests there is a gap in our understanding of the polyp structures that are seen during colonoscopy. For example, with the NICE classification there is a footnote in the original paper suggesting that the white structures 'may represent the pits and the epithelium of the crypt opening' (171).

- *Pathology*

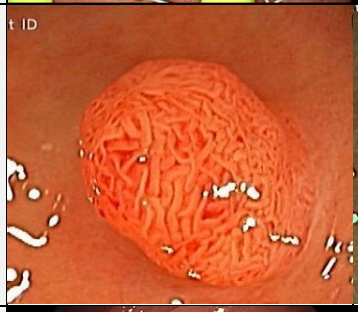
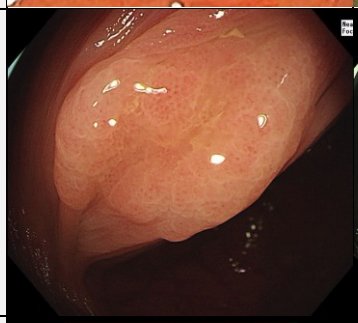
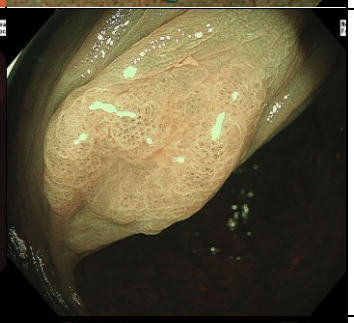
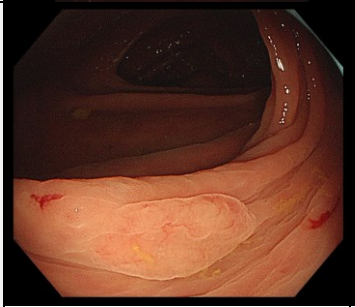
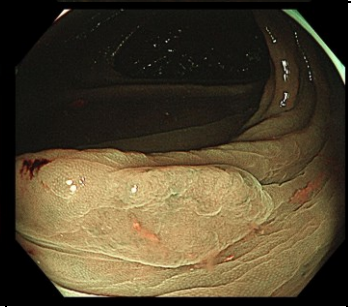
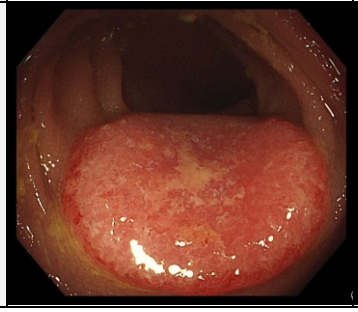
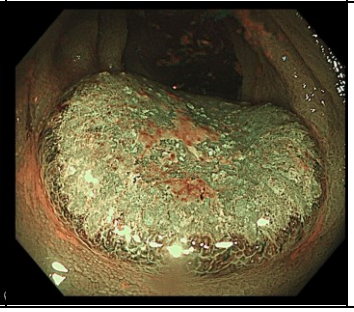
In some cases there is a false 'error' in OD caused by limitations in histopathology. This error is either due to human reporting error or due to a processing error. Processing errors are usually caused by a failure to visualise polyps on superficial levels of the polyp specimen (see Chapter 9).

- *Scope*

Use of low definition scopes without image enhancement affects the appearance of polyp structures and makes accurate OD more difficult. However, it is interesting to note a meta-analysis performed by Wanders et al, showed using high definition decreased performance when using NBI (168). This suggests that the additional visual information provided by higher definition did not help with application. The NICE classification system was validated without magnification 'as colonoscopy without high

magnification is standard in most parts of the world'. However, there is an argument for revalidating classification systems with higher resolution imaging systems as although picture clarity is enhanced, we cannot assume that classification criteria will be easier to apply.

Figure 44 Examples of classic lesions diagnosed using NICE criteria

| | White light | NBI | NICE | Histology |
|---|---|---|---|---|
| 1 |  |  | **Colour:** brown relative to background<br>**Vessels:** brown vessels<br>**Surface:** branched white structures | Adenoma |
| 2 |  |  | **Colour:** brown relative to background<br>**Vessels:** brown vessels<br>**Surface:** branched white structures | Adenoma |
| 3 |  |  | **Colour:** lighter than background<br>**Vessels:** no vessels<br>**Surface:** dark spots of uniform size | Serrated |
| 4 |  |  | **Colour:** lighter than background<br>**Vessels:** no vessels<br>**Surface:** dark spots of uniform size | Serrated |
| 5 |  |  | **Colour:** brown relative to background<br>**Vessels:** disrupted vessels<br>**Surface:** amorphous surface pattern | Cancer |

### c What is known about the accuracy of the NICE criteria?

The NICE classification is most commonly used for small polyp OD and relies on the use of non-magnified NBI which enhances mucosal surface structures such as vessels. This classification assesses polyp colour, surface appearance and vessel pattern to allow categorisation into three types. NICE type 1 polyps are adenomas, type 2 are serrated polyps (the original classification classified these as hyperplastic but it is recognised now that sessile serrated polyps also fit within this category), and type 3 are cancers.

In 2012, the NICE criteria was validated in a study showing a specificity of 94.9-100% when all three criteria were applied (171). The study also assessed the effect of using individual NICE criteria for OD which gave high sensitivities but lower specificities for each criteria. Endoscopists were found to diagnose polyps with high confidence in 75% of small colorectal polyps assessed consecutively during screening colonoscopy. There was 89% accuracy with a 98% sensitivity and a 95% negative predictive value.

### 10.1.2 Aims

1. Classify small polyp OD errors identified following root cause analysis
2. Understand likely causes of OD error in small polyps

### a

## 10.2 Methods

### 10.2.1 Study design

This is a sub-study of DISCARD3 (see Chapter 9), a prospective feasibility study evaluating implementation of OD with a "resect and discard" strategy in a bowel cancer screening setting. As part of DISCARD3, a novel quality assurance process was trialled to help provide a framework for implementation in clinical practice. This included a root cause analysis of all high confidence OD error.

In all cases of OD error, there was a second blinded pathology review after which a minimum of 6 tissues sections of each specimen were analysed. Where a high

confidence adenoma OD error occurred 12 levels were cut and analysed. In addition, all polyp photodocumentation for OD-histopathology discrepancies was reviewed by a blinded expert endoscopist to further assess the most likely cause of error.

Where discordance persisted despite this enhanced histological review, endoscopic photodocumentation (white light and NBI images) a blinded expert endoscopist undertook further review or all photos in detail. They then classified photodocumentation as adequate or inadequate and identified factors that may have contributed to OD error. The most likely cause of OD error was then categorized as a 'NICE mismatch' (where NICE criteria could not be fully applied to the polyp), 'NICE not applied' (where retrospective application of the NICE criteria appear to show this had not been correctly applied) and 'inadequate photodocumentation' (where photo quality was insufficient to make a high confidence diagnosis). In some cases, photodocumentation review concluded a 'likely pathology error' as polyp photodocumentation clearly showed, for example, an adenoma meeting all three NICE criteria but the histopathology result was normal.

The diagnostic outcomes for OD and histopathology diagnosis were classified as adenoma, serrated or normal. Discordance between OD and histopathology was categorised into 4 groups (see Table 24).

The study protocol was approved by the local review board (9/10/19; 19/EE/0234).

## 10.3 Results

### 10.3.1 Overview

Of the 1560 <10 mm polyps optically diagnosed, 1169 were high confidence diagnoses. There were 184 cases of high confidence OD-histopathology discordance (15.7%). 50/184 cases were attributed to pathology error either due to deeper levels being required (43/50) or observer/laboratory error (7/50). The remaining 134 cases underwent a detailed photodocumentation review due to persistent OD-histopathology discordance despite deeper level histopathology review up to 12 levels. In these cases photodocumentation was inadequate in 85/134 (63.4%) and adequate in 49/134

(36.6%). The outcome of the photodocumentation review was that the OD-histopathology discordance was due to: inadequate photodocumentation in 64/134 (47.8%), NICE mismatch in 36/134 (26.9%), NICE not being applied in 22/134 (16.4%) and 'likely pathology error' in 12/134 (9.0%). There was one case categorized as 'inadequate photodocumentation' where uncertainty about the cause of error was due to a lack of NBI and white light photos. After excluding this cases, the remaining 133 cases were classified into four groups according to the type of OD-histopathology discrepancy (see Table 24).

Table 24 Classification of significant optical diagnosis errors

| Error Type | Optical diagnosis | Histology result | Error Frequency |
|---|---|---|---|
| A | Adenoma | Serrated | 45/133 (33.8%) |
| B | Serrated | Adenoma | 55/133 (41.4%) |
| C | Adenoma | Normal | 19/133 (14.3%) |
| D | Serrated | Normal | 14/133 (10.5%) |

The majority of cases of discrepancy were assigned as low confidence diagnoses by the expert photodocumentation reviewer (120/133, 90%) so histopathology would have been the default. Only 13 cases of discrepancy were diagnosed with high confidence by the expert reviewer. Of these, 8/13 cases showed a clearly visualised polyp that met all three NICE criteria but the histology result returned normal; the reviewer felt these were likely histopathology (or processing) errors. In the remaining 5/13 cases, the reviewer felt that the original endoscopist did not appear to have correctly applied the NICE criteria.

Type A error, where a serrated polyp was optically diagnosed as an adenoma occurred in 45/133 (review outcome: 19 inadequate photodocumentation, 12 NICE not applied, 10 NICE mismatch, 4 likely pathology error). Type B error, where an adenoma was optically diagnosed as serrated occurred in 55/133 (review outcome: 31 inadequate photodocumentation, 7 NICE not applied, 16 NICE mismatch, 1 likely pathology error). Type C error, where normal mucosa was optically diagnosed as adenoma occurred in 19/133 (review outcome: 5 inadequate photodocumentation, 7 NICE mismatch, 7 likely pathology error). Type D error, where normal mucosa was optically diagnosed as serrated occurred in 14/133 (review outcome: 8 inadequate photodocumentation, 3 NICE not applied, 3 NICE mismatch).

The following sections detail the results of the root cause analysis performed for each error type which identified common themes resulting in OD error. These are explored in the following sections with photographic examples and potential strategies suggested to help improve diagnostic accuracy.

### 10.3.2 Type A Error

Optical diagnosis: adenoma

Histology: serrated

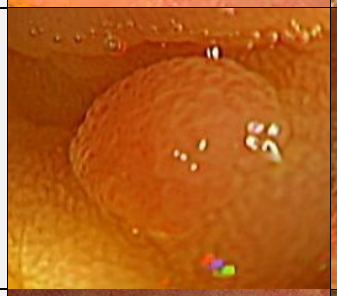
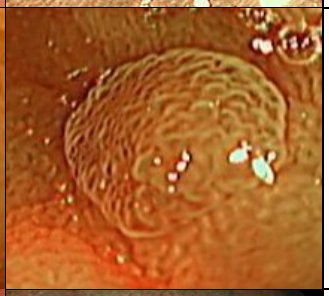
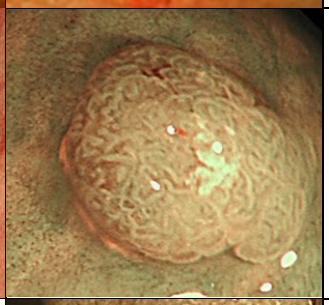
A Type A OD error is where serrated polyps are misdiagnosed as adenomas and occurs in 33.8% of cases. This error often occurs due to a sub-group of serrated polyps which have a specific polyp morphology and due to traumatised mucosal/polyp surface altering application of the NICE criteria.

#### a Serrated polyps with elongated crypts

There are a group of serrated polyps that have tubular/elongated crypts without visible vessels around the crypts (see Figure 45). Although the surface pattern is similar to a true adenoma, these “pseudoadenomas” do not have a capillary network which alters the appearance under NBI.

In true adenomas crypt openings are seen as dark narrow slits within a white structure. In “pseudoadenomas”, the lack of a capillary network gives an inverse appearance where the crypt openings appear dark with white surrounding intercryptal tissue. Another characteristic of these serrated polyps, which helps to distinguish them from true adenomas, is that when sized 4mm or greater they tend to have an irregular polyp border compared with true adenomas.

Figure 45 Examples of Type A optical diagnosis error (optical diagnosis: adenoma; histology: serrated). These may be described as pseudoadenomas.

| | White light | NBI | NICE | Histology |
|---|---|---|---|---|
| 1 |  |   | **Colour:** lighter than background<br>**Vessels:** appears to have brown vessels but these are elongated, empty crypts without mucus<br>**Surface:** regular surface pattern, alternating darker and lighter structures | Serrated |
| 2 |  |  | **Colour:** similar to background<br>**Vessels:** appears to have brown vessels but these are elongated empty crypts without mucus<br>**Surface:** regular surface pattern, alternating darker and lighter structures | Serrated (Hyperplastic) |
| 3 |  |  | **Colour:** similar to background<br>**Vessels:** appears to have brown vessels but these are elongated empty crypts without mucus<br>**Surface:** regular surface pattern, alternating darker and lighter structures. NB irregular polyp outline | Serrated |
| 4 |  |  | **Colour:** lighter than background<br>**Vessels:** appears to have brown vessels but these are elongated empty crypts without mucus<br>**Surface:** regular surface pattern, alternating darker and lighter structures . NB irregular polyp outline | Serrated |

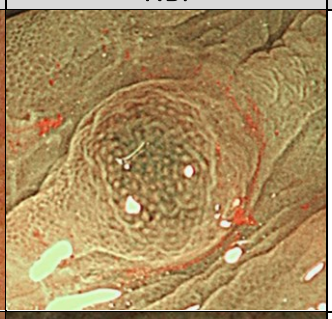
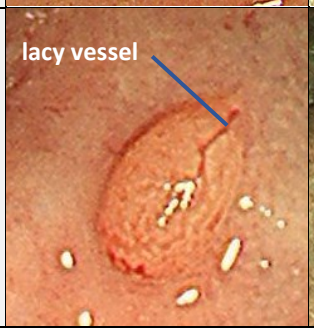
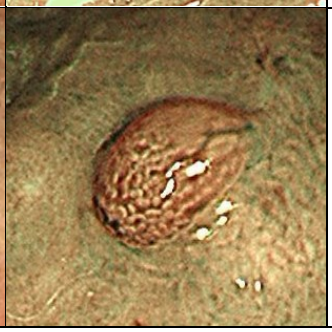
### b Traumatised mucosa/polyp surface

Mucosal trauma is frequently seen during colonoscopy as a result of bowel preparation, inadvertent mucosal suction or mucosal abrasion due to scope contact. It may occur for physiological reasons such as peristalsis and the presence of reactive lymph follicles.

Although trauma can affect any mucosal surface, polyp surface trauma is often seen in rectal and sigmoid serrated polyps as a result of propulsive forces during faecal evacuation. Under NBI, the surface of the serrated polyp appears darker than usual

due to polyp surface blood extravasation. This can cause NICE Type 1 polyps to be misdiagnosed optically as NICE Type 2 polyps (see Figure 46).

Figure 46 Serrated polyps with traumatised surface

| | White light | NBI | NICE | Histology |
|---|---|---|---|---|
| 1 |  |  | **Colour:** peripheries similar to background; most superficial aspect darker than background<br>**Vessels:** no vessels<br>**Surface:** white spots of uniform size | Serrated |
| 2 |  |  | **Colour:** darker than background due to trauma<br>**Vessels:** appears to have vessels but these are spaces between the crypts and a single lacy vessel<br>**Surface:** white spots of uniform size | Serrated |

### 10.3.3 Type B Error

Optical diagnosis: serrated

Histology: adenoma

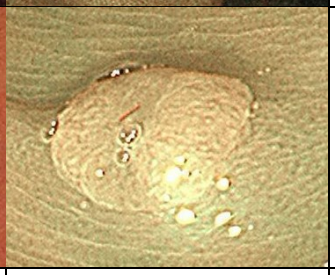
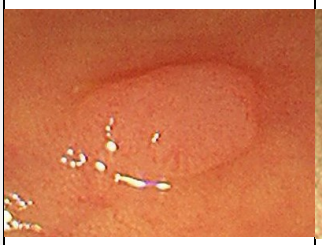
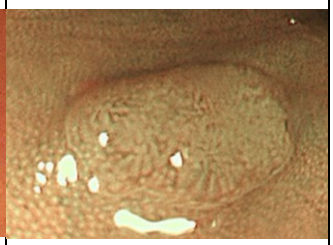
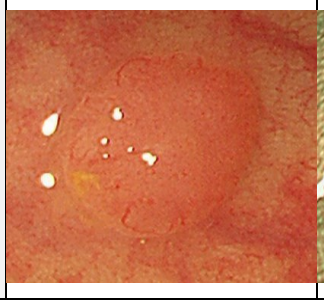
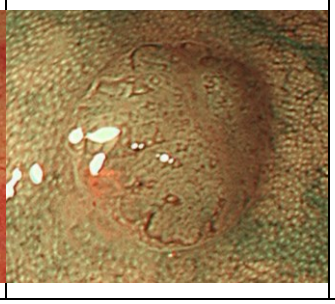
Type B errors occur where adenomas are misdiagnosed optically as serrated polyps. This frequently occurs due to limitations of the NICE criteria itself as all three NICE criteria cannot be applied to all adenomas. In addition, interpretation of NICE criteria could result in this error as discussed below.

#### a Some adenomas are light or similar to background colour

Although NICE criteria suggest adenomas are darker than the background colour this is not always the case as they are often lighter or similar to the background mucosa under NBI (see Figure 47). This can result in optical diagnosis uncertainty or error in cases where the colour attribute is relied on for decision-making or sways the ultimate OD.

White light imaging allows vessel and surface appearance to be appreciated with both attributes enhanced by NBI. The colour attribute, however relies mainly on NBI to highlight the vascular structures.

Figure 47 Examples of Type B optical diagnosis error (optical diagnosis: serrated; histology: adenoma)

| | White light | NBI | NICE | Histology |
|---|---|---|---|---|
| 1 |  |  | **Colour:** similar to background<br>**Vessels:** vessels only clear under NBI<br>**Surface:** white structures surrounded by vessels on NBI view | Adenoma |
| 2 |  |  | **Colour:** lighter than background<br>**Vessels:** brown vessels surrounding white structures<br>**Surface:** regular white tubular structures surrounded by vessels. NB. the valley sign is present | Adenoma |
| 3 |  |  | **Colour:** similar to background in white light but slightly darker in NBI<br>**Vessels:** vessels only clear under NBI<br>**Surface:** white tubular structures surrounded by vessels on NBI view | Adenoma |
| 4 |  |  | **Colour:** darker than background<br>**Vessels:** vessels around white structures (these are not 'lacy vessels' seen in serrated polyps as they do not course across the polyp and are not isolated)<br>**Surface:** white tubular/oval structures surrounded by vessels on NBI view | Adenoma |

### b NICE classification ambiguity: 'oval structures' versus 'white spots'

The surface pattern for NICE Type 1 polyps is described as uniformly-sized 'dark or white spots' and for NICE Type 2 polyps, includes white 'oval, tubular or branched white

structures'. The distinction between 'white spots' and 'white oval' structures may not be clear-cut and could result in misapplication of NICE.

Sometimes the immediate OD impression may suggest a particular diagnosis which is altered on closer inspection. For example, Polyp 1 in Figure 47 appears under white light to have white uniform dots which could lead to a serrated polyp diagnosis. However, under NBI, the surface pattern although showing mainly small white dots in the centre shows that some of these are more oval in shape particularly towards the polyp periphery. These white structures are surrounded by brown vessels confirming the diagnosis of an adenoma.

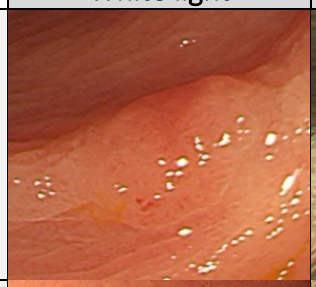
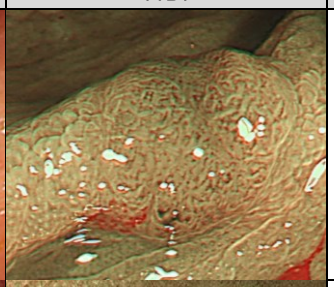
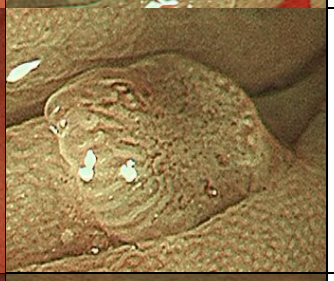
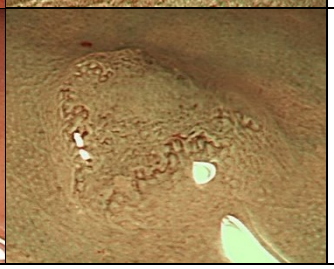
### c NICE classification ambiguity: 'lacy vessels' versus 'brown vessels'

The NICE criteria refers to 'isolated lacy vessels' in NICE Type 1 polyps. Sometimes more prominent peripheral vessels might be interpreted as lacy vessels when they are in fact brown vessels of an adenoma as part of the mesh capillary network (eg Polyp 4 in Figure 47)

### d The 'valley sign' is an OD adjunct that can help overcome Type B error.

The NICE criteria does not take into account polyp morphology and doing so may help overcome Type B errors. The 'valley sign' is a highly specific morphological sign for adenomas (90.2%-91.7%) and is seen at the polyp centre as an apparently depressed area which in fact has sloped edges giving the appearance of a valley (see Figure 48) (220). This is distinct from true depression as there is no disruption of vascular pattern, and the depth of the valley does not reach the level of the surrounding normal mucosa. In addition, in true depression, the edges fall sharply. When viewed under white light the valley is relatively red and under NBI it is browner relative to the surrounding polyp; this is thought to be due to vessel concentration in the valley.

Figure 48 Examples of the valley sign in adenomas

| | White light | NBI | NICE | Histology |
|---|---|---|---|---|
| 1 |  |  | **Colour:** brown relative to background under NBI<br>**Vessels:** brown vessels<br>**Surface:** white structures NB. Valley sign | Adenoma |
| 2 |  |  | **Colour:** brown relative to background under NBI<br>**Vessels:** brown vessels<br>**Surface:** white structures NB. Valley sign | Adenoma |
| 3 |  |  | **Colour:** brown relative to background under NBI<br>**Vessels:** brown vessels<br>**Surface:** white structures NB. Valley sign | Adenoma |

### 10.3.4 Type C Error

Optical diagnosis: adenoma

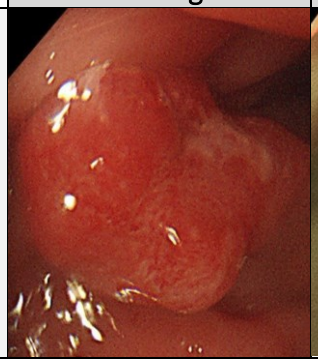
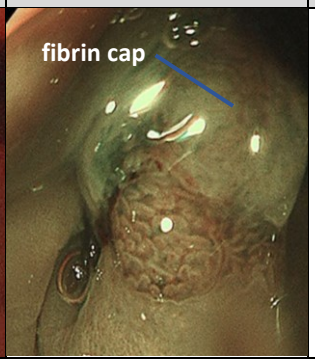
Histology: normal/non-serrated

#### a Inflammatory polyps

Mucosal inflammation, whether active or quiescent, can result in an adenomatous appearance under NBI as crypts are distorted and elongated. In combination with prominent surrounding blood vessels, the colour under NBI is darker than the background which can result in a Type C error where an inflammatory polyp is optically diagnosed as adenoma (see Figure 49).

A useful adjunct to the NICE criteria, to help overcome Type C error is the fibrin cap. This whitish cap consists of fibrinopurulent exudate and is an apparently reliable sign to help diagnose an inflammatory polyp as it is not present on adenomas.

Figure 49 Example of Type C optical diagnosis error (optical diagnosis: adenoma; histology: normal/non-serrated)

| | White light | NBI | NICE | Histology |
|---|---|---|---|---|
| 1 |  |  | **Colour:** darker than background mucosa where polyp seen. Fibrin cap is lighter.<br>**Vessels:** white structures surround vessels where polyp seen.<br>**Surface:** Fibrin cap obscures polyp tip. | Inflammatory |

### 10.3.5 Type D Error

Optical diagnosis: serrated

Histology: normal/non-adenoma

#### a Inverted diverticula

Small diverticula may become inverted and thus have a polypoid appearance mimicking a sessile polyp (see Figure 50). Accurately diagnosing these lesions optically is important to avoid the risk of inadvertent 'polypectomy'. A number of adjuncts can help with diagnosis. Assessment of the lesion with an attempt at retroverting the lesion carefully with biopsy forceps and the presence of surrounding diverticula are useful markers. In addition, the presence of concentric pale rings around the lesion, so-called 'Aurora' rings, accompanied by a pit pattern similar to the surrounding mucosa are helpful diagnostic markers.

Figure 50 Example of Type D optical diagnosis error (optical diagnosis: serrated; histology: normal/non-adenoma)

| | White light | NBI | NICE | Histology |
|---|---|---|---|---|
| 1 |  |  | **Colour:** lighter than background<br>**Vessels:** None<br>**Surface:** regular. NB. irregular concentric rings (Aurora rings) | Normal (Inverted diverticulum) |

# 10.4 Discussion

## 10.4.1 Key findings

a OD error may occur due to limitations of the NICE criteria and may be classified into 4 groups

b A newly identified subset of serrated polyps, with elongated crypts not surrounded by vessels, may be mistaken as adenomas ("pseudoadenomas")

c NICE colour assessment may be confounded by traumatised polyp surface and the fact that some adenomas are lighter or similar in colour to the background mucosa

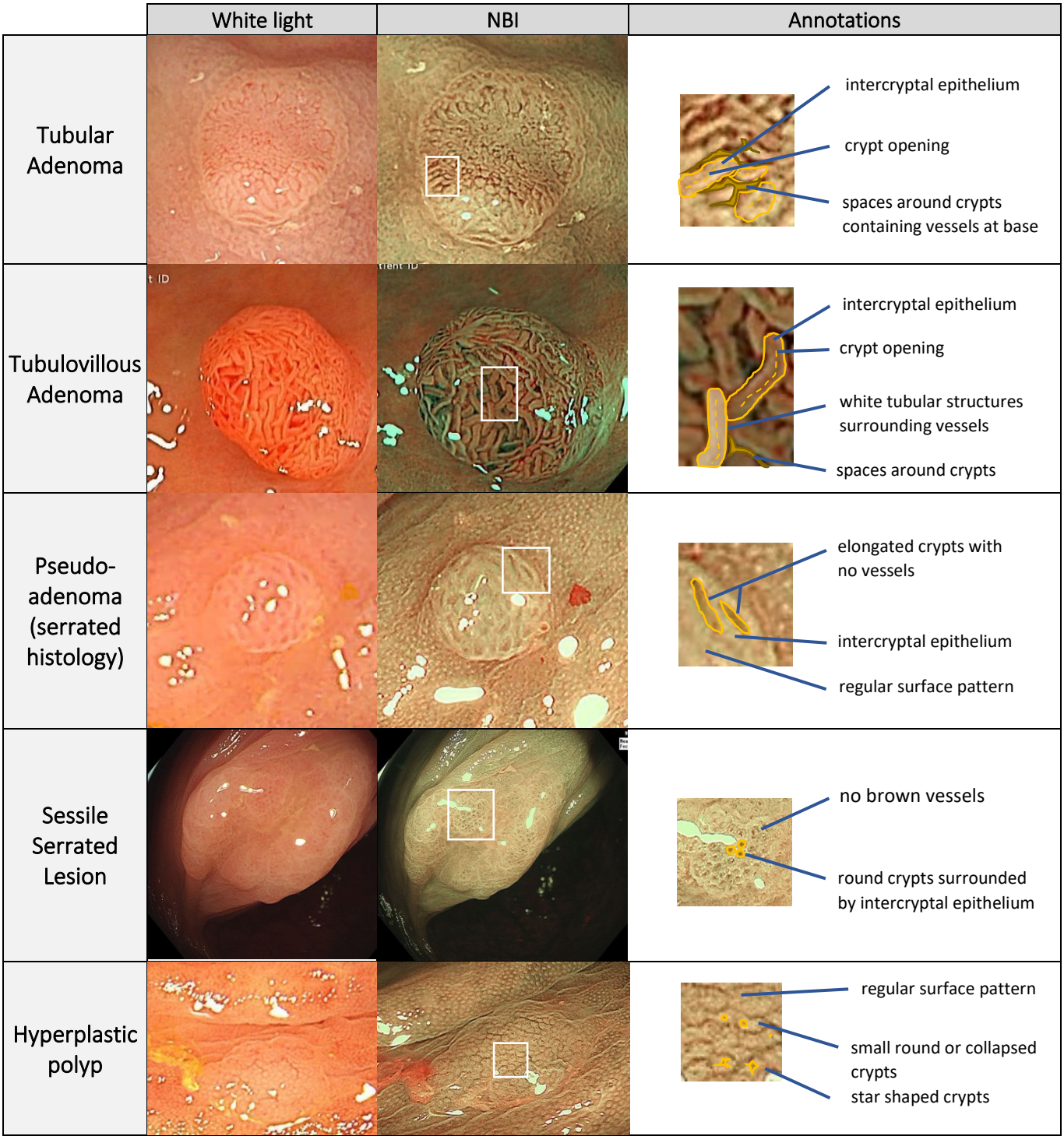
d Human error in NICE criteria application may occur due to ambiguity or similarity in the terminology such as 'oval spots' and 'round spots'

e The 'fibrin cap', 'valley sign' and 'Aurora rings' sign are useful OD adjuncts to help avoid OD error

Implementation of a "resect and discard" strategy requires competent OD and could significantly reduce the burden on histopathology. In this study, we analysed the appearance of all polyps that were incorrectly optically diagnosed from the DISCARD3 study. Incorrect OD may be due to factors relating to the classification system itself, atypical polyp features or endoscopist misinterpretation. This process has helped

enhance our understanding of polyp structures visible with white light and NBI for all major polyp types (see Figure 51).

Figure 51 Schematic showing differences in optical appearance between adenomas, 'pseudodenomas', sessile serrated lesions and hyperplastic polyps




There are a number of polyp classification systems of which the NICE classification is widely used in the West. NICE is validated and has an accuracy as high as 96% (171). In the DISCARD2 study, which included endoscopists with a broad range of experience, overall accuracy was 83.4% (205). A more recent retrospective study assessing 735

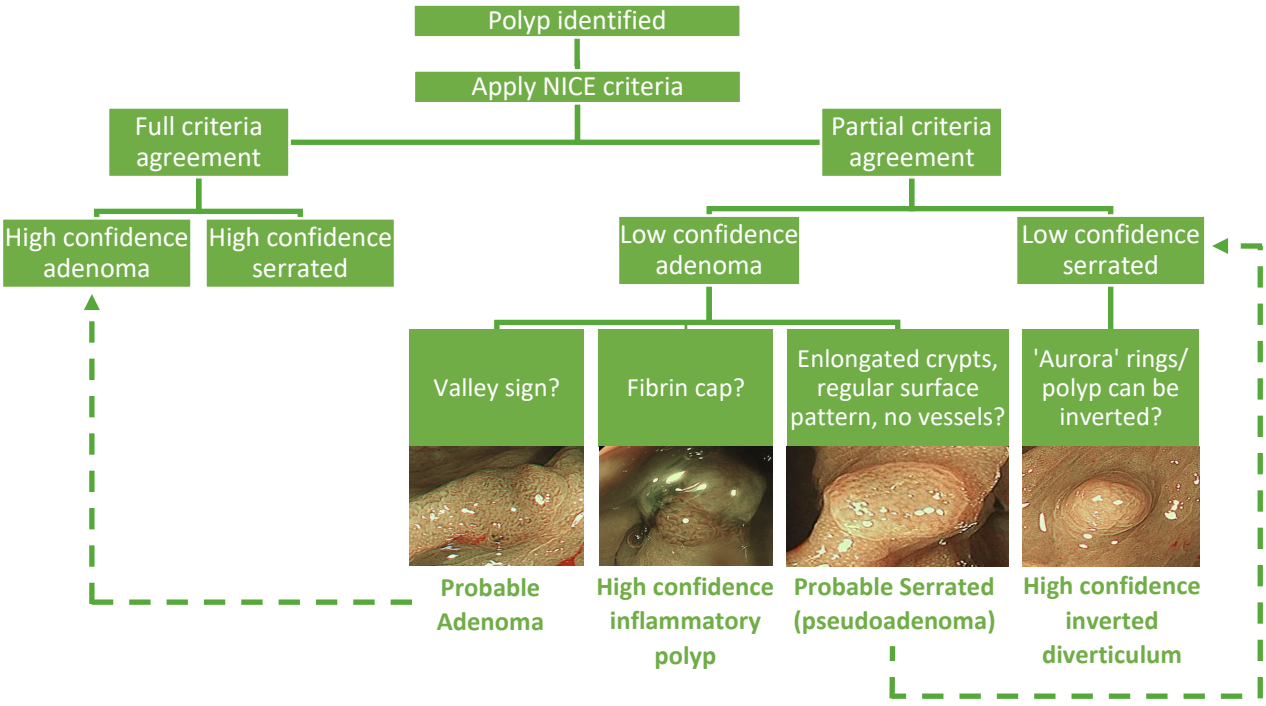
polyps, showed a diagnostic accuracy of the NICE classification compared with histopathology of 76.7% (221). This study showed performance varied amongst the 10 endoscopists and the importance of training was emphasized as endoscopists with the highest accuracy also performed the highest number of optical diagnoses. They found NICE 1 and NICE 2 polyps were most frequently mistaken for each other. 64.8% (70/108) of serrated polyps were misdiagnosed as adenomas (Type A error) and 9.4% of adenomas were misdiagnosed as serrated polyps (Type B error). These figures vary from our respective figures of 33.8% and 41.4% (see Table 24) which may reflect differences in endoscopist expertise and training. Accuracy of the NICE classification may be highly dependent on the endoscopist as inadequate experience or training might lead to poor polyp visualization or inadequate NBI use, therefore leading to unreliable polyp assessment.

Atypical appearing polyps may also affect accuracy of the NICE classification. We have identified a subgroup of serrated polyps that on first sight appear to be adenomas and are therefore frequently misdiagnosed. These may be described as 'pseudoadenomas' as they appear to have tubular crypts consistent with an adenoma. These are actually elongated crypts with no surrounding vessels (see Figure 51). This appearance is, optically, the inverse of an adenoma which has crypt openings (seen as a narrow dark slit) within a white structure. In contrast, pseudoadenomas have crypt openings that appear dark and are surrounded by white intercryptal tissue. Interestingly, we have found some adenomas are not a 'browner color relative to the background mucosa' according to the classical description but are in fact similar or even lighter than the background mucosa (see Figure 47).

It is recognized that the NICE classification is limited as it cannot distinguish between hyperplastic polyps and sessile serrated lesions and this has now been addressed with the WASP classification (222). Another potential limitation of the NICE classification is that it does not take polyp morphology into account. A recent multicentre study showed incorporating morphological features into the NICE classification may help identify >10 mm lesions with deep invasion (223). Morphological feature assessment could also be helpful to enhance accuracy in smaller lesions.

Given the limitations of the NICE classification system, we propose an algorithm to improve OD accuracy in polyps <10 mm in size, without recourse to magnification endoscopy. This uses the NICE classification but also provides a framework for assessing a polyp that only partially meets the NICE criteria. In these cases of 'incomplete agreement', we suggest the addition of gross morphology assessment and other OD adjuncts (see Figure 52). These include the 'valley sign', recognition of 'pseudoadenomas', fibrin caps and the aurora rings sign. The 'valley sign', first described by Rex et al, is included as it is an easily identifiable feature that requires little additional training and strongly indicates an adenoma (220). 'Pseudoadenomas' account for almost half of Type A errors and are therefore part of the algorithm; we suggest additional training will be necessary on their recognition for endoscopists performing OD. The fibrin cap and aurora rings sign have little evidence base, but a large anecdotal experience that they are diagnostic of inflammatory polyps and inverted diverticula respectively (224,225). All these findings do not require magnification so are accessible for interpretation by all endoscopists and, if applied, this algorithm offers potential for OD error to be further minimized.

Figure 52 Proposed algorithm to improve optical diagnosis accuracy



Even with revision, OD algorithms will not allow complete certainty in OD as there will always be cases where diagnostic confidence is low and histopathology assessment is required. However, a high confidence diagnosis rate of 75% or above appears to be an achievable and clinically effective target for OD to allow a "resect and discard" strategy in clinical practice (169,170,187,198,226). The recently published ESGE competence standards recommend a "resect and discard" strategy is acceptable if 'at least 80% sensitivity and 80% specificity is achieved for high confidence endoscopic characterization of colorectal neoplasia' in 1-5 mm polyps (227). When evaluated in a simulation analysis of FIT-positive screening patients, 79% of 1-5 mm polyps would be correctly diagnosed and surveillance interval agreement would exceed 90% for both ESGE and US guidelines (211). Enhancing the OD algorithm will likely increase high confidence levels and widen the beneficial impact of a "resect and discard" strategy.

We have developed a new categorisation for OD errors into 4 types (A-D). The most frequent errors were where serrated polyps were mistaken for adenomas and vice versa (Type A and B errors). Both polyps have malignant potential but the distinction is important as dysplasia risk varies and may influence surveillance interval assignment (197). Even where the surveillance interval is unaffected, the distinction is of value to ensure clinical accuracy and understanding of pathophysiology. In some cases, normal mucosa may be misdiagnosed optically as adenoma or serrated polyp (Type C and D errors). This might expose patients to unnecessary and potentially harmful 'polypectomy' as well as the risks of performing a surveillance colonoscopy at an interval sooner than required.

Computer-aided diagnosis (CADx) of polyps is now possible using AI derived algorithms. Although some have suggested this might obviate the need for skilled OD we feel it strengthens the case. In cases of false positives, where AI software fails or is unavailable, the endoscopist needs to be confident in their OD skill. From a medico-legal perspective, the responsibility for diagnosis remains with the endoscopist even where AI assists the operator.

### 10.4.2 Conclusion

Small polyp OD during colonoscopy is now possible to allow real-time decision making, avoidance of unnecessary polypectomy, as well as a reduction in histopathology burden with a corresponding huge cost-saving potential. Although the NICE classification is widely used, we have found a significant error rate of 15.7% in polyps diagnosed with high confidence. The new classification system for OD error we have developed will help provide a framework for future research in this area. We have also proposed an algorithm to improve OD accuracy when using the NICE criteria which should help raise endoscopist confidence in OD.

# Chapter 11 Optical diagnosis 5: Economic impact of a "resect and discard" strategy (DISCARD3)

The contents of this chapter are based on a published manuscript[16] (228).

## 11.1 Background and Aims

### 11.1.1 Background

#### a What is known about the economic impact of a "resect and discard" strategy?

Polypectomy is an important therapeutic intervention performed during colonoscopy which reduces the incidence and mortality of colorectal cancer by 40-60% (229). For this reason, many countries have introduced a bowel cancer screening programme (230). In England, 2.5 million people are screened annually within the BCSP resulting in performance of more than 50,000 colonoscopies (231,232). During these procedures, when polyps are identified, the standard approach is for all polyps to be resected and sent for histology (resect and send) except typical hyperplastic appearing rectosigmoid polyps which are left in situ (diagnose and leave).

The cost of a "resect and send" strategy is significant due to the requirements of specimen processing within the endoscopy room, histopathology analysis/reporting and storage of specimens. However, when compared to the burden of a delayed colorectal cancer diagnosis, colonoscopy with polypectomy is cost-effective.

Despite this, the rationale for the standard "resect and send" approach should be interrogated as technological advances now allow confident optical diagnosis (OD) in real-time to the extent that histopathological examination of specimens is no longer required. The NICE classification, for example, has been validated for OD of small polyps (171). Furthermore, the vast majority of colorectal polyps (90%) are diminutive

[16] Orlovic M, Ahmad A, Saunders B. Economic impact of implementing optical diagnosis with a "resect and discard" strategy within the English Bowel Cancer Screening Programme: findings from the DISCARD3 study. *Gastrointestinal Endoscopy*. 2023. Tables and figures reproduced with permission.

(≤5 mm) or small (6-9 mm) and rarely contain advanced histology or colorectal cancer (233). In the scenario where there is high grade dysplasia effective polypectomy should eliminate this risk. For this reason, a "resect and discard" strategy has been proposed as an alternative approach so that diminutive (or small) polyps with neoplastic potential are resected and discarded rather than sent for histology.

A "resect and discard" strategy has huge potential to improve efficiency and reduce cost with only minor changes required in clinical practice. However, there is a risk with this strategy that OD-derived surveillance intervals may not fully correlate with histology-derived surveillance intervals. This might result in surveillance intervals that are too short thereby increasing the risk of adverse events and procedure cost, or surveillance intervals that are too long potentially increasing the risk of colorectal cancer and costs associated with this (234). In order to manage this risk, the ASGE have set PIVI thresholds that must be achieved before a "resect and discard" strategy is adopted in clinical practice (94,95). This includes the requirement for a ≥90% OD-histopathology derived surveillance interval concordance. The DISCARD3 study has demonstrated that this can be achieved where there is a quality assurance process in place (see Chapter 9) (187).

#### b Knowledge gap

Previous economic studies have suggested OD with a "resect and discard" strategy can be cost-effective with a significant reduction in histopathology service demand. However, these studies were performed prior to the proposed quality assurance process in DISCARD3 which has been designed to ensure safe implementation in real life clinical practice. In addition, previous studies have often included endoscopists with variable experience which has affected the achievement of PIVI thresholds.

### 11.1.2 Aim

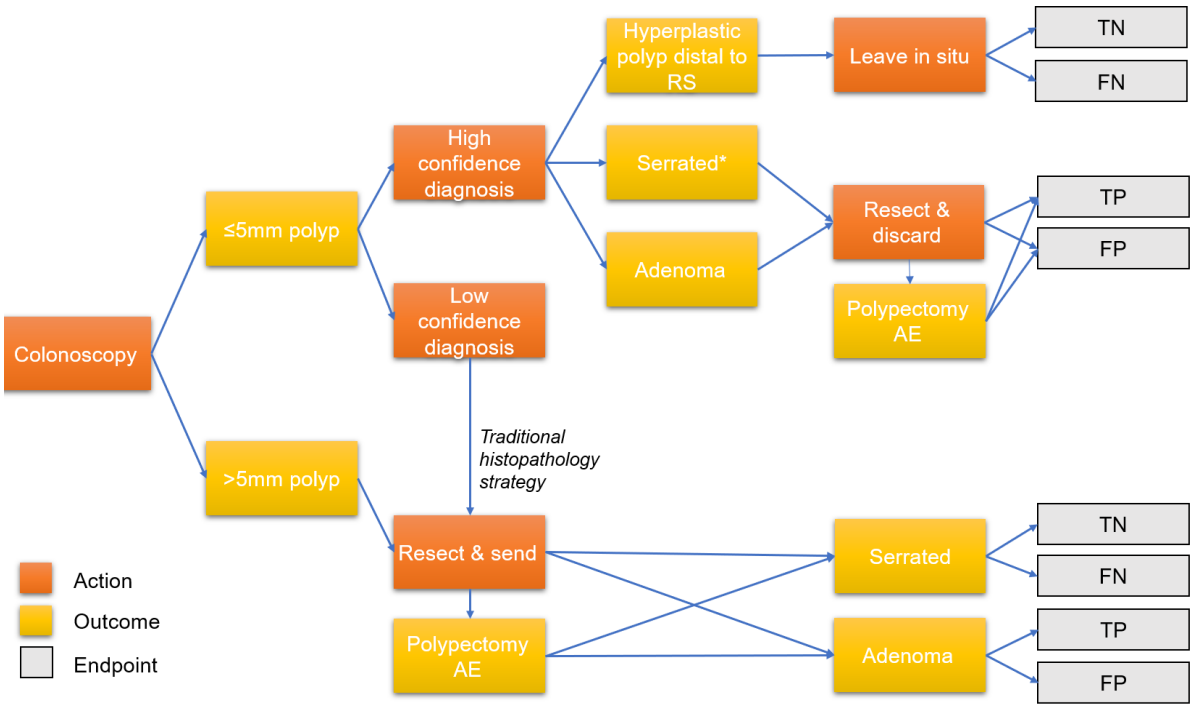
1. Assess the costs and benefits of optical diagnosis with a "resect and discard" strategy performed in the setting of the English BCSP performed only by accredited endoscopists with a quality assurance process in place.

# 11.2 Methods

## 11.2.1 Study design

This economic analysis is a sub-study of DISCARD3 (see Chapter 9) (187). A decision tree was formulated to compare the standard "resect and send" approach with a "resect and discard" strategy within an English BCSP cohort (see Figure 53).

**Figure 53 Decision tree for "resect and discard" strategy compared with standard "resect and send" strategy**




TN – true negative, FN – false negative, TP – true positive, FP – false positive, AE – adverse event, RS – rectosigmoid. This figure is adapted from a previous study (235).

* excluding hyperplastic polyps distal to rectosigmoid colon

We considered two alternative approaches to "resect and discard" differentiated by size with either only diminutive polyp or small polyp optical diagnoses considered (see Table 25).

In the diminutive polyp "resect and discard" strategy, ≤5 mm polyps optically diagnosed with high confidence were resected and discarded without histopathology assessment.

All other polyps, i.e. ≤5 mm polyps diagnosed with low confidence and all polyps >5 mm were sent to histopathology as standard. For surveillance interval determination, only high confidence optical diagnoses of ≤5 mm polyps were considered and for all other polyps histology results were used to complete the surveillance interval polyp dataset.

In the small polyp "resect and discard" strategy polyps <10 mm diagnosed with high confidence were resected and discarded without histopathology assessment. All other polyps, i.e. low confidence diagnoses and all polyps >10 mm in size were sent to histopathology as standard. For surveillance interval determination, only high confidence optical diagnoses of <10 mm polyps were considered and for all other polyps histology was used to complete the surveillance interval dataset.

Table 25 Characteristics of "resect and discard" strategies compared with the traditional "resect and send" strategy

| Diminutive polyp "resect and discard" strategy | Small polyp "resect and discard" strategy | Traditional "resect and send" strategy |
|---|---|---|
| • Diminutive polyps (≤5 mm) characterised with high confidence are resected and discarded<br>• Polyps diagnosed with low confidence are resected and sent to histopathology | • Small polyps (<10 mm) characterised with high confidence are resected and discarded<br>• Polyps diagnosed with low confidence are resected and sent to histopathology | • All diminutive and small polyps are resected and sent for histopathological assessment |

In "resect and discard" cases where all polyps were diagnosed with high confidence, an immediate surveillance interval could be given avoiding the need for a follow up appointment. In all cases, histopathology-derived surveillance intervals were also determined using BSG guidelines to allow optical diagnosis-histopathology surveillance interval concordance to be assessed (197).

The strategies were costed using NHS reference costs (see Table 26) (236,237). DISCARD3 data was used to calculate population distribution and outcome probabilities. We did not assume a 100% histopathology accuracy unlike previous

studies (196,235,238) and instead used more detailed observations from the DISCARD3 study. There were no adverse events during the trial period but at the population size of the English BCSP adverse events related to polypectomy would be expected and a standard risk rate sourced from the literature was assumed (239).

The base case analysis included patients with at least one diminutive polyp as used in other economic analyses. In DISCARD3, we also considered a small polyp (<10 mm) optical diagnosis approach as we found the PIVI threshold for surveillance interval concordance was achieved when using BSG guidelines. We therefore performed a scenario including patients with at least one diminutive or small polyp. In each scenario, a deterministic sensitivity analysis was performed where model inputs varied by ± 20%. In addition, a pathology expert at St Mark's Hospital in London was interviewed to help understand the resources required to perform histopathology analysis of resected polyps.

We performed interviews with key stakeholders and took into consideration resources required for optical diagnosis following these. In particular, the resource required for the quality assurance process proposed in DISCARD3 to allow safe implementation of a "resect and discard" strategy was evaluated. We also measured procedure time for the standard approach versus a "resect and discard" strategy. A t-test was used to evaluate for statistically significant differences between the strategies.

Table 26 Clinical and cost inputs

| Input | Value | Source |
|---|---|---|
| Cost of histopathology per polyp | £37 | National Schedule of NHS costs (2019/20) (236); Cost for DAPS02 histopathology and histology |
| Cost of follow up appointment | £85 | 2022/23 National Tariff Payment System: Annex A - National tariff workbook; Outpatient appointment, gastroenterology service, follow up attendance (237) |
| Histology sensitivity (≤5 mm polyp) | 99.3% | DISCARD3 (187) |
| Histology specificity (≤5 mm polyp) | 89.4% | DISCARD3 (187) |
| Histology sensitivity (<10 mm polyp) | 99.4% | DISCARD3 (187) |
| Histology specificity (<10 mm polyp) | 89.8% | DISCARD3 (187) |
| Optical diagnosis sensitivity (≤5 mm polyp) | 93.0% | DISCARD3 (187) |
| Optical diagnosis specificity (≤5 mm polyp) | 74.2% | DISCARD3 (187) |
| Optical diagnosis sensitivity (<10 mm polyp) | 92.9% | DISCARD3 (187) |
| Optical diagnosis specificity (<10 mm polyp) | 75.5% | DISCARD3 (187) |
| Number of colonoscopies (national BCSP) | 65,500 (2021) | Calculated based on Gavin et al. (2013) (49) and Joint Advisory Group on GI Endoscopy data on file (240) |
| % of patients with polyps ≤ 5mm | 34.7% | DISCARD3 (187) |
| % of patients with polyps <10 mm | 51.2% | DISCARD3 (187) |
| Average number of polyps ≤5 mm | 5.0 | DISCARD3 (187) |
| Average number of polyps <10 mm | 3.4 | DISCARD3 (187) |
| BCSP Centres | 119 | Joint Advisory Group on GI Endoscopy (240) |
| Specialist Screening Practitioner daily rate | £131 | Band 6 nurse, intermediate point, £34,172 per year (241); NHS Terms and Conditions of Service Handbook |
| Consultant daily rate | £366 | NHS Consultant with 4 years completed as consultant, £91,144 per year (242); NHS Pay and Conditions Circular (M&D) 3/2021 |
| Quality assurance process personnel needs | 1 day/week of SSP time 0.5 day/week of consultant time | DISCARD3 (187) |

### 11.2.2 Outcomes

Key outcomes of interest were:

- Healthcare costs and savings
- Surveillance interval assignment

## 11.3 Results

### 11.3.1 Overview

Of the 565 patients invited to DISCARD3, 525 were included. Of those, 269 patients had at least one diminutive and/or small polyp, 135 had polyps ≥10 mm, 85 did not have any polyps and 36 had colorectal cancer. After excluding cases with polyps ≥10 mm and those with colorectal cancer, 354 patients were assessed for surveillance intervals (see Table 27). These patients had a total of 920 polyps of which 810 were ≤5 mm and 110 were 6-9 mm.

Table 27 Distribution of polyp size and optical diagnosis confidence level in DISCARD3

| Patient group | Patients | Polyps ≤5 mm | Polyps 6-9 mm | Total polyps | Diagnosis confidence summary |
|---|---|---|---|---|---|
| Diminutive polyps only | 182 | 503 | 0 | 503 | 37 L, 65 M, 80 H |
| Small and diminutive polyps | 77 | 307 | 98 | 405 | 2 L, 47 M, 28 H |
| Small polyps only | 10 | 0 | 12 | 12 | 1 L, 1 M, 8 H |
| No polyps | 85 | 0 | 0 | 0 | - |
| **Total** | **354** | **810** | **110** | **920** | **-** |

L – 'low confidence', H – 'high confidence', M – 'mixed confidence' (combination of high- and low-confidence diagnoses).

### 11.3.2 Outcomes at single-centre level

The OD-histopathology surveillance interval concordance was 97.9% (142/145) in patients with at least one diminutive polyp and 98.7% (226/229) in patients with at least one diminutive or small polyp (see Table 28). In both groups, there were 3 cases where the OD derived surveillance interval was shorter which would have resulted in a small increase in the number of colonoscopies performed. However, with a "resect and discard" approach there would be fewer histological examinations and follow up appointments. In DISCARD3, this would reduce overall direct healthcare costs by £35,468.8 (-72.3%) for patients with at least 1 diminutive polyp or by £42,666.2 (-75.0%) for patients with at least 1 diminutive or small polyp.

Table 28 Outcomes and costs for patients with at least 1 diminutive or small polyp in DISCARD3

| Category | "Resect and discard" strategy | Traditional "resect and send" strategy | Difference |
|---|---|---|---|
| **Per patient analysis (patients with at least 1 diminutive polyp, N=182)** | | | |
| ***Outcomes*** | | | |
| True Negatives | 159 | 182 | - 23 |
| False Negatives | 44 | 21 | 23 |
| True Positives | 669 | 701 | - 32 |
| False Positives | 37 | 5 | 32 |
| Histological exams | 251 | 908 | - 657 |
| Follow up appointments | 74 | 182 | - 108 |
| Surveillance intervals concordance (BSG guidelines) | *97.9% (142/145)*<br>*For 3 cases "resect and discard" surveillance interval was shorter*<br>*Outcomes for 145 patients (80 H and 65 M diagnoses)* | | |
| ***Costs*** | | | |
| Histological exams | £9,301.9 | £33,596.0 | -£24,294.1 (-72.3%) |
| Follow up appointments | £4,295.3 | £15,470.0 | -£11,174.7 (-72.2%) |
| *Total costs* | *£13,587.2* | *£48,066.0* | *-£35,468.8 (-72.3%)* |
| **Per patient analysis (patients with at least 1 diminutive or small polyp N=269)** | | | |
| ***Outcomes*** | | | |
| True Negatives | 175 | 234 | - 60 |
| False Negatives | 45 | 28 | 17 |
| True Positives | 622 | 653 | - 31 |
| False Positives | 36 | 5 | 32 |
| Histological exams | 230 | 920 | - 690 |
| Follow up appointments | 161 | 269 | - 108 |
| Surveillance intervals concordance (BSG guidelines) | *98.7% (226/229)*<br>*For 3 cases "resect and discard" surveillance interval was shorter*<br>*Outcomes for 229 patients (116 H and 113 M diagnosis)* | | |
| ***Costs*** | | | |
| Histological exams | £8,507.9 | £34,040.0 | -£25,532.1 (-75.0%) |
| Follow up appointments | £5,730.9 | £22,865.0 | -£17,134.1 (-74.9%) |
| *Total costs* | *£14,238.8* | *£56,905.0* | *-£42,666.2 (-75.0%)* |

H – 'high confidence', M – 'mixed confidence'

### 11.3.3 Extrapolation of outcomes to national level

The findings from DISCARD3 were extrapolated to the national level based on colonoscopy volume within the English BCSP (more than 65k colonoscopies were performed in 2021 (240)), the proportion of patients with diminutive and small polyps, and average polyp number. Using a "resect and discard" strategy for patients with diminutive polyps would save £4.4m which increases to £5.3m if small polyps are included. These substantial savings are primarily driven by the cost of colonoscopy and

histopathological assessment of diminutive and small polyps. Even after including the cost of implementation of a quality assurance process for OD, the savings are almost £2.4m for patients with diminutive polyps or £3.4m for patients with diminutive and small polyps.

Table 29 Extrapolation of costs for patients with at least 1 diminutive or small polyp to the level of the English BCSP (NHS England)

| **Calculation for patients with diminutive polyps** | | | |
|---|---|---|---|
| Number of colonoscopies (BCSP 2021) (240) | | | 65,500 |
| % of people with diminutive polyps (DISCARD3) (187) | | | 34.67% |
| Number of people with diminutive polyps (DISCARD3) (187) | | | 22,707 |
| Average number of polyps ≤5 mm (DISCARD3) (187) | | | 4.99 |
| **Costs** | **"Resect and discard"** | **Traditional "Resect and send"** | **Difference** |
| Histopathology | £1,160,521.6 | £4,191,501.0 | -£3,030,979.4 |
| Follow up appointments | £535,887.6 | £1,930,066.7 | -£1,394,179.1 |
| *Total costs* | *£17,086,846.6* | *£22,024,663.0* | *-£4,425,158.4* |
| QAP for NHS centres (119 centres) | £1,943,032.0 | - | £1,943,032.0 |
| *Net savings* | | | **-£2,428,126.4** |
| **Calculation for patients with diminutive and small polyps** | | | |
| Number of colonoscopies (BCS 2021) (240) | | | 65,500 |
| % of people with diminutive polyps (DISCARD3) (187) | | | 51.24% |
| Number of people with diminutive polyps (DISCARD3) (187) | | | 33,561 |
| Average number of polyps <10 mm (DISCARD3) (187) | | | 3.42 |
| **Costs** | **"Resect and discard"** | **Traditional "Resect and send"** | **Difference** |
| Histopathology | £1,061,465.7 | £4,246,895.2 | -£3,185,429.5 |
| Follow up appointments | £714,998.9 | £2,852,681.0 | -£2,137,682.1 |
| *Total costs* | *£24,276,242.8* | *£30,604,700.7* | *-£5,323,111.6* |
| QAP for NHS centres (119 centres) | £1,943,032.0 | - | £1,943,032.0 |
| *Net savings* | | | **-£3,380,079.6** |

A one-way sensitivity analysis demonstrated that for both patient groups total savings are most sensitive to the proportion of high confidence diagnoses, histopathology cost and colonoscopy cost (see Figure 54 and Figure 55). This analysis highlights the importance of endoscopist competence in OD which we would recommend is supported with a quality assurance process that provides training, monitoring and feedback.

Figure 54 Deterministic sensitivity analysis of top factors impacting uncertainty in total savings for patients with at least 1 diminutive polyp relative to base case

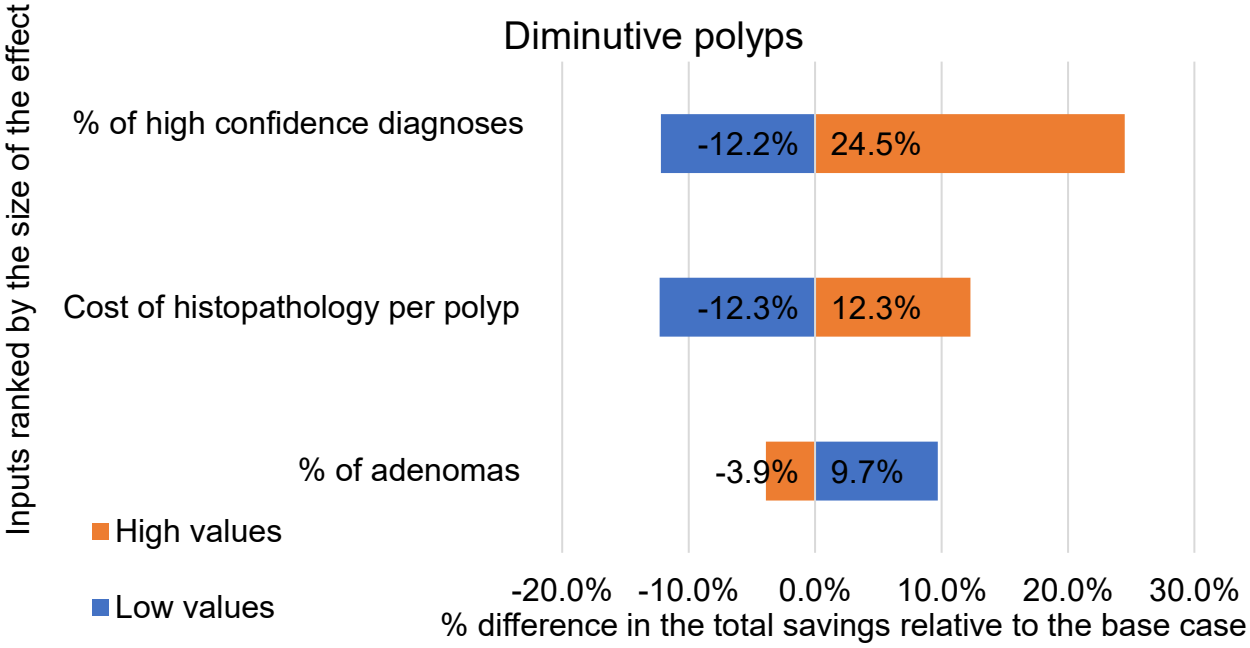
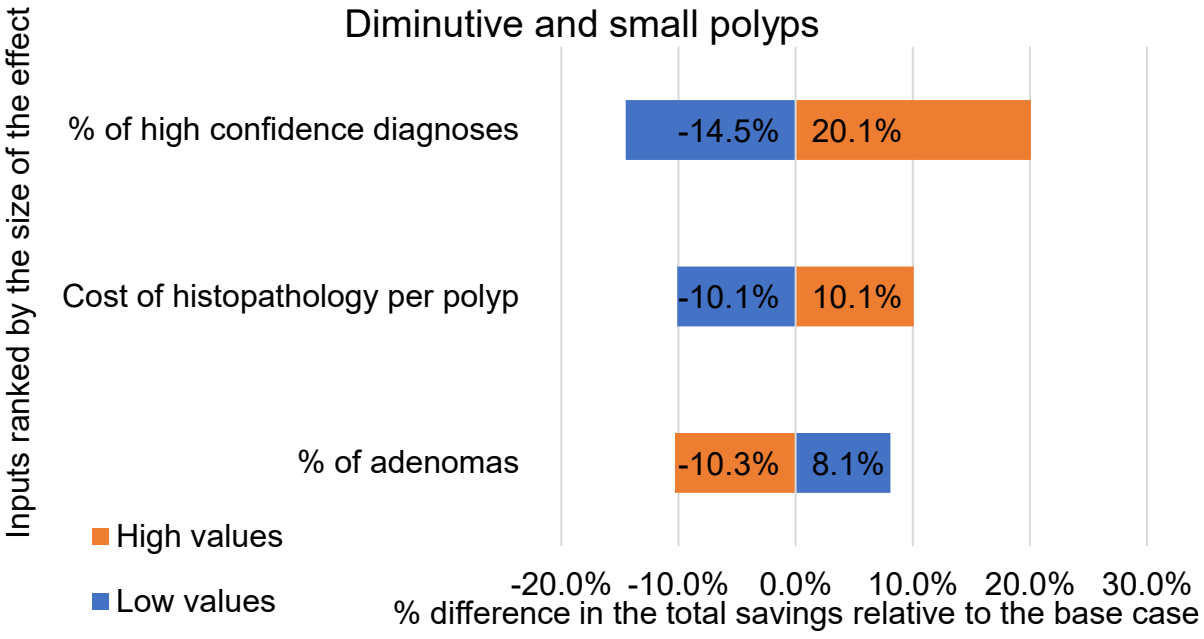



Figure 55 Deterministic sensitivity analysis of top factors impacting uncertainty in total savings for patients with at least 1 diminutive or small polyp relative to base case



## 11.4 Discussion

### 11.4.1 Key findings

a A "resect and discard" strategy is a cost-saving strategy compared to current standard of care with no adverse impact on health outcomes

b Up to £3.4m could be saved per annum after taking into account the cost of a quality assurance process (depending on whether a diminutive or small polyp OD approach is used)

c The majority of cost saving is due to reduced histopathology examinations and the need for follow up appointments

Implementation of a "resect and discard" strategy within the English BCSP would result in major cost-savings for the NHS. At the level of the DISCARD3 study, a diminutive polyp "resect and discard" approach provides £35k savings and a small polyp "resect and discard" approach increases this to £43k savings compared with a traditional "resect and send" approach. When extrapolated to the national level, and after adjusting for the cost of implementing a quality assurance process, savings amount to £2.4m or £3.4m for each respective "resect and discard" approach. Key factors driving cost savings include a reduced need for histopathology assessment of polyps and the need for follow up appointments.

Amongst the 184 cases of high confidence OD-histopathology discordance, there were 33 false positive cases where normal mucosa was classified as either adenoma or serrated. Despite this small false positive rate, there would only be a 1.3% (3/229) increase in cases where surveillance intervals are performed sooner than required by BSG guidelines. Amongst cases assessed for surveillance intervals, 33% had only high confidence diagnoses so an immediate surveillance interval could be provided to patients post-procedure without the need for a follow up appointment. Also, 31% of patients had both high and low confidence diagnoses providing further opportunity to

save on histopathology assessment and clinical time for those polyps diagnosed with high confidence.

Although histopathology has traditionally been seen as the 'gold standard' for polyp assessment, DISCARD3 demonstrated a significant error rate. 27.2% of cases of discordance, between high confidence optical diagnosis and histopathology, were due to pathology error where deeper level polyp specimen analysis was required (23.4%) or a processing error occurred (3.8%).

A NICE advisory committee report (196), and our own interviews with a pathology expert in the NHS, support the finding that technical and administrative errors in polyp characterisation can occur with histopathology assessment. Our pathology expert interview also revealed an average of 3 days are required from receiving the polyp specimen to informing the specialist of the results. Where additional levels are required there is usually a one-day delay. In view of this, we feel previous analyses have overestimated the effectiveness of histopathology.

Optical diagnosis offers the potential for a major reduction of histopathology service demand compared with the traditional "resect and send" approach. High confidence optical diagnosis allows a "resect and discard" strategy to be employed avoiding the cost and time involved in histopathology analysis. Where small typical hyperplastic-appearing polyps are optically diagnosed in the rectosigmoid these can safely be left in situ ("diagnosis and leave") avoiding the risks of perforation or bleeding from unnecessary polypectomy.

From an efficiency perspective, a "resect and discard" strategy allows a large proportion of patients to receive an immediate surveillance interval post-procedure without the need for a follow up appointment which speeds up decision making and reduces anxiety. In a post-procedure survey we found 98.7% were satisfied with an OD approach and 82.5% accepted real-time characterisation of small polyps found during the procedure (see Chapter 9).

A "resect and discard" strategy may also help reduce the environmental impact of endoscopy which is a major contributor to the environmental impact of healthcare (243). In a recent study, it was suggested 3 histology pots are equivalent to driving 2

miles in a petrol car (244). As such, a "resect and discard" strategy would result in a major reduction in use of histopathology pots which would directly mitigate the carbon footprint associated with colonoscopy.

Demand for colonoscopy in the NHS has increased more than 5% per year on average between 2014 and 2019 (245). It is expected this trend will increase so the demonstrated cost savings associated with OD will likely increase. Covid-19 has increased pressure on endoscopy services with a marked increase in waiting times; at the peak of the pandemic 60% of patients waited longer than the six-week target set by the NHS (246).

Average procedure time in DISCARD3 was 27 minutes exactly and in the 100 colonoscopies performed after the study ended, using a "resect and send" approach, procedure time was 27 minutes and 22 seconds (p=0.672). There was therefore no significant difference in procedure time with a "resect and discard" strategy compared with the traditional "resect and send" approach. In a further analysis of polyp characterisation time (time taken to describe the polyp +/- state optical diagnosis with confidence level) this was 19 seconds in the "resect and discard" group and 22 seconds in the standard group (p=0.734). Therefore, on a per-polyp basis there was no significant increase in time required during the procedure with a "resect and discard" strategy.

DISCARD3 showed a "resect and discard" strategy for polyps diagnosed with high confidence is feasible and safe with performance exceeding the 90% surveillance interval concordance threshold required for implementation. Most NHS hospitals already have image-enhancing colonoscopes so implementation would not require large scale investment. However, to ensure this is safe, we suggest implementation should be restricted to accredited BCSP endoscopists as part of a quality assurance process. In DISCARD3 we found the highly experienced and rigorously monitored endoscopists could consistently perform at the standard required with any drop in performance detected by a quality assurance process (see Figure 43). We propose each BCSP centre has an 'Optical Diagnosis Champion' responsible for delivering training and providing ongoing feedback. The resources required to implement this, such as an additional specialist screening practitioner and consultant time, are worthwhile and can

be absorbed at the institution level. This approach would allow widespread and safe implementation across BCSP centres throughout England.

Several previous studies have assessed the economic value of real-time optical diagnosis of diminutive polyps with similar results showing it is a cost-saving strategy (196,234,235,238,247). In our analysis, we show that extending the strategy to polyps <10 mm in size further reduces the need for histology assessment and increases potential savings of healthcare resources. Even where the cost of a quality assurance process is taken into consideration there is a substantial benefit of implementing a "resect and discard" strategy.

### 11.4.2 Strengths and limitations

The DISCARD3 study evaluated performance of optical diagnosis by 8 experienced endoscopists. A key strength of this was that all endoscopists undertook validated OD training and received feedback as part of a novel quality assurance programme. Some studies have suggested OD accuracy is better in academic centres rather than generalist settings (205). However, we believe that a "resect and discard" strategy is safe and feasible for implementation within the English BCSP which requires all endoscopists to undergo a rigorous accreditation process as well as ongoing monitoring of KPIs. Such accredited endoscopists perform BCSP colonoscopy in both academic and non-specialist centres.

Although cost inputs were based on NHS tariffs and unit costs the actual costs might vary from centre to centre. However, the included costs reflect those for which providers would be reimbursed and assume care is provided in the most efficient and cost-effective way. The histopathology cost per polyp reflects standard assessment involving the polyp specimen being sliced into 3 levels. Additional levels might be required in a minority of cases so the calculated histopathology costs present a conservative estimate.

We did not model long-term outcomes, such as disease progression for patients with small and diminutive polyps, leading to an underestimation of the calculated cost savings. Our model is also conservative as it did not consider equipment and time savings for histopathology and the ability for this to be directed to other areas of

histopathology where resources are stretched; the savings for the healthcare system at large are therefore likely to be much greater. This is important as a Royal College of Pathologist's survey published in 2018 showed only 3% of histopathology services have sufficient staff to meet current workload (248). This results in £27m being spent across the UK outsourcing services and locum doctors. In addition, this report showed a quarter of histopathologists are approaching retirement and there are insufficient trainees to fill the posts. These findings have now been further compounded by the impact of the Covid-19 pandemic which has stretched services further. Implementation of a "resect and discard" strategy in real life clinical practice will help address the challenges facing histopathology services in England. Based on an interview with a pathology expert, on average 20 minutes per polyp is needed for histopathological assessment. For ≤5 mm polyps, histopathologists could reduce their assessment time by 72% and save 3,640 working days (~£1.3m based on a 5-year experienced consultant). In the case of <10 mm polyps, assessment time would be reduced by 75% and could save 3,836 working days (~£1.4m based on a 5-year experienced consultant). Finally, this analysis focused only on the consequences of a "resect and discard" strategy on the healthcare system with the patient perspective addressed separately (see Section 9.3.6).

### 11.4.3 Further work

Further prospective studies are required to evaluate the real-life economic impact of a "resect and discard" strategy. In addition, further economic analyses are required for other healthcare settings and countries.

### 11.4.4 Conclusion

DISCARD3 has demonstrated the English NHS could make a substantial cost saving of £4.4m per year with a diminutive polyp "resect and discard" strategy and £5.3m per year with a small polyp "resect and discard" strategy. Even after taking into account the cost of a quality assurance process the savings are £2.4m and £3.4m respectively. BSG surveillance intervals achieve the PIVI criteria for safe implementation. Based on these findings, we would support the implementation of a "resect and discard" strategy with a quality assurance process in place within the English BCSP.

# Chapter 12 Post-colonoscopy colorectal cancer (PCCRC): Validation of nationally reported PCCRC cases at local level to help improve quality (REFLECT)

The contents of this chapter is based on a publication in Frontline Gastroenterology[17] (249).

## 12.1 Background and Aims

### 12.1.1 Background

#### a What is PCCRC?

One might expect complete reassurance with no colorectal cancer risk, at least in the near future, after having a 'negative' colonoscopy reported as 'normal'. However, the phenomenon of cancer occurring soon after this scenario is real. In the past, a number of terms have been used to describe this and such cases have been analysed and reported in disparate ways making meaningful comparisons between datasets difficult.

The World Endoscopy Organisation (WEO) have provided clarity with a consensus statement recommending that 'post-colonoscopy colorectal cancer' (PCCRC) be the preferred term for cancers appearing after a colonoscopy in which no cancer is diagnosed' (153). In order to allow benchmarking between services, WEO recommends consistent reporting of a 3 year interval (PCCRC-3yr) after the original negative colonoscopy which occurs closest to the colorectal cancer diagnosis (index colonoscopy); see Figure 56.

In the first 6 months of this 3 year period, should a cancer be diagnosed, it is referred to as a 'detected cancer' rather than a PCCRC. The rationale for this is to provide units a

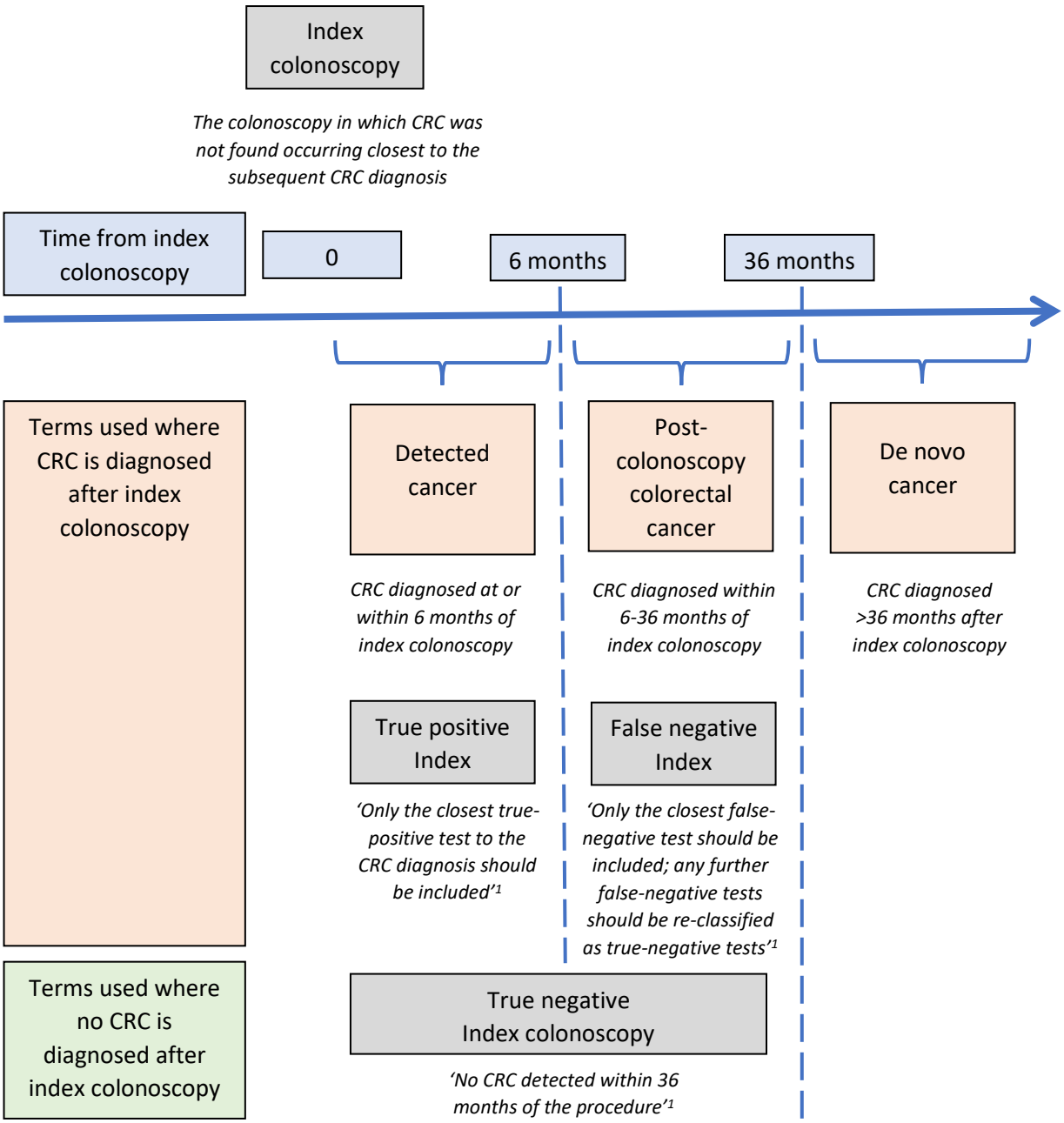
[17] Ahmad A et al. Validation of post-colonoscopy colorectal cancer (PCCRC) cases reported at national level following local root cause analysis: REFLECT study. Frontline Gastroenterology. 2022;13(5): 374–380. Tables and figures reproduced with permission.

grace period to allow more complex procedures to be repeated if necessary (eg poor bowel preparation and incomplete procedures due to looping).

### b How do PCCRC rates vary nationally?

A population based cohort study in England showed significant variation in PCCRC-3yr rates between colonoscopy providers (152). Burr et al linked population based data derived from Hospital Episodes Statistics (HES) data with national cancer datasets. Overall, the unadjusted PCCRC-3yr rate in England was 7.4%. As one might expect, the PCCRC-3yr rate was lower in a bowel cancer screening setting. The rate was found to be higher amongst non-NHS providers. Additionally, PCCRC-3yr rates were higher in women, the elderly, those with more comorbidities, inflammatory bowel disease (IBD), diverticular disease and those with previous cancers.

Figure 56 Overview of terminology used to describe cancer occurring after a negative colonoscopy




## 12.1.2 Aim

1. Determine the most likely cause of PCCRCs occurring at a tertiary referral centre, identified by population-based data, by performing a local root cause analysis

## 12.2 Methods

### 12.2.1 Study design

Population based data, collected by the National Cancer Registration and Analysis Service (NCRAS) was used to identify PCCRC cases occurring during the period 2005-2013 (cases were followed up to 2016). From this national dataset, permission was obtained to receive details of all PCCRC cases at London North West University Healthcare NHS Trust. Our centre has a secondary and tertiary referral service and performs an average of 7700 colonoscopies annually. In accordance with WEO recommendations, we requested data only for cancer cases occurring in a 3-year window after the index colonoscopy (153).

In total, 107 'PCCRC' cases were provided from the national dataset and for each PCCRC case, we received the NHS number, cancer diagnosis date and index colonoscopy date. We excluded 20 cases from the analysis (16 incomplete datasets and 4 duplicates; see Figure 57). The remaining 87 'PCCRC cases' underwent a root cause analysis with a thorough review of patient case notes to firstly validate the 'PCCRC' case and then allow evaluation of the factors more likely responsible for confirmed PCCRC cases.

As part of the case note review, and in accordance with WEO recommendations, all imaging and endoscopic examinations occurring 4 years prior to the cancer diagnosis were taken into consideration when evaluating plausibility. In addition, photodocumentation from the index colonoscopy underwent a second blinded review to check landmarks were documented.

Cases were categorised according to the WEO classification as one of the following:

- Possible missed lesion, prior examination adequate
- Possible missed lesions, prior examination inadequate
- Detected lesion, not resected
- Likely incomplete resection of previously identified lesion
- Likely new cancer
- Other

In terms of adequacy (required for the first 2 categories) caecal/neo-terminal ileum photodocumentation, rectal retroflexion and bowel preparation quality were assessed. Cases were classified as inadequate where caecal photodocumentation was not documented and/or bowel preparation was inadequate. After a review of patient case notes we recorded our assessment of the factors (patient, clinician and/or service) we considered primarily responsible for PCCRC occurrence.

### 12.2.2 Statistical analysis

The analysis was largely descriptive. Number and percentage are provided for categorical variables. Median and range were used for descriptive statistics. The exact binomial method was used to calculate the confidence interval for false PCCRCs.

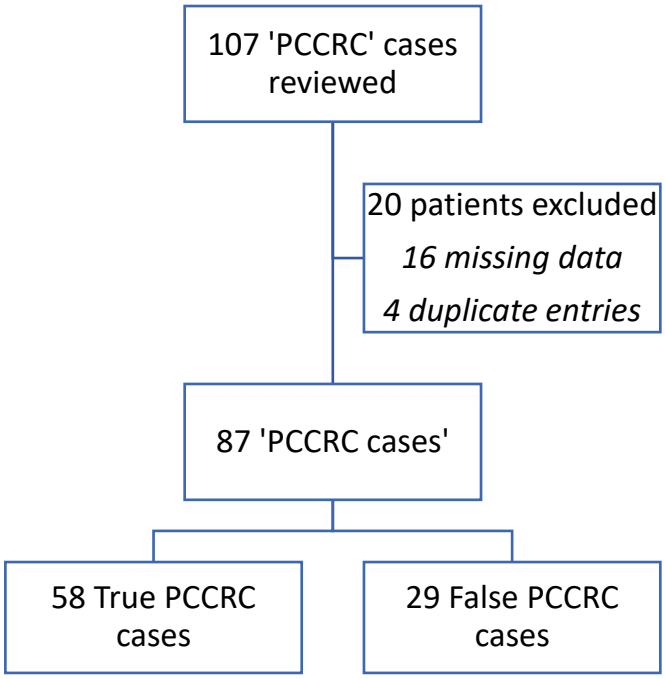
## 12.3 Results

### 12.3.1 Overview

#### a Study participants

In total, 87 'PCCRC cases' underwent detailed case note review. Of these, 33% (29/87; CI 23.6-44.3%) were false PCCRCs (see Figure 57). The false PCCRCs comprised 17 detected cancers and 12 national data errors. The data errors included cases where the index examination was not a colonoscopy, where cancer was diagnosed before the 'index' colonoscopy and where the 'index colonoscopy' date was incorrect as there was another colonoscopy that occurred closer to the cancer diagnosis date.

Figure 57 Study overview




The true PCCRCs occurred in 56.9% (33/58) of males and 43.1% (25/58) of females (see Table 30). PCCRCs were diagnosed at a mean age of 63.3 years (range 28-93 years). There was a median time of 16.2 months from index colonoscopy to cancer diagnosis. IBD (18/58, 31.0%) was the most common primary indication for the procedure followed by a history of previous polyps (17/58, 29.3%).

In PCCRC cases the site of cancer was most common in the rectum (19/58; 32.8%) then ascending colon (8/58; 13.8%) and sigmoid (7/58; 12.1%). Cancer site was unknown in 4 cases as there was no locally available information which is most likely due to cancer being diagnosed at a different hospital.

The endoscopist performing the index colonoscopy was most commonly a consultant (29/58; 50.0%) followed by independent non-consultant endoscopists (25/58; 43.1%) and nurse endoscopists (4/58; 6.9%).

Bowel preparation was not documented in 27/58 (46.6%) of cases. This had not yet become a mandatory field on endoscopy reporting software during the study period. Inadequate bowel preparation was recorded in 6/58 (10.3%) of cases. In the remainder of cases, bowel preparation was excellent (3/58, 5.2%) or adequate (22/58, 37.9%).

In terms of photodocumentation, this was adequate for caecal landmarks and/or terminal ileum (TI)/neo-TI/anastomosis in 30/58 (51.7%) cases and for rectal retroflexion in 20/58 (34.5%) cases. A blinded endoscopist reviewed all photodocumentation and agreed with the photodocumentation outcomes. In 29/58 (50%) of cases the lesion/segment in question was photodocumented.

In 93.1% (54/58) of cases TI (29/58, 50.0%) or caecum (25/58, 43.1%) was reached. There were four incomplete procedures: 2 had previous surgery (right hemicolectomy), 1 had an impassable rectal tumour, and 1 had a 'fixed sigmoid' secondary to pericolic adhesions.

Table 30 Characteristics of validated PCCRC cases

| | **Number of cases** |
|---|---|
| **Total patients** | 58 |
| Male | 33 (56.9%) |
| Female | 25 (43.1%) |
| **Age (median, years)** | 63.4 (range 28-93) |
| **Risk factors** | |
| IBD | 18 (26.5%) |
| Previous polyps | 17 (25.0%) |
| Previous colorectal cancer | 9 (11.8%) |
| Hereditary forms of CRC | 6 (8.8%) |
| Declined surgery | 5 (7.4%) |
| Family history | 2 (2.9%) |
| None | 9 (13.2%) |
| Other | 3 (4.4%) |
| **Cancer site** | |
| Caecum | 4 (6.9%) |
| Ascending colon | 8 (13.8%) |
| Hepatic flexure | 6 (10.3%) |
| Transverse colon | 3 (5.2%) |
| Splenic flexure | 1 (1.7%) |
| Descending colon | 1 (1.7%) |
| Sigmoid colon | 7 (12.1%) |
| Rectosigmoid junction | 3 (5.2%) |
| Rectum | 19 (32.8%) |
| Anastomosis | 1 (1.7%) |
| Multifocal | 1 (1.7%) |
| Unknown | 4 (6.9%) |
| **Endoscopist (primary)** | |
| Consultant | 29 (50.0%) |
| Independent endoscopist (non-consultant) | 25 (43.1%) |

| | |
|---|---|
| Nurse endoscopist | 4 (6.9%) |
| **Quality of bowel preparation** | |
| Excellent | 3 (5.2%) |
| Adequate | 22 (37.9%) |
| Inadequate | 6 (10.3%) |
| Not documented | 27 (46.6%) |
| **Photodocumentation** | |
| At least 2 or 3 caecal landmarks or TI/neo-TI/anastomosis | 30 (51.7%) |
| Rectal retroflexion | 20 (34.5%) |
| Lesion or segment in question | 29 (50.0%) |

### b Most plausible explanation for PCCRC

PCCRC cases were categorised according to most plausible explanation with the most frequent category 'possible missed lesion, prior examination negative but inadequate' (23/58, 39.7%; see Table 31).

Table 31 Most plausible explanation of validated PCCRC cases

| Most plausible explanation for PCCRC | Number of patients |
|---|---|
| Possible missed lesion, prior examination adequate | 8 (13.8%) |
| Possible missed lesion, prior examination negative but inadequate | 23 (39.7%) |
| Detected lesion, not resected | 14 (24.1%) |
| Likely incomplete resection of previously identified lesion | 11 (19.0%) |
| Likely new cancer | 0 (0%) |
| Other | 2 (3.4%) |

The second most frequent explanation was a 'detected lesion, not resected' (14/58, 24.1%). Of these cases, 9/14 (64.3%) had a history of IBD with uni/multifocal dysplasia, 2/14 had previous polyps and 1/14 had Peutz-Jeghers syndrome.

The third most frequent explanation was 'likely incomplete resection of previously identified lesion' (11/58, 19.0%). Of these cases 6/11 (54.5%) occurred in more difficult polypectomy sites (3 hepatic flexure, 1 splenic flexure, 1 rectosigmoid junction, 1 ileocaecal valve). The remaining cases occurred in the rectum (3/11), sigmoid (1/11) and ascending colon (1/11). There were no cases classified as due to a 'likely new cancer'.

#### c Factors most likely responsible for true PCCRC

As part of the root cause analysis of all true PCCRC the factors most likely responsible were assessed (see Table 32).

Table 32 Most likely factors responsible for validated PCCRC cases

| | Number of patients |
|---|---|
| Clinician | 37 (63.8%) |
| Service | 7 (12.1%) |
| Patient | 5 (8.6%) |
| Combination | 9 (15.5%) |

The majority of PCCRC cases were due primarily due to clinician factors (37/58, 63.8%). This included cases where the clinician performed an 'inadequate' examination (incomplete photodocumentation, poor bowel preparation) or where lesions were identified and incompletely resected.

The remainder of cases were due to service factors (7/58, 12.1%), patient factors (5/58, 8.6%) or a combination of factors (9/58, 15.5%). Service factors were due to delays in endoscopy/surgery follow up appointment scheduling or surgery. Patient factors were due to surgery being declined (3/58) or where delays in surgery occurred due to reluctance or failure to attend presurgical optimisation (2/58).

## 12.4 Discussion

### 12.4.1 Key findings

#### a Population-based data can misclassify detected cancers as PCCRCs

In this study, population-based data from the national COloRECTal cancer Repository (CORECT-R) was provided by The UK Colorectal Intelligence Hub. This links HES, National Cancer Registration and Analysis Service and English NHS BCSP datasets. 'PCCRC' cases underwent a detailed root cause analysis to validate the case and determine the most plausible explanation.

33.3% (29/87) of cases identified as 'PCCRCs' from this population-based data were, after local root cause analysis, found not to meet the definition. Of these, 58.6% (17/29) were detected cancers and 41.4% (12/29) were data errors. In all case the index and diagnosing colonoscopies occurred within the same trust with no errors due to missing data between trusts.

National registries vary in accuracy and are often affected by administrative error including errors due to data merging, inaccurate coding and missing data (250–254). For example, after adjusting for administrative error, Gotfried et al showed a 47% reduction in interval CRC (3.9% to 2.1%) in cases identified from registry data for a single institution (253). This theme is consistent with our finding, and suggests PCCRC rates published previously for the English National Health Service based on population-based data, may be an overestimation (152).

### b IBD is the most frequent risk factor occurring in true PCCRCs

In true PCCRC cases, IBD was the most frequent risk factor occurring in 26.5% (18/58) of cases. This is consistent with previous studies showing higher PCCRC-3yr rates amongst IBD patients (152,255). For example, PCCRC-3yr rates in those with IBD were three times higher than the study cohort in an English population (152). This is consistent with a Danish study which showed a similar relative risk with a PCCRC-3yr rate of 24.3% in IBD patients versus 7.5% in non-IBD patients (255).

Previous studies have shown PCCRCs appear to occur more frequently in patients with UC than Crohn's (253,254). In a Danish study, the relative risk of PCCRC occurring in UC and Crohn's was 3.44 and 1.44 respectively (253). Similarly, a Swedish study showed the relative risk was 5.44 and 3.81 respectively (254).

A number of factors may increase PCCRC risk in IBD. Firstly, colorectal cancers occurring in IBD are thought to be faster growing than non-IBD cases (256–258). Secondly, a dysplastic lesion might be detected with subsequent delays due to service, clinician or patient factors resulting in a detected cancer becoming a PCCRC. Thirdly, the more frequent colonoscopic surveillance in this group may increase the chance of a PCCRC being diagnosed.

In this study, the most common explanation for PCCRC where IBD was the procedure indication was 'possible missed lesion' occurring in 56% (10/18) of cases. Dye spray was not used in 61% (11/18) of these cases which may have contributed to reduced detection of subtle dysplastic lesions. In 5/11 cases dye spray was not used for appropriate reasons (poor bowel preparation, active disease and poor procedure tolerance) and in 6/11 cases no reason was documented.

A 'detected lesion, not resected' was the second most common explanation for PCCRC occurring in IBD. The majority of detected lesions (75%, 6/8) had visible dysplasia with the remaining cases (25%, 2/8) having a stricture and suspected mass.

### c PCCRCs occur most commonly in the rectum

We found PCCRCs occur most commonly in the rectum (32.8%) followed by ascending colon (13.8%) and sigmoid colon (12.1%). The high proportion of rectal PCCRCs may in part be due to the high prevalence of colorectal cancer at this site. In addition, a failure to perform rectal retroflexion could contribute (259). In our study, rectal retroflexion was only photodocumented in 34.5% of PCCRCs. In some cases rectal retroflexion is not appropriate such as a small calibre rectum, in the context of active inflammation and in cases of poor patient tolerance.

The high occurrence of PCCRCs in the ascending colon is consistent with previously reported findings that colonoscopy is less effective at preventing right colon cancers (260,261). In this region of the bowel lesions tend to be flatter increasing the risk of failure to detect during colonoscopy. In addition, tumour/polyp biology in this region may result in a higher growth rate in these lesions (256).

The third most common site for PCCRCs was the sigmoid colon. This could be in part due to the long, narrow and mobile sigmoid anatomy with tightly packed haustra, when withdrawing with a straight scope, increasing the risk of missed lesions.

### d PCCRCs occur in all endoscopist grades

In this study, we found 50% of PCCRCs occurred in procedures performed by consultants and 43.1% of cases by a non-consultant independent endoscopist. Although consultant operators are likely to be more experienced, their case-mix might

predispose to PCCRC with more complex cases such as repeat colonoscopy for failed procedures, tertiary referrals and IBD surveillance.

This also highlights the fact that even in the context of an expert colonoscopist performing an optimal colonoscopy, there is always a risk of PCCRC. The colonoscopy procedure has inherent limitations in that complete mucosal visualisation cannot be guaranteed. In addition, other uncontrollable factors include a rapidly occurring cancer which might occur after a true negative colonoscopy, or a patient who declines surgery for a high risk lesion.

### e The most common explanation for PCCRCs was a possible missed lesion in an inadequate examination

In 39.7% of PCCRCs, the most plausible explanation was a 'possible missed lesion, prior examination negative but inadequate'. The colonoscopy was considered inadequate due to lack of photodocumentation of rectal or caecal landmarks. This was followed by 'detected lesion, not resected' occurring in 24.1% of PCCRCs. This category often included patients with IBD dysplasia who declined surgery.

In 19.0% of cases there was 'likely incomplete resection of previously identified lesion'. These cases were frequently associated with previous polypectomy attempts or previous treatment for polyp recurrence (73%, 8/11). In addition, the site of polypectomy was usually at locations where scope stability is more challenging, such as the rectosigmoid junction, hepatic/splenic flexures and ileocaecal valve. In addition, in only 27% (3/11) of cases there was post-polypectomy photodocumentation. Enhanced post-polypectomy photodocumentation would provide evidence of complete endoscopic resection. This would be helpful as histological determination of resection completeness is not always possible. In most cases appropriate follow up had been arranged but there were 3 cases where service factors caused a delay.

### f Patient factors are responsible for a significant proportion of PCCRCs

The clinician is the procedure operator and therefore in a position to influence several factors affecting high quality lesion detection and removal. It is not surprising therefore, that the clinician was assessed to be primarily responsible for 63.8% (37/58) of cases.

A small but significant proportion of PCCRC cases were due entirely to patient factors (8.6%). Here patient refusal or delays due to patient reluctance occurred in patients who were fully aware of the risk of cancer. Variations in patient populations, such as sociodemographic characteristics, might influence the occurrence of PCCRC in cases where patients refuse surgery despite being clearly informed of cancer risk.

As PCCRC is intended to be used as a standardised measure of performance, excluding cases where patient factors are primarily responsible for the PCCRC, might allow more consistent benchmarking across different patient populations.

### 12.4.2 Strengths and limitations

Although the WEO definitions of PCCRCs have allowed standardisation of terminology in this area, there are some assumptions made. For example, it recommends assessment of most plausible explanation for PCCRC be based on assessment of a 4-year period due to the lesion's 'biology'. Uncertainty about the true biology of colorectal cancer could alter the validity of explanations provided for PCCRCs. In addition, we assigned no PCCRC cases as 'likely new cancer' perhaps as this is a more restrictive and subjective category.

When assessing the most plausible explanation for a PCCRC there is often more than one explanation. For instance, there might be an inadequate examination due to poor bowel preparation in a case where there was a cancer found at a segment where polypectomy had been performed. In this case, PCCRC could be due to incomplete resection or a failure to detect the lesion on an inadequate examination. For all cases of ambiguity, the root cause analysis was reviewed by an expert colonoscopist who advised on the most likely explanation for the PCCRC.

### 12.4.3 Further work

Further research is required to assess interventions that might influence PCCRC rate. Also, further studies are required for IBD-related PCCRC cases to better understand causation.

### 12.4.4 Conclusion

Detailed local root cause analysis provides valuable information to help understand PCCRC causation. Using local data at our centre, we found a third of 'PCCRC' cases identified from population-based data were in fact detected cancers or data errors. Enhanced photodocumentation during colonoscopy would help more accurately explain PCCRC causation and could help improve examination quality. Effective feedback systems are required to ensure the growing awareness of PCCRC leads to impactful change in clinical practice.

# Chapter 13 Discussion

The aim of this thesis was to explore efficiency of colonoscopy throughout the patient pathway and to examine at the procedure-level how this could be improved. To address this question, a number of projects examining key points in the colonoscopy pathway were performed. Overall, these have highlighted potential for improvements in the way colonoscopy is practised as well as scenarios where we can achieve the same outcomes more efficiently. In the sections that follow an overview of the key findings from each study and the impact of this research is provided.

### 13.1.1 Bowel preparation: CLEANSE study

In the CLEANSE study, we evaluated a novel bowel preparation regimen (Plenvu) that is not only low-volume but also, unlike standard regimens, allows a same-day administration (see Chapter 2). We found Plenvu offered improved bowel cleansing compared with standard regimens as evidenced by a significantly improved BBPS score. There was also no adverse impact on the inadequate bowel preparation rate and polyp detection. However, in the patient survey, taste was not rated as highly as Senna & Citramag and there was a small but significant increase in patient-reported side effects when compared with Moviprep.

In terms of impact, CLEANSE showed that same day bowel preparation administration can be given safely with high levels of bowel cleansing. This provides patients with an alternative same-day regimen that achieves similar results to 2-day regimens. Where implemented there is potential for patients to be scheduled for colonoscopy at shorter notice which could help fill gaps in endoscopy lists albeit only for afternoon and evening appointments. Same-day Plenvu administration may also help reduce the disruption caused to patients by bowel preparation administration and could help with compliance. Ultimately, we feel decisions about bowel preparation choice should be individualised but CLEANSE shows there are clear advantages from an efficiency perspective of using a same-day Plenvu regimen.

### 13.1.2 Water-assisted colonoscopy: National survey and WAVE study

In a national survey of water-assisted colonoscopy we evaluated current practice (see Chapter 3). We found the majority of respondents used water-assisted colonoscopy, either exclusively or in combination with $CO_2$. However, a significant proportion had no formal training in water-assisted colonoscopy and although there was a perceived improvement in patient comfort there was also a concern about a possible increase in withdrawal time. We also found variation in water-assisted colonoscopy technique with most colonoscopists tending to use water predominately to splenic flexure and then use $CO_2$ predominately to caecum.

The impact of this survey was that it raised awareness of the so-called 'hybrid' technique which had not been previously evaluated in detail unlike other less common techniques such as water-exchange colonoscopy. It also highlighted the need for improved training which needs to be underpinned by high quality evidence and so led to the development of the WAVE study.

In WAVE, we performed a randomised evaluation of a 'hybrid' technique versus a water-exchange technique to examine the efficiency of colonoscope insertion (see Chapter 4). We found water-exchange colonoscopy significantly increased procedure time (by 4 minutes on average), required more patient repositions and failed in 16% of cases (where a switch to 'hybrid' technique was required). However, water-exchange provided significantly better left colon cleansing but there was no significant difference in total BBPS score, overall loop formation, sedation requirement, caecal intubation rate and polyp detection.

The impact of this study is that it provides evidence that a hybrid technique offers more efficient colonoscope insertion with similar outcomes achieved to water-exchange. The hybrid technique appears to harness the beneficial impact of both water and $CO_2$ during colonoscope insertion. This research adds to the evidence base for water-assisted colonoscopy and will help inform future training in colonoscopy to improve insertion technique in clinical practice.

### 13.1.3 Polyp detection: Service evaluation and AI-DETECT study

In an early service evaluation of a computer-aided polyp detection system (GI Genius) during colonoscopy we found no difference in PDR and ADR amongst a group of high performing endoscopists (see Chapter 5). There was also a significant false positive rate but endoscopists reported no adverse effect on the procedure. We explored this further in the AI-DETECT study, a randomised evaluation of CADe during colonoscopy (see Chapter 6). We found amongst high performing colonoscopists in a BCSP setting there was a marginal increase in PDR but no increase in ADR. We observed no improvement in detection of flat and diminutive polyps. There was no adverse effect on procedure time.

In terms of impact, the findings from AI-DETECT contrast with previous studies that showed a more positive effect of using CADe. This most likely reflects the high baseline performance of participating endoscopists who use Endocuff Vision routinely for screening colonoscopy. The potential increase in polyp detection was therefore limited by a plateau effect due to high baseline PDR and ADR. This study showed CADe clearly has a role in colonoscopy but might be more effective amongst low polyp detectors and trainees outside screening programmes. There was no adverse impact on procedure time. As AI algorithms improve, we expect the positive impact of CADe within colonoscopy practice will be further enhanced.

### 13.1.4 Optical diagnosis: National survey, Photodocumentation quality, DISCARD3 study

We performed a national survey of optical diagnosis in colonoscopy to better understand current training and practice (see Chapter 7). We found most endoscopists use optical diagnosis and feel confident with this but only a minority have had formal training. We also found the NICE classification is frequently used for polyp characterisation but is often also supplemented with adjuncts to support decision-making. In terms of whether a "resect and discard" strategy is a desirable goal of colonoscopy there was a mixed response. The impact of this survey was that it highlighted a clear need for enhanced training in optical diagnosis and also the need for

improved understanding of how optical diagnosis with a "resect and discard" strategy could be implemented in real life clinical practice.

A fundamental aspect of optical diagnosis, and a critical component where combined with a "resect and discard" strategy, is high quality photodocumentation. We reviewed photodocumentation quality standards in colonoscopy as well as barriers to high quality photodocumentation (see Chapter 8). This resulted in the development of the "3C" Endoscopy Photo Quality Checklist to provide a framework for endoscopists. The impact of improving photodocumentation quality during colonoscopy, with this simple and often neglected aspect of procedure performance, is wide-ranging from a potential reduction in PCCRC risk to facilitating implementation of a resect and discard strategy.

In DISCARD3, a major feasibility study evaluating optical diagnosis in real life clinical practice, we addressed the survey findings relating to training and implementation (see Chapter 9). In contrast with other studies, DISCARD3 was underpinned with a comprehensive quality assurance process including completion of a validated optical diagnosis training module, group training sessions, continuous monitoring of performance, root-cause analysis of error and individual feedback where required. In this study we learnt that, although the learning curve for optical diagnosis varies, most BCSP accredited colonoscopists are able to consistently perform OD with ≥75% OD accuracy and can maintain this after 75 high confidence diagnoses. However, even those with high initial OD performance require a period of supervised OD as some endoscopists showed a reduction in performance during the study period highlighting the importance of a quality assurance process. In terms of safety of a "resect and discard" strategy, DISCARD3 showed that the PIVI threshold for optical diagnosis-histopathology surveillance interval concordance is exceeded with the BSG, ESGE and US Multi-society task force guidelines when using a diminutive polyp OD strategy. If extended to a small polyp OD strategy the PIVI thresholds are exceeded with the BSG and ESGE guidelines but not the US guidelines. There were no polyp cancers in polyps <10 mm and high risk polyp features, such as high grade dysplasia, were rare.

In a sub-study of DISCARD3, we took a deep-dive into understanding the causes of high confidence optical diagnosis error with a detailed root cause analysis of every case of discordance with histology (see Chapter 10). To facilitate this, we developed a new

OD error classification categorising into 4 types (A to D). During the analysis, we discovered a group of atypical serrated polyps, which may be referred to as pseudo-adenomas, that are frequently misdiagnosed as adenomas. These have tubular/elongated crypts without visible vessels surrounding these and optically have an inverse appearance to adenomas. We also documented some limitations of the NICE criteria. For example, some adenomas are in fact lighter or similar in colour to the background mucosa which can cause diagnostic error or reduced confidence when applying the NICE criteria. For each error type we suggested adjuncts to help improve diagnostic accuracy and incorporated this into a proposed algorithm to support real-life decision making. The impact of this sub-study is that it has improved our fundamental understanding of the optical appearances of major polyp types and the underlying causes of optical diagnosis error. The proposed algorithm will also help improve accuracy and endoscopist confidence in OD further supporting implementation of a "resect and discard" strategy.

We also evaluated the economic impact of implementing a "resect and discard" strategy in a separate sub-study of DISCARD3 (see Chapter 11). Although previous analyses have already shown significant benefit, this was the first detailed analysis extrapolating implementation to a national level within the BCSP and also took into account the cost of a quality assurance process. This found annual savings of £2.4m would be expected with a diminutive polyp OD strategy and £3.4m with a small polyp OD strategy. If implemented, we expect the financial impact would be significantly enhanced over time in view of rising demand for endoscopy services and the expansion of the English BCSP with age-extension and inclusion of patients with Lynch syndrome.

Overall, DISCARD3 provides good evidence that, in the setting of high-performing accredited colonoscopists who complete validated training in OD and are monitored with a quality assurance process in place, a "resect and discard" strategy is feasible, safe and cost-effective. It also has a potential environmental benefit by reducing the carbon footprint of unnecessary, resource-intensive and time-consuming histopathology. This study supports implementation of a "resect and discard" strategy more widely within the English BCSP. Future studies, should ideally include a multi-

centre pilot study within the BCSP as well as detailed evaluation of the environmental impact of a "resect and discard" strategy.

### 13.1.5 Post-colonoscopy colorectal cancer: REFLECT study

PCCRC is an important measure of the quality of a colonoscopy service and population-based data has shown significant variation across England (152). In REFLECT, we performed a root cause analysis with detailed local case note review of all nationally reported PCCRC cases over an 8 year period at a single centre (see Chapter 12). We learnt that a third of 'PCCRCs' reported from population-based data were in fact not PCCRCs and the majority of these cases were detected cancers. IBD was identified as the most frequent risk factor and the rectum was a common site for PCCRC occurrence. The most frequent explanation for a PCCRC was a possible missed lesion in an inadequate prior examination. This was most often due to lack of photodocumentation of rectal and caecal landmarks. We also found a small but significant proportion of PCCRCs were due entirely to patient factors such as patient refusal for surgery in the context of full awareness of the risk of colorectal cancer.

The impact of this study is that it shows the importance of local root cause analysis to accurately identify PCCRC cases and evaluate causation. It further reinforces the need for high quality photodocumentation, not only as a marker of examination quality but also to support root cause analyses of PCCRC cases. Better understanding of the most plausible causes of PCCRC also has educational and training value to improve the quality of colonoscopy performed and ultimately the efficiency of a colonoscopy service.

# Chapter 14 Conclusion

In the context of increasing demand for colonoscopy and rising pressure on healthcare services generally the need for improved efficiency has never been greater. This body of work has examined efficiency in colonoscopy throughout the patient pathway with a focus on the procedure itself. This portfolio of studies evaluating bowel preparation, polyp detection, optical diagnosis, insertion technique, and post-colonoscopy colorectal cancer has provided valuable and practical insights that can be translated directly into clinical practice. We hope these insights will not only lead to improvements in the quality of colonoscopy but will also enhance patient experience for those undergoing this important procedure.

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# Chapter 16 Appendices

## 16.1 Appendix 1 – Publications and presentations arising from this thesis

### 16.1.1 Original articles

Orlovic, M., Ahmad, A., & Saunders, B. P. (2023). Economic impact of implementing optical diagnosis with a "resect and discard" strategy within the English Bowel Cancer Screening Programme: findings from the DISCARD3 study. *Gastrointestinal Endoscopy*. https://doi.org/10.1016/j.gie.2023.01.054

Ahmad, A., Marshall, S., Bassett, P., Thiruvilangam, K., Dhillon, A., & Saunders, B. P. (2023). Evaluation of bowel preparation regimens for colonoscopy including a novel low volume regimen (Plenvu): CLEANSE study. *BMJ Open Gastroenterology*, *10*(1), e001070. https://doi.org/10.1136/bmjgast-2022-001070

Ahmad, A., Wilson, A., Haycock, A., Humphries, A., Monahan, K., Suzuki, N., Thomas-Gibson, S., Vance, M., Bassett, P., Thiruvilangam, K., Dhillon, A., & Saunders, B. P. (2023). Evaluation of a real-time computer-aided polyp detection system during screening colonoscopy: AI-DETECT study. *Endoscopy*, *55*(04), 313–319. https://doi.org/10.1055/a-1966-0661

Ahmad, A., Moorghen, M., Wilson, A., & Saunders, B. P. (2023). NBI International Colorectal Endoscopic–derived high-confidence optical diagnosis of small polyps compared with histology: understanding errors to improve diagnostic accuracy. *Gastrointestinal Endoscopy*, *97*(1), 78–88. https://doi.org/10.1016/j.gie.2022.08.032

Ahmad, A., Moorghen, M., Wilson, A., Stasinos, I., Haycock, A., Humphries, A., Monahan, K., Suzuki, N., Thomas-Gibson, S., Vance, M., Thiruvilangam, K., Dhillon, A., & Saunders, B. P. (2022). Implementation of optical diagnosis with a "resect and discard" strategy in clinical practice: DISCARD3 study. *Gastrointestinal Endoscopy*, *96*(6), 1021-1032.e2. https://doi.org/10.1016/j.gie.2022.06.019

Ahmad, A., & Saunders, B. P. (2022a). Is a location-based resect-and-discard strategy the right approach? Endoscopy, 54(04), 434–434. https://doi.org/10.1055/a-1737-3901

Ahmad, A., & Saunders, B. P. (2022b). Photodocumentation in colonoscopy: the need to do better? *Frontline Gastroenterology*, 13(4), 337–341. https://doi.org/10.1136/flgastro-2021-101903

Ahmad, A., Dhillon, A., Saunders, B. P., Kabir, M., & Thomas-Gibson, S. (2022). Validation of post-colonoscopy colorectal cancer (PCCRC) cases reported at national level following local root cause analysis: REFLECT study. *Frontline Gastroenterology*, *13*(5), 374–380. https://doi.org/10.1136/flgastro-2021-102016

Ahmad, A., & Thomas-Gibson, S. (2019). Optimum colonoscopy withdrawal: Is time everything? *Gastrointestinal Endoscopy*, 89(3), 531–532. https://doi.org/10.1016/j.gie.2018.10.045

### 16.1.2 Oral presentations

Implementation of optical diagnosis with a “resect and discard” strategy in clinical practice; St Mark’s Hospital (UK), grand round presentation (May 2023)

Optical diagnosis with a resect and discard strategy – time for implementation? Medical University of South Carolina (USA); academic meeting (April 2023).

Implementation of optical diagnosis with a resect and discard strategy in clinical practice: the DISCARD3 study; Brighton Symposium 2022.

Post-colonoscopy colorectal cancer (PCCRC): the REFLECT study; Brighton Symposium 2022.

At the frontiers: artificial intelligence in IBD endoscopy; Frontiers 2022.

Optical diagnosis of polyps <10 mm and impact on surveillance interval (DISCARD3); UEG 2022.

Optical diagnosis of polyps <10 mm and impact on surveillance interval (DISCARD3); BSG 2022.

John Nicholls’ Prize Lecture: Efficiency in Colonoscopy; Frontiers 2022.

Learning curve of optical diagnosis with a resect and discard strategy for screening colonoscopy: preliminary results from the DISCARD3 study; DDW 2021.

Improving Colonoscopy Efficiency: Latest Research Insights; St Mark's Hospital (UK), grand round presentation (May 2021)

Learning curve of optical diagnosis with a resect and discard strategy for screening colonoscopy: preliminary results from the DISCARD3 study; ESGE Days 2021, received Registration Grant Award.

High confidence optical diagnosis of small polyps at colonoscopy versus histopathology: moving towards a new gold standard? ESGE Days 2021, received Registration Grant Award.

Colonoscopy Efficiency: Optimising a limited resource; St Mark's Hospital (UK), grand round presentation (Jan 2020)

### 16.1.3 Published abstracts

Ahmad A et al. Evaluation of standard bowel preparation regimes versus Plenvu (novel low volume regime): CLEANSE study. Poster Presentation, UEG 2022.

Ahmad A, et al. Learning curve for optical diagnosis of small polyps at screening colonoscopy (DISCARD3). Poster Presentation, UEG 2022.

Ahmad A, et al. Optical diagnosis practice in the UK: a national survey. Poster Presentation, UEG 2022.

Ahmad A, et al. Water-assisted colonoscopy practice in the UK: a national survey. Poster Presentation, UEG 2022.

Ahmad A, et al. Evaluation of standard bowel preparation regimes versus Plenvu (novel low volume regime): CLEANSE study. Poster Presentation, BSG 2022

Ahmad A, et al. Learning curve for optical diagnosis of small polyps at screening colonoscopy (DISCARD3). Poster Presentation, BSG 2022; awarded 'BSG Best Endoscopy Poster'

Ahmad A, et al. Optical diagnosis practice in the UK: a national survey. Poster Presentation, BSG 2022

Ahmad A, et al. Water-assisted colonoscopy practice in the UK: a national survey. Poster Presentation, BSG 2022

Ahmad A, et al. High confidence optical diagnosis of small polyps at colonoscopy versus histopathology: moving towards a new gold standard? Poster Presentation, Frontiers 2021

Ahmad A, et al. Learning curve of optical diagnosis with a resect and discard strategy for screening colonoscopy: preliminary results from the DISCARD3 study. Poster Presentation, Frontiers 2021

Ahmad A, et al. Small polyps at colonoscopy and the NICE classification: likely causes of optical diagnosis error. Poster Presentation, Frontiers 2021

Ahmad A, et al. No surveillance interval change with optical diagnosis of small polyps during bowel cancer screening colonoscopy. Poster Presentation, Frontiers 2021

Ahmad A, et al. PCCRC cases identified using population-based data may be re-classified as detected cancers when local data is used to perform a root cause analysis. Poster Presentation, Frontiers 2021

Ahmad A, et al. Patient acceptability of optical diagnosis for diminutive polyps with a resect and discard strategy in bowel cancer screening colonoscopy. Poster Presentation, BSG 2021

Ahmad A, et al. High confidence optical diagnosis of small polyps at colonoscopy versus histopathology: moving towards a new gold standard? Poster Presentation, BSG 2021

Ahmad A, et al. Learning curve of optical diagnosis with a resect and discard strategy for screening colonoscopy: preliminary results from the DISCARD3 study. Poster Presentation, BSG 2021

Ahmad A, et al. PCCRC cases identified using population-based data may be re-classified as detected cancers when local data is used to perform a root cause analysis. Poster Presentation, BSG 2021

Ahmad A, et al. Small polyps at colonoscopy and the NICE classification: likely causes of optical diagnosis error. Poster Presentation, BSG 2021

Ahmad A, et al. No surveillance interval change with optical diagnosis of small polyps during bowel cancer screening colonoscopy. Poster Presentation, BSG 2021

Ahmad A, et al. PCCRC cases identified using population-based data may be re-classified as detected cancers when local data is used to perform a root cause analysis. Poster Presentation, UEGW 2021

Ahmad A, et al. No surveillance interval change with optical diagnosis of small polyps during bowel cancer screening colonoscopy. Poster Presentation, UEGW 2021

Ahmad A, et al. Small polyps at colonoscopy and the NICE classification: likely causes of optical diagnosis error. Poster Presentation, UEGW 2021

Ahmad A, et al. Learning curve of optical diagnosis with a resect and discard strategy for screening colonoscopy: preliminary results from the DISCARD3 study. Poster Presentation, UEGW 2021

Ahmad A, et al. High confidence optical diagnosis of small polyps at colonoscopy versus histopathology: moving towards a new gold standard? Poster Presentation, UEGW 2021

Ahmad A, et al. Patient acceptability of optical diagnosis for diminutive polyps with a resect and discard strategy in bowel cancer screening colonoscopy. Poster Presentation, UEGW 2021

Ahmad A, et al. PCCRC cases identified using population-based data may be re-classified as detected cancers when local data is used to perform a root cause analysis. Poster Presentation, DDW 2021; poster of distinction.

Ahmad A, et al. High confidence optical diagnosis of small polyps at colonoscopy versus histopathology: moving towards a new gold standard? Poster Presentation, DDW 2021; poster of distinction.

Ahmad A, et al. PCCRC cases identified using population-based data may be re-classified as detected cancers when local data is used to perform a root cause analysis. Poster Presentation, ESGE Days 2021; Registration Grant Award.

Ahmad A, et al. Patient acceptability of optical diagnosis for diminutive polyps with a resect and discard strategy in bowel cancer screening colonoscopy. Poster Presentation, ESGE Days 2021; Registration Grant Award.

Ahmad A, et al. Early Evaluation of a Computer Assisted Polyp Detection System in Bowel Cancer Screening. Poster Presentation, BSG Campus 2021

# 16.2 Appendix 2 – Supplementary material

## 16.2.1 WAVE: Per-protocol results

Table 33 Procedural outcomes (PP analysis)

| Outcome | Hybrid | | Water-Exchange | | Difference* (95% CI) | P-value |
|---|---|---|---|---|---|---|
| | n | Summary | n | Summary | | |
| **Procedure times (minutes)** | | | | | | |
| Total time | 111 | 25 [21, 35] | 115 | 29 [23, 38] | 4 (1, 6) | **0.009** |
| *Insertion time* | 111 | 9 [7, 14] | 115 | 13 [9, 18] | 3 (2, 5) | **<0.001** |
| *Caecum time* | 111 | 3 [2, 5] | 115 | 4 [2, 5] | 1 (0, 1) | **0.04** |
| *Withdrawal time* | 111 | 11 [8, 16] | 115 | 11 [7, 16] | -1 (-2, 1) | 0.33 |
| | | | | | | |
| **Sedation** | | | | | | |
| Midazolam (mg) | 111 | 1 [0, 2] | 115 | 1.5 [0, 2] | 0 (0, 0) | 0.84 |
| Fentanyl (mg) | 111 | 50 [0, 50] | 115 | 50 [0, 50] | 0 (0, 0) | 0.27 |
| Entonox used | 111 | 40 (36%) | 115 | 37 (32%) | -4% (-16%, 8%) | 0.54 |
| | | | | | | |
| **Fluid volumes (mL)** | | | | | | |
| Infused fluid | | | | | | |
| Total | 108 | 505 [298, 750] | 113 | 780 [550, 1060] | 260 (170, 350) | **<0.001** |
| *Insertion* | 111 | 300 [150, 500] | 115 | 550 [400, 900] | 250 (180, 320) | **<0.001** |
| *Withdrawal* | 108 | 150 [100, 250] | 113 | 150 [100, 300] | 0 (-50, 10) | 0.45 |
| Suctioned fluid | | | | | | |
| Total | 111 | 550 [400, 800] | 115 | 800 [600, 1100] | 200 (150, 300) | **<0.001** |
| *Insertion* | 111 | 300 [200, 400] | 115 | 500 [300, 700] | 200 (100, 250) | **<0.001** |
| *Withdrawal* | 111 | 250 [150, 400] | 115 | 300 [150, 400] | 50 (0, 100) | 0.14 |
| | | | | | | |
| **$CO_2$ insufflation ($cm^3$)** | | | | | | |
| Total | 38 | 36769 [17511, 57246] | 40 | 24502 [11895, 45019] | -10015 (-22257, -127) | 0.05 |
| Insertion | 38 | 15268 [9038, 29675] | 39 | 3417 [2336, 15299] | -8593 (-13693, -4227) | **<0.001** |
| Withdrawal | 38 | 15980 [6578, 24808] | 40 | 12438 [7122, 27344] | -1006 (-7504, 5463) | 0.73 |
| | | | | | | |
| **Patient manoeuvres** | | | | | | |
| Repositions – Total | 111 | 5 [4, 6] | 115 | 6 [5, 7] | 1 (0, 1) | **0.006** |
| Repositions – Insertion | 111 | 2 [1, 3] | 115 | 3 [1, 4] | 1 (0, 1) | **0.002** |
| Repositions – Withdrawal | 111 | 3 [2, 4] | 115 | 3 [2, 4] | 0 (0, 0) | 0.51 |

| | | | | | | |
|---|---|---|---|---|---|---|
| Abdominal pressure episodes | 111 | 0 [0, 0] | 115 | 0 [0, 1] | 0 (0, 0) | 0.08 |
| | | | | | | |
| **Loops** | | | | | | |
| Total number | 111 | 0 [0, 1] | 115 | 0 [0, 1] | 0 (0, 0) | 0.97 |
| Sigmoid alpha loop | 111 | 12 (11%) | 115 | 18 (16%) | 5% (-4%, 14%) | 0.28 |
| Sigmoid n loop | 111 | 13 (12%) | 115 | 13 (11%) | 0% (-9%, 8%) | 0.92 |
| Reverse alpha loop | 111 | 8 (7%) | 115 | 1 (1%) | -6% (-11%, -1%) | **0.01** |
| Splenic flexure loop | 111 | 4 (4%) | 115 | 6 (5%) | 2% (-4%, 7%) | 0.56 |
| Transverse loop | 111 | 7 (6%) | 115 | 8 (7%) | 1% (-6%, 7%) | 0.84 |
| Transverse gamma loop | 111 | 2 (2%) | 115 | 3 (3%) | 1% (-3%, 5%) | 0.68 |
| Other loop | 111 | 0 (0%) | 115 | 0 (0%) | - | - |
| | | | | | | |
| **BBPS score** | | | | | | |
| Right | 111 | 2 [2, 3] | 115 | 2 [2, 3] | 0 (0, 0) | 0.14 |
| Transverse | 111 | 2 [2, 3] | 115 | 3 [2, 3] | 0 (0, 0) | 0.23 |
| Left | 111 | 2 [2, 3] | 115 | 3 [2, 3] | 0 (0, 0) | **0.05** |
| Total | 111 | 6 [6, 9] | 115 | 8 [6, 9] | 0 (0, 1) | 0.10 |
| | | | | | | |
| **Polyp detection** | | | | | | |
| PDR | 111 | 61 (55%) | 115 | 65 (57%) | 2% (-11%, 15%) | 0.81 |
| ADR | 111 | 48 (43%) | 115 | 40 (35%) | -8% (-21%, 4%) | 0.19 |
| SDR | 111 | 20 (18%) | 115 | 27 (23%) | 5% (-5%, 16%) | 0.31 |
| SPDR | 111 | 53 (48%) | 115 | 57 (50%) | 2% (-11%, 15%) | 0.78 |
| SP6 | 111 | 0.0 [0.0, 0.8] | 115 | 0.0 [0.0, 0.8] | 0 (0, 0) | 0.92 |
| | | | | | | |
| **Change in technique** | | | | | | |
| Patients with technique change | 111 | 0 (0%) | 115 | 17 (15%) | 15% (8%, 21%) | <0.001 |
| Fixed sigmoid | | 0 | | 1 | | |
| Looping | | 0 | | 8 | | |
| Poor preparation | | 0 | | 5 | | |
| Stuck at hepatic flexure | | 0 | | 2 | | |
| Polypectomy | | 0 | | 1 | | |

Summary statistics are median [inter-quartile range] or number (percentage)

* differences between groups reported as outcome for water-exchange cases minus outcome for hybrid cases. Either median difference or percentage difference reported

Table 34 Patient evaluation (PP analysis)

| Outcome | Hybrid | | Water-Exchange | | Difference* (95% CI) | P-value |
|---|---|---|---|---|---|---|
| | n | Summary | n | Summary | | |
| **Pain score+** | 111 | 2 [1, 3] | 115 | 2 [0, 3] | 0 (0, 0) | 0.59 |
| | | | | | | |
| **Satisfied with procedure** | 111 | | 115 | | - | 0.06 |
| Strongly agree | | 3 (3%) | | 0 (0%) | | |
| Agree | | 0 (0%) | | 2 (2%) | | |
| Neither agree or disagree | | 2 (2%) | | 3 (3%) | | |
| Disagree | | 20 (18%) | | 35 (30%) | | |
| Strongly disagree | | 86 (77%) | | 75 (65%) | | |
| | | | | | | |
| **Willingness to repeat procedure** | 111 | 103 (93%) | 114 | 109 (96%) | 3% (-3%, 9%) | 0.36 |
| | | | | | | |
| **Noticed difference compared with previous colonoscopy** | 82 | 38 (46%) | 90 | 30 (33%) | -13% (-28%, 2%) | 0.08 |

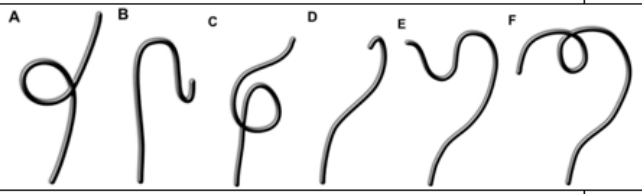
Summary statistics are median [inter-quartile range] or number (percentage)
+ visual analogue scale from 0 (no pain) to 10 (worst possible pain)
* differences between groups reported as outcome for water-exchange cases minus outcome for hybrid cases. Either median difference or percentage difference reported

## 16.2.2 WAVE: Case report form

WAVE STUDY: CASE REPORT FORM

**DATE:** **ENDOSCOPIST:** **PATIENT STICKER:**

| | | | | | | |
|---|---|---|---|---|---|---|
| **PROCEDURE** | **Indication** | | **Technique** | **Water / Hybrid** | **Technique change (why)?** | |
| | **Scope** | | **Endocuff** | **Yes / No** | **Abandoned (why)?** | |
| | **Drugs** | **Midazolam** | **Fentanyl** | **Buscopan** | **Entonox** | |

| | **INSERTION** | | **WITHDRAWAL** | |
|---|---|---|---|---|
| **TIME** | **Procedure start** | **Caecum reached** | **Caecum left** | **Procedure end** |
| | | | | |
| **NO. OF REPOSITIONS** | | | | |
| **NO. OF ABDOMINAL PRESSURES** | | | | |
| **LOOPS FORMED?** |   A: sigmoid alpha loop<br>B: sigmoid N loop<br>C: reverse alpha loop<br>D: splenic flexure hockey stick<br>E: transverse loop<br>F: transverse gamma loop | | **Yes / No**<br>**If yes, specify (or draw):** | |
| **CO2 VOLUMES** | **L** | | **L** | |
| **FLUID VOLUMES** | **Fluid suctioned:** **mL** | | **Fluid suctioned:** **mL** | |
| | **Volume flushed with syringe:** **mL** | | **Volume flushed with syringe:** **mL** | |
| | **Volume washed with pump:** **mL** | | **Volume washed with pump:** **mL** | |
| **Boston Score** | **Right:** | **Transverse:** | **Left:** | |

## 16.2.3 WAVE: Post-colonoscopy patient questionnaire

Patient Questionnaire: WAVE study

St Mark's Hospital

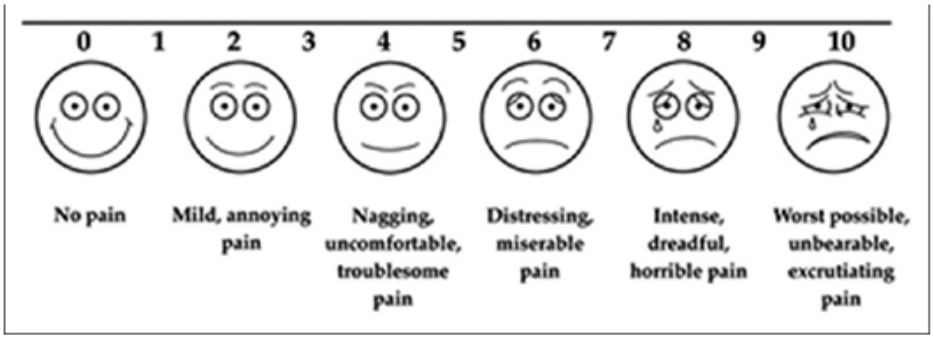
NHS London North West University Healthcare NHS Trust

**Post-colonoscopy Patient Questionnaire**

Thank you for participating in the WAVE study.

We would be very grateful if you could kindly spare a few minutes to complete this short questionnaire. Information about the WAVE study is available in the information leaflet provided.

1. Please score how painful your procedure was today on a scale of 0 to 10:




2. I felt highly satisfied with the procedure today

| 1-Strongly disagree | 2 - Disagree | 3-Neither disagree or Agree | 4 - Agree | 5-Strongly agree |
|---|---|---|---|---|
| | | | | |

3. If you required another colonoscopy in the future would you be happy to have it in the same way?

| No | Yes |
|---|---|
| | |

If no, please specify:

.....

.....

4. If you have had a previous colonoscopy, did you notice any difference in the procedure today compared with previously?

| No | Yes |
|---|---|
| | |

If yes, please specify:

.....

.....

**Thank you for your feedback**

## 16.2.4 GI Genius endoscopist evaluation

Endoscopist name:

List Date:

**GI GENIUS ENDOSCOPIST EVALUATION**

We would be very grateful if you could kindly spare a few minutes to complete this short questionnaire about your experience using GI Genius. Please complete one evaluation at the end of your list.

1. GI genius was helpful in identifying polyps

| 1-Strongly disagree | 2 - Disagree | 3-Neither disagree or Agree | 4 - Agree | 5-Strongly agree |
|---|---|---|---|---|
| | | | | |

2. GI genius helped me identify polyps I might have otherwise missed

| 1-Strongly disagree | 2 - Disagree | 3-Neither disagree or Agree | 4 - Agree | 5-Strongly agree |
|---|---|---|---|---|
| | | | | |

3. Did GI Genius change how you performed the procedures today?

| 1-Yes | 2 - No |
|---|---|
| | |

If yes, please specify:

.....

4. Did GI genius adversely affected the procedures today?

| 1-Yes | 2 - No |
|---|---|
| | |

If yes, please specify:

.....

5. Do you think GI genius should be used in routine clinical practice?

| 1-Yes | 2 - No | 3 - Unsure |
|---|---|---|
| | | |

6. Would you recommend GI Genius to your colleagues?

| 1-Yes | 2 - No | 3 - Unsure |
|---|---|---|
| | | |

7. Any other comments?

.....

.....

**Thank you for your feedback**

*Completed forms to be returned to charge nurse please.*

---

**For internal use:**
Patient sticker: Date: Compliance as per instructions?

### 16.2.5 Optical diagnosis and water-assisted colonoscopy survey

# Optical Diagnosis and Water-Assisted Colonoscopy Surveys

You are invited to participate in this short questionnaire to help us better understand two key aspects of colonoscopy practice; optical diagnosis of small polyps and water-assisted colonoscope insertion. All responses are completely anonymous and the survey will take around 2 minutes to complete.

*Required

Part A: Optical Diagnosis Survey

Colonoscopy experience

1. 1. How many colonoscopies have you performed? *

*Mark only one oval.*

- ◯ <300
- ◯ 300-1000
- ◯ 1000-5000
- ◯ >5000

2. 2. What setting do you perform colonoscopy in? *

*Mark only one oval.*

- ◯ District General Hospital
- ◯ Teaching/Specialist Hospital
- ◯ Other: _____

Optical diagnosis experience

3. 3. Do you send all resected diminutive colorectal polyps (≤5mm) to histopathology where possible? *

*Mark only one oval.*

- ◯ Yes
- ◯ No

4. 4. Do you perform optical diagnosis of diminutive polyps prior to resection?

*Mark only one oval.*

- ◯ Always
- ◯ Sometimes
- ◯ Never

5. 5. Have you had formal training in optical diagnosis of diminutive colorectal polyps? *

*Mark only one oval.*

- ◯ Yes, I have attended a course/training programme
- ◯ No

6. 6. How confident do you feel with optical diagnosis of diminutive polyps during colonoscopy? *

*Mark only one oval.*

| | 1 | 2 | 3 | 4 | 5 | |
|---|---|---|---|---|---|---|
| Not confident | ◯ | ◯ | ◯ | ◯ | ◯ | Confident |

7. 7. Do you think documented optical diagnosis followed by a 'resect and discard strategy' (discarding high confidence adenomas or serrated polyps rather than sending all to histopathology) for diminutive polyps (≤5mm) is a desirable goal of colonoscopy? *

*Mark only one oval.*

| | 1 | 2 | 3 | 4 | 5 | |
|---|---|---|---|---|---|---|
| Strongly agree | ◯ | ◯ | ◯ | ◯ | ◯ | Strongly disagree |

8. 8. Which of these optical diagnosis classification systems do you use for diminutive polyps? More than 1 option can be selected. *

*Tick all that apply.*

- [ ] NICE
- [ ] WASP
- [ ] SIMPLE
- [ ] Hiroshima
- [ ] JNET
- [ ] BASIC
- [ ] SANO
- [ ] Kudo

Other: [ ] _____

## NICE classification

The following questions relate to the NICE classification. If you do not use NICE, please leave blank.

9. 9. Which of the NICE criteria do you consider most important in decision-making? Please select one or more options.

*Tick all that apply.*

- [ ] Surface pattern
- [ ] Colour
- [ ] Vessels

10. 10. Do you use any of the following adjuncts for optical diagnosis, in addition to the NICE criteria?

*Tick all that apply.*

- [ ] Valley sign (adenoma)
- [ ] Aurora rings sign (inverted diverticulum)
- [ ] Fibrin cap (inflammatory polyp)
- [ ] WASP classification (serrated polyps)

Other: [ ] _____

Part B: Water-Assisted Colonoscopy Survey

Colonoscopy insertion technique

11. 1. During colonoscope insertion from rectum to splenic flexure, what do you usually use to distend the colon? *

*Mark only one oval.*

- ( ) Air only
- ( ) CO2 only
- ( ) Water only
- ( ) Combination of CO2 and water
- ( ) Combination of air and water
- ( ) Other: _____

12. 2. During colonoscope insertion from splenic flexure to caecum, what do you use to distend the colon? *

*Mark only one oval.*

- ◯ Air only
- ◯ CO2 only
- ◯ Water only
- ◯ Combination of CO2 and water
- ◯ Combination of air and water
- ◯ Other: _____

13. 3. How frequently do you use water to assist colonoscope insertion? *

*Mark only one oval.*

- ◯ Frequently (most colonoscopies)
- ◯ Occasionally (some colonoscopies)
- ◯ Rarely (not part of routine practice)
- ◯ Never

Water-assisted colonoscopy

14. 4. Have you had formal training in water-assisted colonoscopy? *

*Mark only one oval.*

- ◯ Yes - training course
- ◯ Yes - individual expert tuition
- ◯ Yes - other (eg watching live endoscopy or videos, reading articles or attending lectures)
- ◯ No

15. 5. When using water-assisted colonoscopy what type of water do you use?

*Mark only one oval.*

- ◯ Sterile water
- ◯ Tap water

16. 6. When using water-assisted colonoscopy, do you switch off the CO2 machine during the insertion?

*Mark only one oval.*

- ◯ Yes
- ◯ Sometimes
- ◯ No

17. 7. If you use water-assisted colonoscopy, how do you think this impacts your procedure? *

*Mark only one oval per row.*

| | Lower | No change | Greater |
|---|---|---|---|
| Insertion time | ◯ | ◯ | ◯ |
| Patient comfort | ◯ | ◯ | ◯ |
| Mucosal visualisation | ◯ | ◯ | ◯ |

18. 8. When using water-assisted colonoscopy, have you experienced any issues? *

*Mark only one oval.*

- ◯ Yes (please specify in Question 9)
- ◯ No

19. 9. What issues have you experienced when using water-assisted colonoscopy?

Feedback

20. Do you have any other feedback or comments about the themes covered by these surveys? *

21. All responses are completely confidential, but if you would like to be updated about the survey outcome please provide your email address:

Thank you!

## 16.2.6 AI-DETECT: Per-protocol results

Table 35 Patient-level procedure outcomes with and without AI (PP analysis)

| Outcome | All patients | No AI | AI | P-value |
|---|---|---|---|---|
| Total procedures | 579 | 286 | 293 | |
| | | | | |
| Total polyps | 2089 | 996 | 1093 | |
| Adenomas | 1369 | 650 | 719 | |
| Serrated lesions | 524 | 263 | 261 | |
| *Sessile serrated lesions* | *238* | *115* | *123* | |
| *Hyperplastic polyps* | *286* | *148* | *138* | |
| Inflammatory | 24 | 10 | 14 | |
| Normal | 122 | 53 | 69 | |
| Other | 33 | 15 | 18 | |
| Left in situ | 12 | 2 | 10 | |
| Not retrieved | 5 | 3 | 2 | |
| | | | | |
| Polyps per colonoscopy | | | | |
| Total | 3.6 ± 3.5 | 3.5 ± 3.3 | 3.7 ± 3.7 | 0.43 |
| Adenomas | 2.4 ± 2.8 | 2.3 ± 2.7 | 2.5 ± 3.0 | 0.39 |
| Serrated lesions | 0.9 ± 1.4 | 0.9 ± 1.5 | 0.9 ± 1.4 | 0.64 |
| Sessile serrated lesions | 0.4 ± 0.9 | 0.4 ± 0.9 | 0.4 ± 0.9 | 0.65 |
| Hyperplastic polyps | 0.5 ± 1.0 | 0.5 ± 0.9 | 0.5 ± 1.0 | 0.37 |
| Other (inflammatory and normal mucosa) | 0.31 ± 0.67 | 0.27 ± 0.62 | 0.34 ± 0.72 | 0.08 |
| | | | | |
| Polyp detection rate (%) | 498 (86.0%) | 241 (84.3%) | 257 (87.7%) | 0.23 |
| 'Significant polyp' detection rate (%) (adenoma + SSL) | 78.2 | 75.5 | 80.9 | 0.12 |
| Adenoma detection rate (%) | 412 (71.2%) | 196 (68.5%) | 216 (73.7%) | 0.17 |
| SSL detection rate (%) | 24.0 | 23.1 | 24.9 | 0.61 |
| SP6 | 0.9 ± 0.8 | 0.9 ± 0.9 | 0.9 ± 0.8 | 0.37 |
| | | | | |
| Procedure times (minutes) | 25.1 [19.7, 32.6] | 25.1 [19.4, 32.6] | 25.3 [20.0, 32.6] | 0.45 |
| Insertion time (minutes) | 7.3 [5.4, 9.9] | 7.3 [5.4, 9.9] | 7.3 [5.7, 10.0] | 0.48 |
| Withdrawal time (minutes) | 14.9 [10.2, 21.5] | 14.5 [10.2, 21.0] | 15.2 [10.2, 21.5] | 0.65 |
| | | | | |
| Caecal intubation rate | 579 (100.0%) | 286 (100.0%) | 293 (100.0%) | - |

Summary statistics are mean ± standard deviation, median [inter-quartile range] or number (percentage)

Table 36 Polyp characteristics (PP analysis)

| Outcome | All patients n (%) | No AI n (%) | AI n (%) |
|---|---|---|---|
| Total polyps | 2089 | 996 | 1093 |
| | | | |
| Paris classification | | | |
| Is | 1100 (52.7%) | 527 (52.9%) | 573 (52.4%) |
| Isp | 82 (3.9%) | 45 (4.5%) | 37 (3.4%) |
| Ip | 138 (6.6%) | 55 (5.5%) | 83 (7.6%) |
| IIa | 724 (34.7%) | 347 (34.8%) | 377 (34.5%) |
| IIb | 31 (1.5%) | 16 (1.6%) | 15 (1.4%) |
| IIc | 5 (0.2%) | 4 (0.4%) | 1 (0.1%) |
| III | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) |
| LST-G | 5 (0.2%) | 1 (0.1%) | 4 (0.4%) |
| LST-NG | 4 (0.2%) | 1 (0.1%) | 3 (0.3%) |
| | | | |
| Site of polyps | | | |
| Caecum | 255 (12.2%) | 107 (10.7%) | 148 (13.5%) |
| Ascending Colon | 438 (21.0%) | 208 (20.9%) | 230 (21.0%) |
| Hepatic flexure | 89 (4.3%) | 38 (3.8%) | 51 (4.7%) |
| Transverse Colon | 461 (22.1%) | 231 (23.2%) | 230 (21.0%) |
| Splenic Flexure | 75 (3.6%) | 35 (3.5%) | 40 (3.7%) |
| Descending colon | 193 (9.2%) | 95 (9.5%) | 98 (9.0%) |
| Sigmoid colon | 356 (17.0%) | 176 (17.7%) | 180 (16.5%) |
| Rectosigmoid Junction | 10 (0.5%) | 6 (0.6%) | 4 (0.4%) |
| Rectum | 212 (10.1%) | 100 (10.0%) | 112 (10.2%) |
| | | | |
| Polyp size | | | |
| 1-5 mm | 1600 (76.6%) | 761 (76.4%) | 839 (76.8%) |
| 6-9 mm | 276 (13.2%) | 141 (14.2%) | 135 (12.4%) |
| 10+ mm | 213 (10.2%) | 94 (9.4%) | 119 (10.9%) |

### 16.2.7 Key performance indicators for participating endoscopists

Table 37 2019 key performance indicators for participating endoscopists

| | Endoscopist | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| **Performance Indicator** | **1** | **2** | **3** | **4** | **5** | **6** | **7** | **8** | **Overall** |
| Screening colonoscopies performed | 70 | 99 | 79 | 82 | 109 | 83 | 91 | 46 | 659 |
| Caecal intubation rate (with confirmed photographic evidence) (%) | 100% | 98% | 96% | 95% | 96% | 95% | 96% | 98% | 97% |
| Polyp detection rate (%) | 63% | 85% | 70% | 77% | 63% | 66% | 68% | 78% | 71% |
| Adenoma detection rate (%) | 57% | 80% | 65% | 72% | 61% | 63% | 56% | 72% | 66% |
| Polyp retrieval rate (%) | 98% | 98% | 95% | 99% | 100% | 99% | 100% | 100% | 99% |
| Withdrawal time for negative colonoscopy (minutes) | 8 | 11 | 7 | 10 | 9 | 8 | 10 | 12 | 9 |
| Colonoscopies with no, minimal or mild discomfort (%) | 100% | 95% | 99% | 94% | 97% | 98% | 96% | 93% | 96% |

## 16.2.8 DISCARD3: Post-colonoscopy optical diagnosis patient survey

**Post-colonoscopy Patient Questionnaire**

Thank you for participating in the DISCARD3 study.

We would be very grateful if you could kindly spare a few minutes to complete this short questionnaire. Information about the DISCARD3 study is available in the information leaflet provided.

**Please score the following statements from 1 to 5 where 1 is strongly disagree and 5 is strongly agree:**

1. My colonoscopy was comfortable

| 1-Strongly disagree | 2 - Disagree | 3-Neither disagree or Agree | 4 - Agree | 5-Strongly agree |
|---|---|---|---|---|
| | | | | |

2. I would be happy for any small polyps found during colonoscopy to be assessed by the endoscopist at the time of the colonoscopy (rather than to wait for laboratory results to get the polyp diagnosis)

| 1-Strongly disagree | 2 - Disagree | 3-Neither disagree or Agree | 4 - Agree | 5-Strongly agree |
|---|---|---|---|---|
| | | | | |

3. If a further follow up colonoscopy in the future is considered necessary I would prefer to be informed immediately after the initial procedure rather than wait to be told later by telephone or in the outpatient department

| 1-Strongly disagree | 2 - Disagree | 3-Neither disagree or Agree | 4 - Agree | 5-Strongly agree |
|---|---|---|---|---|
| | | | | |

4. I feel confident that the endoscopist could accurately diagnose small polyps without sending them to the laboratory

| 1-Strongly disagree | 2 - Disagree | 3-Neither disagree or Agree | 4 - Agree | 5-Strongly agree |
|---|---|---|---|---|
| | | | | |

5. I felt highly satisfied with the procedure today

| 1-Strongly disagree | 2 - Disagree | 3-Neither disagree or Agree | 4 - Agree | 5-Strongly agree |
|---|---|---|---|---|
| | | | | |

6. If you have had a previous colonoscopy, did you notice any difference in the procedure today compared with previously?

| No | Yes |
|---|---|
| | |

If yes, please specify:

……

……

**Thank you for your feedback**