Cost and resource requirements for Colorectal Cancer Screening in Ireland

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Rajani Pokharel

Acknowledgements and dedication

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Finally, I want to dedicate this thesis to my son, Rian, who arrived in the second year of my PhD. You made my life more meaningful and given me the strength to carry on. You spent your early years with a mother who was often busy and tired, and for that, I owe you a lot of quality time.

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Glossary of terms

CEA	Cost-effectiveness analysis (CEA) is a type of full economic evaluations that evaluates the effectiveness of two or more health technology relative to their cost.
CEA threshold	The cost-effectiveness threshold is the maximum amount a decision-maker is willing to pay for a unit of health outcome.
CRC	Colorectal cancer (CRC) is a type of cancer that affects the colon (large intestine) or rectum.
Direct costs	Direct costs are costs that are directly attributable to patient care such as nursing services, consumables, drugs, equipment cost etc.
Gross costing	Gross costing is a costing methodology that identifies and measures resources at an aggregated level.
Health Technology	Health technology encompasses a wide range of health interventions used to promote health; to prevent, diagnose or treat a disease; or in rehabilitation or long-term care.
ICER	An incremental cost-effectiveness ratio (ICER) is a summary measure representing the economic value of a health technology, compared with an alternative (comparator). It is usually the main output or result of an economic evaluation.
Indirect costs	Indirect costs are costs that are not directly related to patient care such as administrative cost, overhead cost etc.
Micro-costing	Micro-costing is a cost estimation methodology employing detailed resource utilization and unit cost data to generate precise estimates of economic costs.
TNM classification	The TNM Classification is a system for classifying a malignancy based on the size of the primary tumor and its' invasion into adjacent tissues (T), regional lymph node involvement of the tumor (N), and the presence of distant metastases of the primary tumor (M).

Summary

Colorectal cancer (CRC) is a global public health problem. CRC screening reduces the colorectal cancer burden through the removal of precursor lesions and identifying the disease at an early stage. CRC screening is cost-effective when offered at appropriate intensity. The effective implementation of CRC screening requires quantification of colonoscopy volume required for screening and surveillance activities for service planning and resource allocation. The cost of colonoscopy is required to evaluate the cost-effectiveness of CRC screening, to assess the cost implications and feasibility of adopting various CRC screening strategies. The aim of this thesis is to answer various policy-related questions on CRC screening specifically about the optimal screening strategy, colonoscopy requirement and updated costs of colonoscopy service.

This thesis comprises three studies. The first study assessed the range of strategies analysed in European cost-effective analyses (CEAs) of CRC screening using stool-based tests. In particular, it examines the range of simulated screening intervals, age ranges and test cut-offs used to define positivity to examine how this might influence the identification of the optimal strategy. Further, the study compared the findings with the current CRC screening policies in Europe. The study found that many CEAs have not included an annual screening strategy in their analysis but those that also considered annual screening found it to be optimally cost-effective. Most CRC screening programmes in Europe employ biennial screening using stool-based tests which is likely of sub-optimal intensity. More CRC-related deaths might be prevented if programmes could offer annual screening.

The second study estimated the direct cost of colonoscopy procedure from the health service perspective in Ireland using bottom-up micro-costing study. A prospective study was conducted to enumerate the direct cost of all resources used for a patient in a colonoscopy procedure. The study found significant differences in the time and cost of colonoscopy procedures based on whether the intervention was performed. The cost of colonoscopy was €277 without additional intervention, €424 with biopsy, €812 with polypectomy and €824 with both polypectomy and biopsy. Similarly, the cost of screen indicated was €522 and clinically indicated colonoscopy was €587. This cost estimate could be valuable for healthcare policymakers in Ireland given current policy commitments to the expansion of CRC screening. Similarly, our cost data could inform future economic evaluations of CRC screening strategies in Ireland. Furthermore, the data also offers insights for private sector reimbursement comparison.

The third study was a resource modelling that estimated the volume of colonoscopy required for CRC screening and surveillance in Ireland for the next decade. The Dutch version of MISCAN-Colon model was recalibrated to Irish data on CRC incidence and stage distribution prior to the introduction of population-based CRC screening to develop an Irish version of the model. The outputs of the natural history simulation in the Irish model were used to develop a simulation model in R programming language to simulate various screening scenarios to estimate the colonoscopy capacity requirements of each. Under the current screening strategy, the study estimated on average 28 colonoscopies per 1000 population are required for the coming decade for screening and surveillance activities. The colonoscopy volume increases as the policy is intensified with more frequent screening interval, lower FIT cut-off and wide age range. The NBSP would require double the colonoscopy capacity to effectively implement the planned age expansion of 55-74 years and nearly 8.5-fold increase to implement the optimal cost-effective strategy of screening 45-80 years old annually at the FIT cut-off of 50 ng Hb/mL. The distribution of adherence density among the population has an impact on the resulting volume of colonoscopy.

Outputs

Publications

Pokharel, R., Lin, Y. S., McFerran, E., & O'Mahony, J. F. (2023). A systematic review of cost-effectiveness analyses of colorectal cancer screening in Europe: have studies included optimal screening intensities? Applied Health Economics and Health Policy, 1-17.

Conference presentations

Pokharel, R., Lin, Y. S., McFerran, E., & O'Mahony, J. F. Colorectal cancer screening intensity in Europe: A systematic review of cost-effectiveness analyses addressing the optimal screening interval. Poster presentation. Trinity St James's Cancer Institute 12th International Cancer Conference. 13-14 October, Dublin, 2022.

Pokharel, R., Lin, Y. S., McFerran, E., & O'Mahony, J. F. Intensity of colorectal cancer screening strategies and the optimal policy choice: A systematic review of European cost-effectiveness analyses. Poster presentation. ISPOR, 6-9 November, Vienna, 2022.

Pokharel, R., Lin, Y. S., McFerran, E., & O'Mahony, J. F. Colorectal cancer screening intensity in Europe: A systematic review of cost-effectiveness analyses addressing the optimal screening interval. Oral presentation. Department of Public Health, Erasmus Medical Centre (EMC), VO Internal Seminar Series. 12 January 2023.

Pokharel, R., Lin, Y. S., McFerran, E., & O'Mahony, J. F. Why Colorectal Cancer Screening Programmes in Europe are of Sub-Optimal Intensity: A Systematic Review of Cost-Effectiveness Analyses. Poster presentation. Society for medical Decision Making, 21-23 May, Berlin, 2023.

Pokharel, R., Lin, Y. S., McFerran, E., & O'Mahony, J. F. Colorectal cancer screening intensity in Europe: A systematic review of cost-effectiveness analyses addressing the optimal screening interval. Poster presentation. International Cancer Screening Network, 21-23 July, Turin, 2023.

LIST OF ABBREVIATIONS

ABF	Activity Based Funding
ACP	American College of Physicians
ACS	American Cancer Society
AERs	Automated Endoscopic Reprocessors
aOR	adjusted Odds Ratio
ASCCA	Adenoma and Serrated pathway to Colorectal Cancer
ASR	Age Standardised Rate
CAD	Canadian Dollar
CBA	Cost Benefit Analysis
CCE	Colon Capsule Endoscopy
CEA	Cost-effectiveness Analysis
CI	Confidence Interval
CIMP	CpG Island Methylator Phenotype
CIN	Chromosomal Instability
CISNET	Cancer Intervention and Surveillance Modelling Network
CRC	Colorectal Cancer
CSO	Central Statistics Office
CTC	Computed Tomographic Colonography
CTFPHC	Canadian Task Force on Preventive Health Care
CUA	Cost Utility Analysis
DCBE	Double Contrast Barium Enema
DES	Discrete Event Simulation
dMMR	Mismatch Repair Deficiency
EGFR	Epidermal Growth Factor Receptor
EoCRC	Early Onset Colorectal Cancer
ESDO	European Society of Digestive Oncology
EU	European Union
FAP	Familial Adenomatous Polyposis
FDA	Food and Drug Administration
fDNA	faecal DNA
FIT	Immunochemical Faecal Occult Blood Test
FSIG	Flexible Sigmoidoscopy
GDPR	General Data Protection Regulation
FOBT	Faecal Occult Blood Test
GGPO	German Guideline Programme in Oncology
GI	Gastrointestinal
GOF	Goodness of Fit
HCMC	Hereditary Cancer Model of Care
HDI	Human Development Index
HIQA	Health Information and Quality Authority
HNPCC	Hereditary Nonpolyposis Colorectal Cancer
HR	Hazard Ratio

HSE	Health Service Executive
HTA	Health Technology Assessment
IARC	International Agency for Research on Cancer
IBD	Inflammatory Bowel Disease
ICD	International Classification of Disease
ICER	Incremental Cost-effectiveness Ratio
ISPOR	International Society for Pharmacoeconomics and Outcomes Research
LYG	Life Years Gained
MISCAN	Microsimulation Screening Analysis
MMUH	Mater Misericordiae University Hospital
mSEPT9	Methylated SEPT9
MSI	Microsatellite Instability
MSI-H	Microsatellite Instability-High
MT-sDNA	Multi Target-stool DNA
NBSP	National Bowel Screen Programme
NCI	National Cancer Institute
NCRI	National Cancer Registry Ireland
NCSS	National Cancer Screening Service
NEQI	National Endoscopic Quality Improvement
NHMRC	National Health and Medical Research Council
NORCCAP	Norwegian Colorectal Cancer Prevention
NSS	National Screening Service
NTPF	National Treatment Purchase Fund
PICO	Population, Intervention, Comparator, Outcome
pDNA	plasma DNA
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta Analyses
PRSI	Pay Related Social Insurance
PYs	Person Years
QA	Quality Assurance
QALY	Quality Adjusted Life Year
RCT	Randomised Controlled Trial
SD	Standard Deviation
SEOM	Spanish Society of Medical Oncology
SMDM	Society of Medical Decision Making
ScHARR	The University of Sheffield School of Health and Related Research
SSE	Sum of Squared Errors
STM	State Transition Model
UK	United Kingdom
US	United States
USMSTF	US Multi-Society Task Force on Colorectal Cancer
USPSTF	US Preventive Services Task Force
VAT	Value Added Tax
VEGF	Vascular Endothelial Growth Factor

Thesis Outline

This thesis is presented in six chapters. Chapter 1 provides a general introduction to CRC screening followed by a specific background to the studies included in the thesis. The thesis includes three individual studies: 1) Systematic review of Cost-Effective Analyses (CEAs) of CRC screening in Europe, 2) Direct cost of colonoscopy using a micro-costing approach and 3) Resource modelling to estimate colonoscopy volume in Ireland. Each study is presented in detail from introduction to discussion across Chapters 2, 3, and 4, respectively. The first study has been published in the Journal of Applied Health Economics and Health Policy (PMID: 37380865). Chapter 5 includes a general discussion, as well as sections on policy implications, recommendations for further research, and challenges and lessons learned during the research process. Finally, Chapter 6 summarizes the conclusions drawn from each study and provides the overall conclusion of this thesis. The references are listed after the conclusion chapter, and the supplementary materials for all the studies are included in the appendix.

CHAPTER 1 GENERAL INTRODUCTION

1.1 Colorectal cancer

Colorectal cancer (CRC) refers to the malignancies that occur in the colon (large intestine or rectum) [1]. The colorectum is approximately 1.5m long and is generally subdivided into sections that include cecum, ascending colon, hepatic flexure, transverse colon, splenic flexure, descending colon, sigmoid colon and rectum (Figure 1-1). Transverse colon to cecum is called proximal or right part and rectum to descending colon is called the distal or left part. The cecum starts where the small intestine ends, and the rectum opens to the outside at the anus [2]. Conventionally, subtypes of CRC are categorised based on tumour anatomical site in three segments as right-sided CRC (caecum, ascending colon, hepatic flexure and transverse colon), left-sided CRC (splenic flexure, descending colon and sigmoid colon) and rectal cancer [3]. The International Classification of Disease (ICD) codes for CRC are given in Appendix 1.

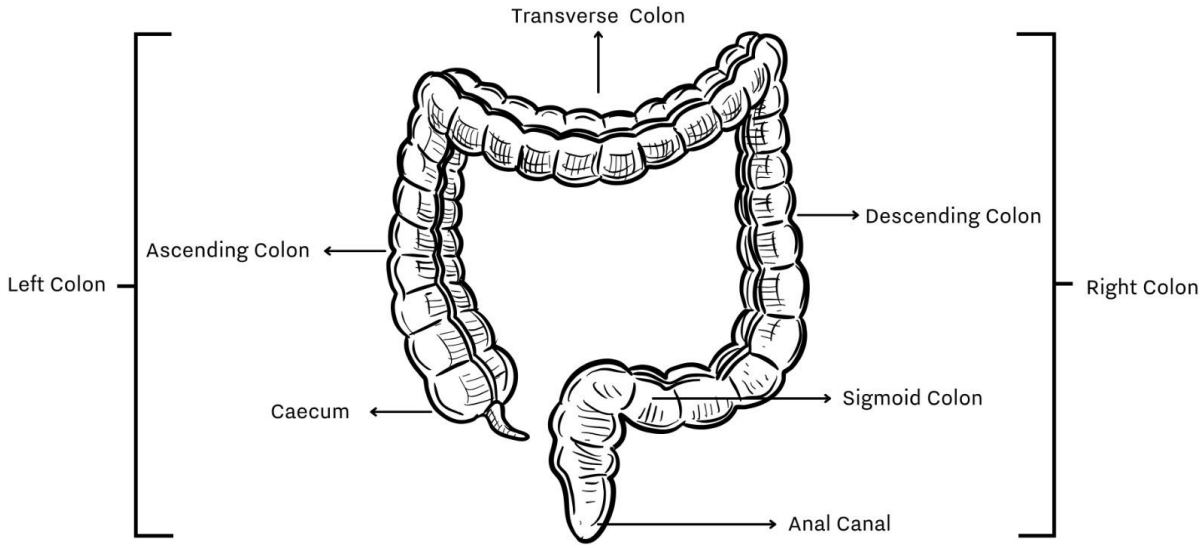


Figure 1-1. Schematic overview of the colorectum. Recreated from National Cancer Institute [2].

1.2 Epidemiology

Globally, CRC is the third most common cancer and the second leading cause of cancer-related deaths, accounting for approximately 10% of all cancer cases and 9.4% of cancer deaths [4]. The

International Agency for Research on Cancer (IARC) estimated more than 1.9 million new cases of CRC and 935,000 deaths due to CRC have occurred in 2020 [5]. Overall, 60.4% of all cases were aged between 50 and 74 years at diagnosis [6]. The burden of CRC is expected to rise to 3.2 million new cases and 1.6 million deaths by 2040, an increment of 63% and 73% respectively [5]. The incidence of CRC appears to be positively correlated with Human Development Index (HDI) which is a composite index of life expectancy, education, and per capita income indicators that the World Bank uses to rank countries into 4 categories [6, 7]. CRC is four times more common in high HDI countries compared to low HDI countries [6]. The age-standardised rate (ASR) of CRC incidence is highest in Australia and New Zealand (35.3 cases per 100,000), followed by Europe (30.5 cases per 100,000), North America (27.2 cases per 100,000) and Eastern Asia (22.2 cases per 100,000). The lowest incidence rates were observed in Africa (8.2 cases per 100,000) and South-Central Asia (5.5 cases per 100,000) [8] (Figure 1-2).

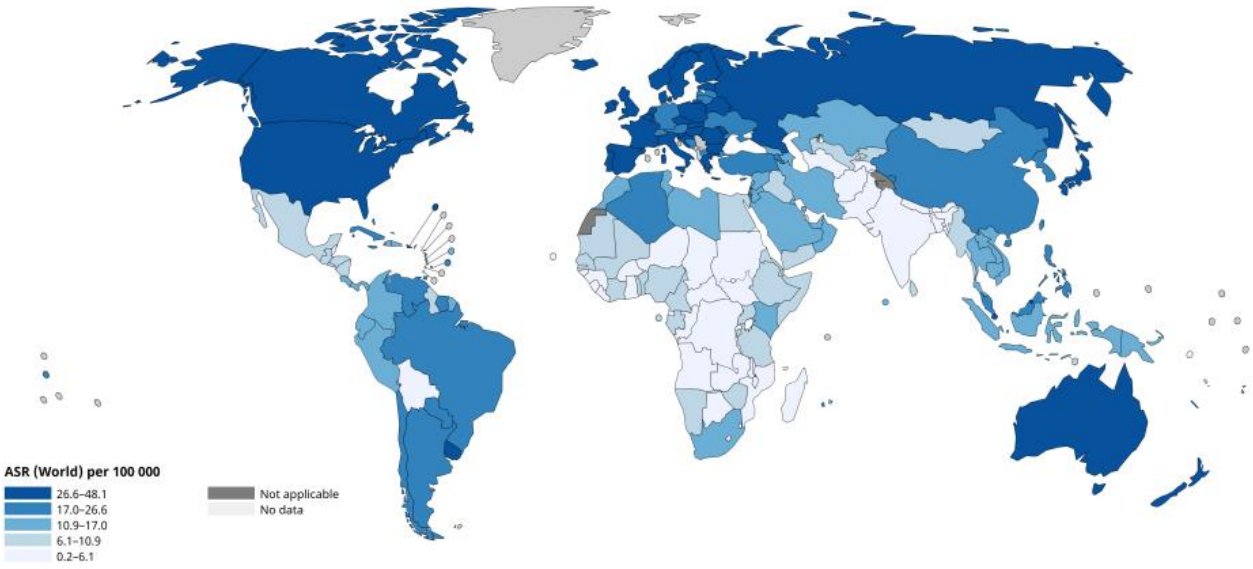


Figure 1-2. Age Standardised Rate Incidence of CRC per 100000 person years in both sexes in 2022, Data source: GLOBOCAN 2022 Graph production: IARC (http://gco.iarc.fr/today) World Health Organization [8]

Ireland is among the countries with higher ASR CRC incidence in Europe with 32.3 cases per 100,000 [8]. CRC is the second most common cancer in males and the third most common cancer in females, contributing to 11% in males and 10% in females of all invasive cancers excluding non-melanoma skin cancer [9]. Overall, it is the second most common cause of cancer death attributable to 11.2% in males and 9.7% cancer deaths in females [9]. In 2020, the estimated age-standardised mortality rate of CRC in males in Ireland was 36.1 per 100,000 while the estimated age-standardised mortality rate in females was 21.4 per 100,000 [10]. Based on demographic projection, annually, the number of cases is projected to rise by 115% in males and 108% in females by 2045 with an overall increase of 112% (both sexes) [11]. Figure 1-3 shows the incidence of CRC in younger and older age groups in Ireland from 1994 to 2021.

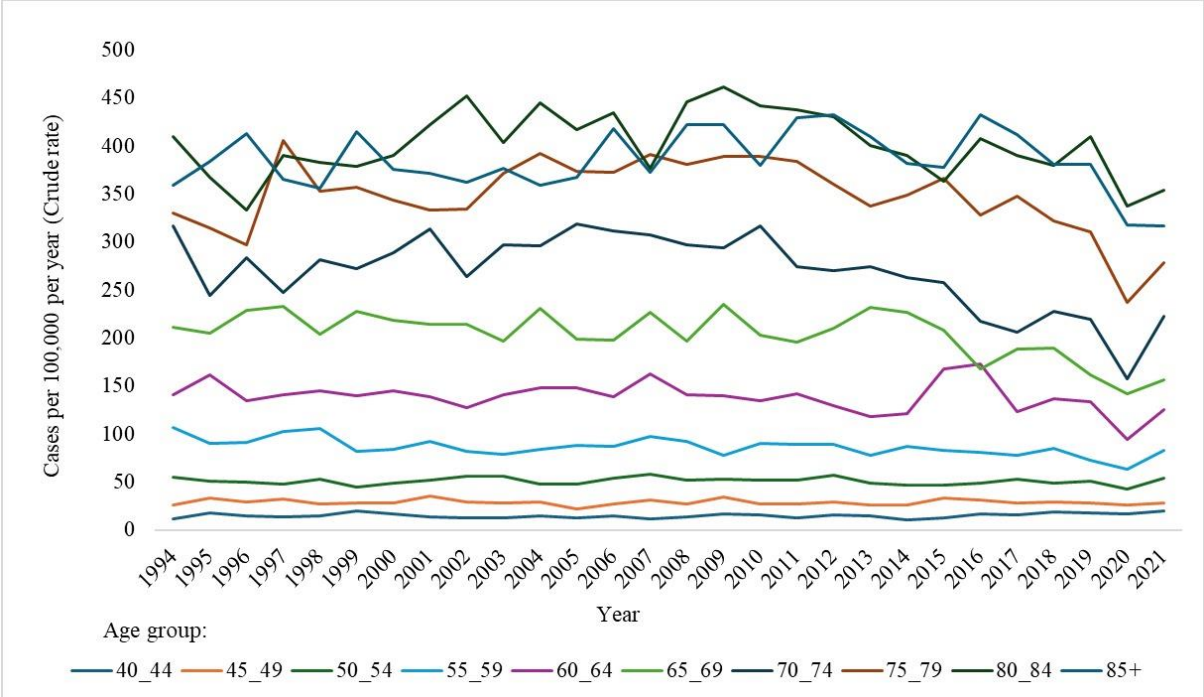


Figure 1-3. CRC incidence rates per 100,000 individuals in Ireland (1994-2021) in different age groups. Recreated using the data obtained from the National Cancer Registry Ireland [12]

1.3 Trends

CRC incidence rates among older adults are in decline or being stabilised in many high-income countries such as the UK, Australia, New Zealand, the Netherlands, the US, Austria, the Czech Republic, and Germany [3, 5, 13, 14]. This decline has largely been attributed to the

implementation of population-based screening programmes [13]. In contrast, there has been a rise in rates in several historically lower risk transitioning countries such as those in Eastern Europe, Southeastern and South-Central Asia, and South America [6, 13]. The rising incidence of CRC in these countries has been attributed in part to the adoption of Western lifestyle, including increased red and processed meat consumption, sedentary living, and obesity, as well as an ageing population as a result of industrialization and economic growth [7, 13]. In terms of mortality, the rates are decreasing in high-income countries whereas it is increasing in countries with limited medical resources (for example, Brazil and Russia) [3].

There is a notable global increase in CRC incidence observed in individuals below the age 50 years which is termed as early-onset colorectal cancer (EoCRC). Approximately 10% of newly diagnosed cases occurred in adults younger than the age of 50 worldwide [6]. This trend has been observed in high income countries like Canada, the US, Australia, Brazil, China, Japan, and the United Kingdom [13, 15]. Further, patients with EoCRC are often diagnosed with advanced stage disease due to lack of screening in this age group [16]. Thus, there is potential to enhance the effectiveness of screening programmes in reducing CRC incidence and mortality by lowering the screening start age.

1.4 Risk factors

The risk factors for CRC can be grouped into modifiable and non-modifiable risk factors [17]. About 60-65% of CRCs are sporadic attributable to unidentified genetic factors in the context of dietary and environmental factors. These include cigarette smoking, alcohol consumption, overweight and obesity, physical inactivity, diet high in red and processed meat, diet low in fibre, fruits and vegetables, diet low in calcium, vitamin D and dairy products [3, 18].

The non-modifiable risk factors include family history and personal medical history, age, sex and race [17]. Approximately 35-40% of CRC cases are linked to hereditary factors, with the majority around 25% having a family history without any identifiable genetic cancer syndrome, while around 2-8% are associated with specific inherited cancer syndromes like hereditary nonpolyposis

CRC (HNPCC or Lynch syndrome) and familial adenomatous polyposis coli (FAP) (Figure 1-4) [3, 19]. On average, the risk is two times higher in individuals with one affected first degree relative (FDR) compared to those with no family history [3, 19]. In HNPCC, the risk of developing of developing CRC is 20% by the age of 50 increasing to 80% by the age of 85 [19]. In patients with untreated FAP syndrome, the risk of CRC virtually reaches 100% by age 40 years, yet it accounts for less than 1% of all CRC cases [3]. Inflammatory bowel disease (IBD) is the third-highest risk factor for developing CRC with two to six times higher risk of developing CRC compared to healthy individuals. Type 2 diabetes is also associated with two to three times greater risk of CRC [19].

Older age is another significant risk factor for CRC, with 90% of all new cases occurring in individuals over 50 years [5]. It is estimated that people after the age of 65 years have about three times greater risk of developing CRC in comparison to those at the age of 50–64 years and about 30 times greater risk than people at the age of 25–49 years [19]. Males have a higher risk of developing CRC compared to females with a 45% higher age-standardized incidence rate and a 50% higher cumulative risk. Non-Hispanic Black individuals have one of the highest rates of all racial groups, approximately 50% higher than in Asians/Pacific Islanders and about 20% higher than in non-Hispanic Whites [19].

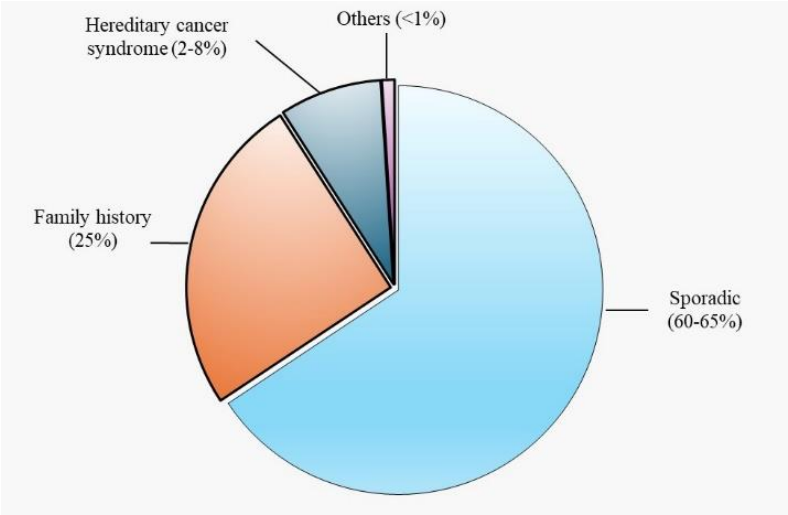


Figure 1-4. Contributions of sporadic and hereditary factors to total CRC cases. Recreated from data obtained from Keum et al, 2019 [3] and Sawicki et al, 2021 [19].

1.5 Colorectal Cancer staging and survival

The Tumour, Node, Metastasis (TNM) classification is one of the common ways to classify cancer. Under the TNM classification, T reflects the invasiveness of the primary tumour, N the number of lymph nodes affected, and M the metastasis to distant organs and the combination of the three factors can serve to define the overall stage of the tumour (Table 1-1) [20].

Table 1-1 Description of CRC stages under TNM classification

Stage	TNM	Description
0	Tis, N0, M0	This stage is also known as carcinoma in situ or intramucosal carcinoma (Tis). The cancer is in its earliest stage. It has not grown beyond the inner layer (mucosa) of the colon or rectum. There are no lymph nodes containing cancer cells, the cancer has not spread to other organs.
1	T1-T2, N0, M0	This stage is localized cancer. The cancer has grown through the muscularis mucosa into the submucosa (T1), and it may also have grown into the muscularis propria (T2). It has not spread to nearby lymph nodes (N0) or to distant sites (M0).
2	T3-T4, N0, M0	This stage is locally advanced cancer in early stages. The cancer has grown through the muscle wall or through the outer layer of the colon or rectum and may have spread to nearby tissues or organs (T2-T4). It has not yet spread to nearby lymph nodes (N0) or to distant sites (M0).
3	Any T, N1, M0	This stage is locally advanced cancer in late stages. The tumour is any size (T1-T4) and affects 1 to 3 regional lymph nodes (N1) but has not spread anywhere else in the body (M0).
4	T1-4, N0-2, M1	This stage is metastatic cancer. The tumour is any size (T1-T4) and involve any number of lymph nodes nearby (N0-2) and there is only one distant metastasis to a single organ or site or multiple distant metastases to different organs or sites (M1).

Adapted from Cancer Research UK [21]

Globally, the survival rates of CRC are showing a remarkable upward trend from the 1960s to 1990s gradually stabilising after the 21st century [22-24]. This is the result of improved sensitivities of diagnostic and staging procedures, refined surgical techniques, the use of preoperative radiation for rectum cancer, the introduction of novel agents, and regimens for chemotherapy [22]. Survival of CRC strongly depends on the stage of diagnosis. Estimates from several countries have shown improved survival when the disease is detected and diagnosed at an earlier stage. The five-year survival rate is more than 90% for CRCs diagnosed at an early stage compared to just slightly over 10% for patients diagnosed with metastatic (stage IV) disease [24].

1.6 Natural history

CRCs mostly arise from a benign precursor, defined as a polyp or adenoma, which is an abnormal growth of tissue projecting from a mucous layer of the colorectum. Adenomatous polyps (adenomas) and serrated polyps are two major subtypes that serve as direct precursors to the majority of CRCs [19]. So far, three distinct carcinogenic pathways have been suggested: adenoma–carcinoma pathway, serrated neoplasia pathway and inflammatory pathway (Figure 1-5) [3, 19].

Approximately 85–90% of sporadic CRCs evolve from adenoma carcinoma pathway. Conventional adenomas may have a tubular, tubulovillous, or villous histology. Over a lifetime, 30-50% of individuals develop one or more adenomas of which the large majority remain benign. Less than 10% of adenomas progress to CRC [3]. However, when a small adenoma progresses, it increases in size and may develop malignant potential. An adenoma that exceeds 10 mm in size, contains high-grade dysplasia or has a villous histology of 25% or more is classified as an advanced adenoma. Such adenomas carry 30-50% higher risk of transitioning into CRCs, compared to only 1% risk for non-advanced adenomas [25]. The genetic alterations in the pathway include Chromosomal instability (CIN) and KRAS mutations [26]. The average duration of the adenoma-carcinoma sequence is unobservable, but it is estimated to take approximately 20 years [3].

An alternative carcinogenic pathway is the serrated pathway in which CRC develops through serrated polyps which is believed to be precursors to approximately 10–15% of sporadic CRCs. Serrated polyps represent a group of heterogeneous lesions (hyperplastic polyp, traditional serrated adenoma, sessile serrated adenoma and mixed polyp) with saw-toothed morphological appearance [3, 26]. The genetic alteration in this pathway includes BRAF mutation and gene promoter hypermethylation (CpG island methylator phenotype or CIMP) and Microsatellite instability (MSI) [3, 26]. Compared to adenomas, serrated polyps are likely to be missed in the screening and diagnostic test due to the flat or sessile morphology, similar colour to the epithelium and camouflage by a mucus cap [27]. However, recent evidence indicates that serrated polyps without dysplasia generally have a long dwell time of at least 15 years, comparable to conventional adenomas highlighting their importance in the CRC screening [28].

Another distinct carcinogenic pathway involving chronic inflammation has been suggested. The inflammatory bowel disease (IBD) contributes to less than 2% of all CRCs. In this pathway, due to chronic inflammation, normal cells progress to indefinite dysplasia, to low-grade dysplasia, to high-grade dysplasia and, finally, to cancer [3].

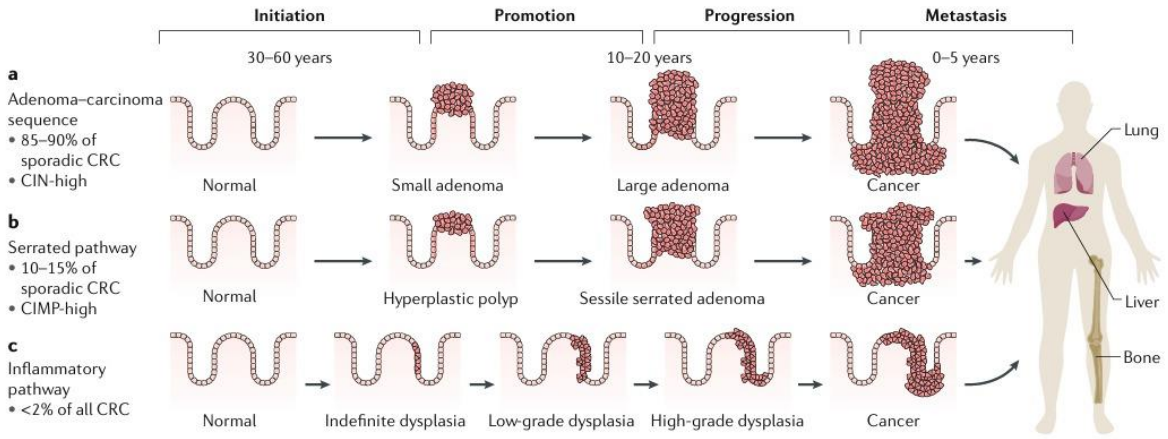


Figure 1-5. Different pathways for development of CRC. Figure obtained from Keum N, Giovannucci E, 2019 [3] with permission of Springer Nature. License Number: 5795870365395

1.7 Overview of treatment

Significant advancements have been made in the treatment of CRC. Treatments are based on several factors, including the type and stage of cancer, possible side effects, and the patient's preferences and overall health. Early detection of CRC can lead to better treatments and outcomes. The treatment options include surgery, radiotherapy, chemotherapy, targeted therapy, and immunotherapy [29].

In the early stage, the primary treatment is the removal of the tumour and nearby lymph nodes. Some tumours may be removed during colonoscopy and others require surgery. Surgery may involve a colectomy (removal of a portion of the colon) or a proctectomy (removal of the rectum). Chemotherapy and/or radiotherapy may be administered before or after surgery. Patients with a higher risk of cancer recurrence are typically recommended for adjuvant chemotherapy [29]. Perioperative chemoradiotherapy has been widely used for rectal cancers which has shown to effectively reduce the size of tumours and reach complete response in 15-20% of the patients [30].

In the advanced stage, systemic therapy is the primary treatment approach. The first line of treatment is chemotherapy, including fluoropyrimidine, irinotecan, oxaliplatin, and leucovorin. Targeted therapy may be used in combination with chemotherapy for specific genetic mutations, such as KRAS or BRAF mutations. Two classes of monoclonal antibody therapies have been approved by the FDA and the European Medicines Agency (EMA) to treat CRC: the vascular endothelial growth factor (VEGF) inhibitor, e.g., bevacizumab and the epidermal growth factor receptor (EGFR) inhibitor, e.g., cetuximab and panitumumab [31-33].

Immunotherapy drugs are used for patients with tumours that exhibit specific genetic markers, such as microsatellite instability-high (MSI-H) or mismatch repair deficiency (dMMR). In some cases of metastatic CRC, surgery may be recommended to remove distant metastases from organs such as the lungs and liver. Radiation therapy may be used to help control the disease and manage symptoms, such as pain or bleeding [33, 34].

1.8 Colorectal cancer screening

Screening is the detection of an undetected disease in asymptomatic individuals. Screening can be broadly categorized into two approaches: opportunistic and organized screening. Opportunistic screening occurs when requested by a patient or healthcare provider during a routine appointment [35]. The International Agency for Research on Cancer defines an organized screening programme as one that has the following elements: (i) an explicit policy with specified age categories, method, and interval for screening; (ii) a defined target population; (iii) a management team responsible for implementation; (iv) a health care team for decisions and care; (v) a quality assurance structure; and (vi) a method for identifying cancer occurrence in the population [36]. The effectiveness of a screening programme depends on the proper implementation of these elements [37].

Wilson and Jungner's Principles of Screening (Box 1) are considered the gold standard for judging the suitability of a disease for a screening programme [38]. CRC is highly suitable for screening mainly because of the high disease burden, a long screen detectable latent phase and improved prognosis when the disease is detected at an earlier stage. Approximately 40% of people at the age of 50 years or older have one or more adenomatous polyps. These intermediate lesions are readily removable during a screening endoscopy, and their progression to CRC generally takes at least 10 years. It is of great importance to identify these polyps and remove them prior to cancer transition [19]. Thus, CRC screening prevents both incidence and mortality of CRC.

CRC screening programmes can be implemented in a single step and in two steps. In the single step approach, colonoscopy is used which allows the detection and removal of polyps. This approach is the most common in the US, with colonoscopy being the primary CRC screening modality [39]. In the two-step approach, a stool-based test is used as the primary test and a

colonoscopy is used as a follow-up procedure in case of a positive initial screening test. Most of the CRC screening programmes use the two-step approach [40].

Box 1. Wilson and Jungner's Principles of Screening

1. The condition sought should be an important health problem.
2. There should be an accepted treatment for patients with recognized disease.
3. Facilities for diagnosis and treatment should be available.
4. There should be a recognizable latent or early symptomatic stage.
5. There should be a suitable test or examination.
6. The test should be acceptable to the population.
7. The natural history of the condition, including development from latent to declared disease, should be adequately understood.
8. There should be an agreed policy on whom to treat as patients.
9. The cost of case-finding (including diagnosis and treatment of patients diagnosed) should be economically balanced in relation to possible expenditure on medical care as a whole.
10. Case-finding should be a continuing process and not a 'once and for all' project.

Harms of CRC screening include unintended psychological and physical harm [41]. Psychological harms include anxiety about false-positive results with stool-based tests. False-negative results also pose significant harms by delaying diagnosis and treatment, allowing cancer to progress to more advanced, less treatable stages. Psychologically, false reassurance can lead individuals to overlook symptoms and delay seeking medical consultation, causing increased anxiety upon eventual diagnosis [42]. Harms related to colonoscopy are complications such as bleeding, perforation of the colon and adverse reactions to sedation. Risks of complications in organized screening programmes are lower compared to general practice colonoscopies and tend to increase with age. Overall risks of complications of colonoscopy have declined over time [43]. The rate of complications in the screening population is 2.8/1000 colonoscopies compared to 5/1000 colonoscopies in a symptomatic population [44]. Overdiagnosis is another major harm related to screening, which is a diagnosis of a disease that would not have developed to cause symptoms or death in the patient's lifetime if not detected by screening [45].

1.9 Type of Colorectal cancer screening tests and their effectiveness

For CRC screening, there are multiple tests available, each with its strengths and weaknesses. Broadly, the tests can be categorized into three groups. They are stool-based tests, endoscopy tests, imaging tests and blood-based tests.

1.9.1 Stool-based tests

Stool-based tests include Guaiac faecal occult blood test (FOBT), immunochemical faecal occult blood test (FIT) and multitarget stool DNA test (MT-sDNA). The FOBT test detects traces of any blood, requires two samples from consecutive bowel movements and avoidance of diet containing animal blood prior to the test. Whereas the FIT test is specific for human blood, requires one sample and does not require dietary restrictions. Further FIT test can quantify the amount of blood in the stool and hence allow the policy makers to choose the positivity threshold on the desired balance between the test sensitivity and specificity. Previously, FOBT was the dominant stool-based test used in screening programmes. However, currently FIT has replaced FOBT in a majority of these programmes [46, 47]. The MT-sDNA test includes FIT to detect haemoglobin and tests to detect traces of blood or DNA mutation markers in stool shed by advanced adenomas or CRC neoplastic lesions [39].

We conducted a targeted literature search to identify randomized control trials that have reported the effectiveness of the FOBT test followed up by index colonoscopy to reduce the mortality from CRC. Table 1-2 summarizes the key characteristics of these RCTs, including the population intervention, comparator, and outcome (PICO). The targeted search revealed that there are no randomised controlled trial (RCT) data to confirm the efficacy of the FIT test in CRC incidence and mortality reduction. However, there are observational cohort studies that showed the efficacy of FIT in reducing the CRC mortality and morbidity. FIT has higher diagnostic performance compared to FOBT in screening programmes [48]. Therefore, despite no RCT data so far to confirm FIT efficacy in CRC incidence and mortality reduction, FIT is now widely recommended, or already adopted, for population-wide organized screening programmes [40, 49].

Ireland was one of the first countries to adopt this technology for organised population-based CRC screening [50].

MT-sDNA test is approved for screening in average-risk adults only in the US. Even though the test has high specificity compared to FIT, the use of the MT-sDNA test as a potential first-line screening test is limited due to relatively low sensitivity and prohibiting cost [51].

Table 1-2 Evidence on effectiveness of stool-based tests, NR- Not Reported

Study author	Study type	Country	Study Period	Participants (N)	Intervention test	Comparator	Age range (years)	Screening Interval	Follow-up period (years)	Outcomes	
										Incidence rate ratio (95% CI)	CRC mortality RR (95% CI)
Scholefield at al [52]	RCT	UK	1981–1995	S- 76,056 C- 75,919	FOBT	No intervention	45-74	Biennial	28	0.97 (0.91 -1.03)	0.91 (0.65-0.93)
Kronborg et al [53]	RCT	Denmark	1985–2002	S- 30,762 C- 30,966	FOBT	No intervention	45-75	Biennial	13.9	1.02 (0.93-1.12)	0.84 (0.73-0.96)
Jorgensen et al [54]	RCT	Sweden	1982–1995	S- 34,144 C- 34,164	FOBT	No intervention	60-64	Biennial	8 -15	0.96 (0.86-1.06)	0.84 (0.71-0.99)
Hamza et al [55]	Quasi experimental	France	1988-1998	S- 45,642 C- 45,557	FOBT	No intervention	45-74	Biennial	11	1.01(0.91-1.12)	0.84 (0.71-0.99)
Mandel et al [56] Shaukat et al [57]	RCT	USA	1975–1992	(annual) S- 15,570 C- 15,394 (biennial) S- 15,587 C- 15,394	FOBT	No intervention	50-80	Annual/ Biennial	30	Annual: 0.80(0.70-0.90) Biennial: 0.83(0.73-0.94)	Annual 0.68 (0.56-0.82) Biennial 0.78 (0.65-0.93)
Chiu et al [58]	Prospective cohort study	Taiwan	2009-2014	S-1,160,895	FIT	No intervention	50-69	Biennial	6	NR	0.38 (0.35-0.42)
Ventura et al [59]	Cohort	Italy	1993-1999	S - 6961 C- 26,285	FIT	No intervention	50-70	Biennial	11	0.78 (0.63-0.97)	0.59 (0.37 -0.93)
Rossi et al [60]	Cohort	Italy	2005 – 2012	171,785	FIT	No intervention	50-74	Biennial	8	0.59(0.50 – 0.69)	0.64 0.52 -0.78)

FIT- Faecal Immunochemical Test, FOBT- Faecal Occult Blood Test, S – Screened population, C – Control, CI – Confidence Interval, RR – Rate Ratio, RCT – Randomised Control Trial

1.9.2 Endoscopic tests

Endoscopic tests involve either colonoscopy or flexible sigmoidoscopy (FSIG). A colonoscopy is typically conducted on an outpatient basis in a hospital's gastroenterology department. During the procedure, an endoscopist inserts a flexible camera-equipped tube through the rectum to visually examine the colon. Prior to the examination, patients are instructed to take laxatives to ensure the bowels are empty for a clear view. Sedatives and analgesics are commonly used to enhance patient comfort and improve examination quality. During a colonoscopy, abnormal growths known as adenomas or polyps can be removed through polypectomy, tissue samples may be collected for biopsy, or both could be conducted. Thus, colonoscopy can be used for both diagnostic and therapeutic purposes. Colonoscopy is also used as a primary screening modality in several countries, typically with an interval of ten years [40]. A targeted literature search has revealed that, to our knowledge, there are no randomized trial comparing the long-term effectiveness of colonoscopy screening to either no screening or another screening method, has been published and indirect evidence is used to justify its implementation [61]. The fact that FOBT screening trials have reported a significant reduction in CRC mortality supports the idea that colonoscopic screening also reduces CRC mortality, as diagnostic colonoscopy is an essential component of the screening strategy used in the FOBT trials. Additionally, to our knowledge, there are three large scale RCTs are currently underway in the US and Europe, comparing the effectiveness of colonoscopy with no screening and annual or biennial FIT tests, with results expected in the next decade [62-64].

A FSIG is similar to a colonoscopy but is less invasive. It only examines the left-sided or the descending colon and the rectum where approximately 60% of all CRCs develop [65]. Sedation is less frequently used as with colonoscopy, and it requires less heavy bowel preparation. It requires referral to colonoscopy if lesions are found during FS screening. A targeted literature search has revealed that, to our knowledge, four RCTs have evaluated one-time or three to five times yearly CRC screening with FSIG with up to 17 years of follow-up data. These RCTs reported a 20-30% reduction in CRC incidence and mortality respectively (Table 1-3). However, not many countries

have adopted FSIG in the screening programme as it requires similar infrastructure as a colonoscopy but does not provide as much therapeutic benefit as colonoscopy [40, 41].

Table 1-3 Evidence of effectiveness of endoscopy-based tests

Authors	Study type	Country	Study Period	Participants (N)	Intervention Screening modality	Comparator	Age range	Interval Frequency	Follow-up (years)	Outcome	
										Incidence Rate Ratio (95% CI)	CRC mortality RR (95% CI)
Atkin et al [66]	RCT	UK (UKFSST)	1994–1999	S- 57,099 C-112,939	Sigmoidoscopy	No screening intervention	55–64	Only once	11.2	0.77(0.70-0.84)	0.69 (0.59-0.80)
Miller et al [67]	RCT	US (PLCO)	1993–2001	S-77,445 C-77,455	Sigmoidoscopy	No screening intervention	55-74	Twice	11.9	0.79(0.72-0.85)	0.74 (0.63-0.87)
Segnan et al [68]	RCT	Italy (SCORE)	1995–1999	S-17,136 C-17,136	Sigmoidoscopy	No screening intervention	55-64	Only once	10.5 - incidence 11.4 - mortality	HR 0.82(0.69-0.96)	0.78 (0.56-1.08)
Holme et al [69]	RCT	Norway (NORCCAP)	1999–2001	S- 20,572 C-78,220	Sigmoidoscopy	No screening intervention	50–64	Only once	11.0	HR 0.80(0.70-0.92)	0.80 (0.62-1.04)
Manser et al [70]	Cohort	Switzerland	2009-2014	S-1912 C-20,774	Colonoscopy	No screening intervention	50-80	Only Once	6.0	aOR 0.31(0.16-0.59)	0.12(0.01-0.93)

HR – Hazard Ratio, aOR – adjusted Odds Ratio, UKFSST - UK FS Screening Trial, PLCO - The Prostate, Lung, Colorectal and Ovarian (PLCO), SCORE - sigmoidoscopy screening for colorectal cancer, NORCCAP - Norwegian colorectal cancer prevention, S – Screened Population, C – Control, RR - Rate Ratio, CI – Confidence Interval

1.9.3 Imaging tests

Imaging tests include barium enema, colon capsule endoscopy (CCE), Computed Tomographic Colonography (CTC), MR-colonography. CCE involves a capsule with two cameras which is swallowed by the patient to capture the images as it travels through the colorectum. These images are wirelessly transmitted to a computer and reviewed by an examiner. It requires a bowel preparation; however, it does not require sedation or dietary or medication adjustments. CCE does not allow for biopsy or polyp removal during the test. CCE achieved some improvement in screening in recent years due to both software and hardware enhancement, and it demonstrated a sensitivity at 81% and specificity at 93% for lesions smaller than 6mm, while the completion rate was 79% in a prospective study [71]. CTC uses a low dose CT scan of the colon and the rectum and is also called virtual colonoscopy. CTC was shown to have 68-98% sensitivity and 80-93% specificity for lesions smaller than 6mm [72]. However, some concerns about CTC in detecting right-sided and flat lesions exist, and the sensitivity for SSLs was only 0.8%, which was significantly lower when compared with colonoscopy (3.1%) in the same study [73]. Most of the guidelines recommend both CTC and CCE only as alternatives for those who are unable to undergo colonoscopy or FIT screening [41].

Barium enema uses injection of a liquid containing a metallic substance called barium into the colon through a small tube that coats the lining of the colon to produce quality images during X-ray examination [74]. The use of barium enema, either single-contrast or double-contrast (DCBE) has declined with the increasing use of endoscopic and CT procedures that have better sensitivity and specificity. Barium enema tests are no longer recommended by expert groups as options for CRC screening and are no longer performed in some locations [75].

1.9.4 Blood-based tests

These tests are novel and detect CRC markers from the blood. The mSEPT9 is the only blood-based test approved by the US Food and Drug Administration (FDA) [51]. The advantage of this test is a blood sample may be preferred for some patients over collecting a stool sample or a more

invasive test. However, the mSEPT9 is not recommended by major guidelines due to its inadequate sensitivity and unclear role in early detection [39]. The sensitivity of mSEPT9 is reported to be slightly over 20% for adenomas, 68% for CRC with 80% specificity for all stages of cancer [51].

1.10 Test accuracy

Sensitivity and specificity are essential indicators of test accuracy. The ability of a test to accurately identify persons who truly have a disease and those who truly do not have a disease is called its sensitivity and specificity, respectively. Tests with a high sensitivity have a better chance of detecting disease while tests with a high specificity limit the number of people with false-positive screening test results [76].

The threshold chosen as the cut-off between a positive and negative result can affect whether a screening test is considered more sensitive and less specific or vice versa. Ideally, a test should have both high sensitivity and specificity. However, no test is entirely precise, as a result, some individuals who do not have the condition may get a positive test outcome (known as a false positive), while some individuals with the condition may get a normal or negative outcome (known as a false negative).

Quantitative tests have adjustable cut-off thresholds that can result in a trade-off between sensitivity and specificity. In the case of stool-based tests used in CRC screening, setting the positivity threshold low would increase sensitivity and lower specificity, resulting in fewer false negatives. This will prevent a large proportion of precursor lesions or preclinical cancers from being missed; however, this results in a high false positive rate which could overwhelm colonoscopy services. Conversely, selecting a high positivity threshold would lower sensitivity and increase specificity, resulting in fewer false positives, which would reduce the immediate burden on patients and colonoscopy resources. However, a high positivity threshold would increase the number of false negatives and result in the detection of fewer lesions and preclinical

cancers. Thus, the choice of positivity threshold poses significant trade-offs between the risks of false negatives and false positives.

1.11 Recommendations for colorectal cancer screening

Several internationally recognized guidelines and recommendations for best practice in CRC screening have been published. Table 1-4 provides a summary of these guidelines.

Recommendations on screening age range

The majority of the guidelines from the US expanded the recommended ages for CRC screening to 45 to 75 years which was previously 50-75 years [77, 78]. While the European guidelines recommend the start age of 50 years and stopping at age 74 years [79-82]. In general, most US guidelines advise against screening after 75 years. Guidelines also recommend tailoring screening in individuals between ages 76 and 85 years based on their screening history, life expectancy, co-morbidities, and preference [77, 78].

Recommendations on screening tests and interval

Various stool-based and image-based screening modalities are recommended by the guidelines including FIT, FOBT, multitarget stool MT-sDNA, colonoscopy, sigmoidoscopy, CTC, and CCE. The preferred option in the European context is the FIT test except for Germany where FOBT is the test of choice [83]. Similarly, the US Multi-Society Task Force on CRC (USMSTF) [84] provides a tier-based approach and suggests colonoscopy or FIT as the first tier followed by other options whereas the other guidelines recommend screening without identifying a preferred option [77, 78, 85, 86].

Recommendations on FIT test positivity threshold

Typically, guidelines do not recommend an explicit threshold to define the FIT test positivity, but a few suggest a cutoff point that guarantees an optimal balance between sensitivity and specificity, depending on the availability of colonoscopies [81].

Table 1-4 Recommendations for CRC screening across Europe, Australia and North America [83]

Continent	Country/Association	Age range in years	Screening tests, interval	Note
Europe	European Society of Digestive Oncology (ESDO), 2020 [82]	50-74	Colonoscopy, 10 years OR FS every 5-10 years combined with annual FOBT OR FIT every year or no later than 3 years	Capsule colonoscopy is not recommended.
	European Guidelines, 2013 [79]	50-74	FOBT/FIT, 1-2 years or no later than 3 years OR Other options include colonoscopy, 10-20 years OR FS, 10-20 years	Further improvement in diagnostic performance and cost-effectiveness required for CTC, CCE, stool DNA before recommendations for use in screening.
	Spanish Society of Medical Oncology (SEOM), 2014 [81]	50-74	FIT, 2 years OR FOBT, 1-2 years OR FS, 5 years OR Colonoscopy, 10 years	Combination of FOBT and FS, and CT colonography are not recommended.
	German Guideline Programme in Oncology (GGPO), 2019 [80]	50 or greater	Colonoscopy, 10 years OR FS 5 years and annual FOBT or high specificity and sensitivity FIT	Genetic stool tests, CT colonography, MR-colonography and capsule endoscopy are not recommended.

Continent	Country/Association	Age range in years	Screening tests, interval	Note
				No upper age limit is given. An individual decision should be made considering comorbidities.
Australia	National Health and Medical Research Council (NHMRC), 2018 [87]	50-74	FIT every 2 years	Extending the screening beyond the age of 74 years is not recommended as it is not cost-effective
North America	US Multi Society Task Force (USMSTF), 2017 [84]	45-75	Colonoscopy, 10 years or an annual FIT as first-tier options FS every 5 to 10 years CTC every 5 years Capsule colonoscopy every 5 years when individuals decline colonoscopy, FIT, FIT–faecal DNA, CTC, and FS	Guideline suggests selective screening of 76-85 years depending on consideration of their age and comorbidities
	National Comprehensive Cancer Network (NCCN),2022 [85]	45-75 76-85	Colonoscopy every 10 years FOBT every 1-year OR FIT every 1-year OR MT-sDNA every 1year OR FS every 5-10 years OR CTC every 5 years	Screening at greater than 75 years should be done conditionally
	US Preventive Services Task Force (USPSTF), 2021 [77]	45-75	High sensitivity FOBT or FIT every year OR sDNA-FIT every 1 to 3 years OR CT colonography every 5 years OR Flexible sigmoidoscopy every 5 years OR Flexible sigmoidoscopy every 10 years + FIT every year OR	Guideline recommends selective screening of 76-85 years based on patients' health status prior screening status, and individual preferences

Continent	Country/Association	Age range in years	Screening tests, interval	Note
			Colonoscopy screening every 10 years	
	American College of Physicians (ACP), 2019 [86]	50-75	High sensitivity FOBT/FIT (1 year) OR FS (5 years) OR FOBT/FIT (3 yr) + FS (5 yr) OR colonoscopy (10 yr)	Guideline recommends discontinuing screening in average-risk adults older than 75 years or in adults with a life expectancy of 10 years or less
	American Cancer Society, 2018 [78]	45-75	FIT 1 year OR High Sensitivity FOBT 1 year OR MT-sDNA 3 years OR Colonoscopy screening every 10 years OR FS (5 yr) OR CTC, every 5 years	The decision to continue screening at 76-85 years depends on the patient's preferences, life expectancy, health status, and previous screening history
	Canadian Task Force on Preventive Health Care (CTFPHC), 2016 [88]	60–74	FIT or high sensitivity FOBT every 2 years or FS every 10 years	

Multi-Society Task Force on CRC represents the American College of Gastroenterology, the American Gastroenterological Association, and the American Society for Gastrointestinal Endoscopy. FIT – Faecal Immunochemical Test, FOBT – Faecal Occult Blood Test, MT-sDNA- Multi-target stool DNA, CTC- Computed Tomography Colonoscopy, FS- Flexible sigmoidoscopy, DNA – Deoxyribonucleic Acid

1.12 Colorectal Cancer Screening in Ireland

The first policy commitment for CRC screening in Ireland came from the National Strategy for Cancer Control 2006. The strategy recommended the Department of Health and Children to work on the preparation for CRC control programme encompassing population screening [89]. Following that, the Department of Health and Children requested advice from the National Cancer Screening Service (NCSS) on the development of a national CRC screening programme in Ireland [90]. The NCSS in consultation with national expert advisory board members and an international validation panel provided recommendations in December 2008. At the same time, a Health Technology Assessment (HTA) analysis on the Cost-effectiveness analysis of CRC screening was conducted by Health Information and Quality Authority (HIQA) [91]. These two documents informed the implementation of the current Bowel screening programme.

Ireland began a nationwide CRC screening programme known as the National Bowel Screen Programme (NBSP) or BowelScreen in late 2012 with the goal of reducing mortality due to CRC in people aged 55-74 years in Ireland. HTA conducted by HIQA in 2009 recommended biennial FIT among the population aged 50-74 years as the optimally cost-effective screening strategy in Ireland [91]. However, the recommended strategy was not implemented because of the insufficient colonoscopy capacity within the system. A resource modelling was conducted that suggested implementing the programme on a phased basis with a narrower age group [92]. The programme started with offering screening to people aged 60-69 years biennially. For an individual who began screening at age 60 years, this means they would receive five successive screens, with the last at age 68 years. The programme uses FIT test as the primary test followed by colonoscopy as the diagnostic test. FIT test is a quantitative test that allows to define the positivity threshold. In early 2014, the programme adjusted the threshold for FIT from 100 nanograms of blood per millilitre of stool (100 ng Hb/mL) buffer to 225 ng Hb/mL (45 mg Hb/g faeces) [93]. Recently, the start age of the screening is dropped to 59 years after ten years since the initiation of the programme [94].

Patient pathway for screening and surveillance under National Bowel Screening Programme

The NBSP sends a FIT test kit to the eligible population with instructions for self-administration of the test at home. The completed test can then be sent by free post to an accredited laboratory for analysis. In case of a positive result, people are offered a screening colonoscopy at a hospital contracted by the National Screening Service (NSS). A pre-assessment telephone interview is conducted by a nurse to establish suitability for colonoscopy. People who are considered medically unfit for colonoscopy are considered for CTC [93]. People with intermediate to high-risk adenomas are placed into a surveillance programme of periodic colonoscopy. The surveillance programme is based on European guidelines [95]. People with high-risk adenomas (five or more small adenomas or at least one big adenoma of 20mm) are offered a surveillance colonoscopy at 1 year and those with intermediate risk adenomas (three to four small adenomas or an adenoma 10 mm or larger) are offered a colonoscopy in three years. The colonoscopy intervals are further revised based on the findings of surveillance colonoscopy. For people in intermediate risk surveillance group, the surveillance interval extends to five years after one negative colonoscopy result, and they return to routine screening programme after two consecutive negative results. For people in the high-risk surveillance group, the surveillance interval extends to three years after one negative colonoscopy result and to 5 years after two consecutive negative results. The patient pathway through the bowel cancer screening and surveillance process is demonstrated in Figure 1-6.

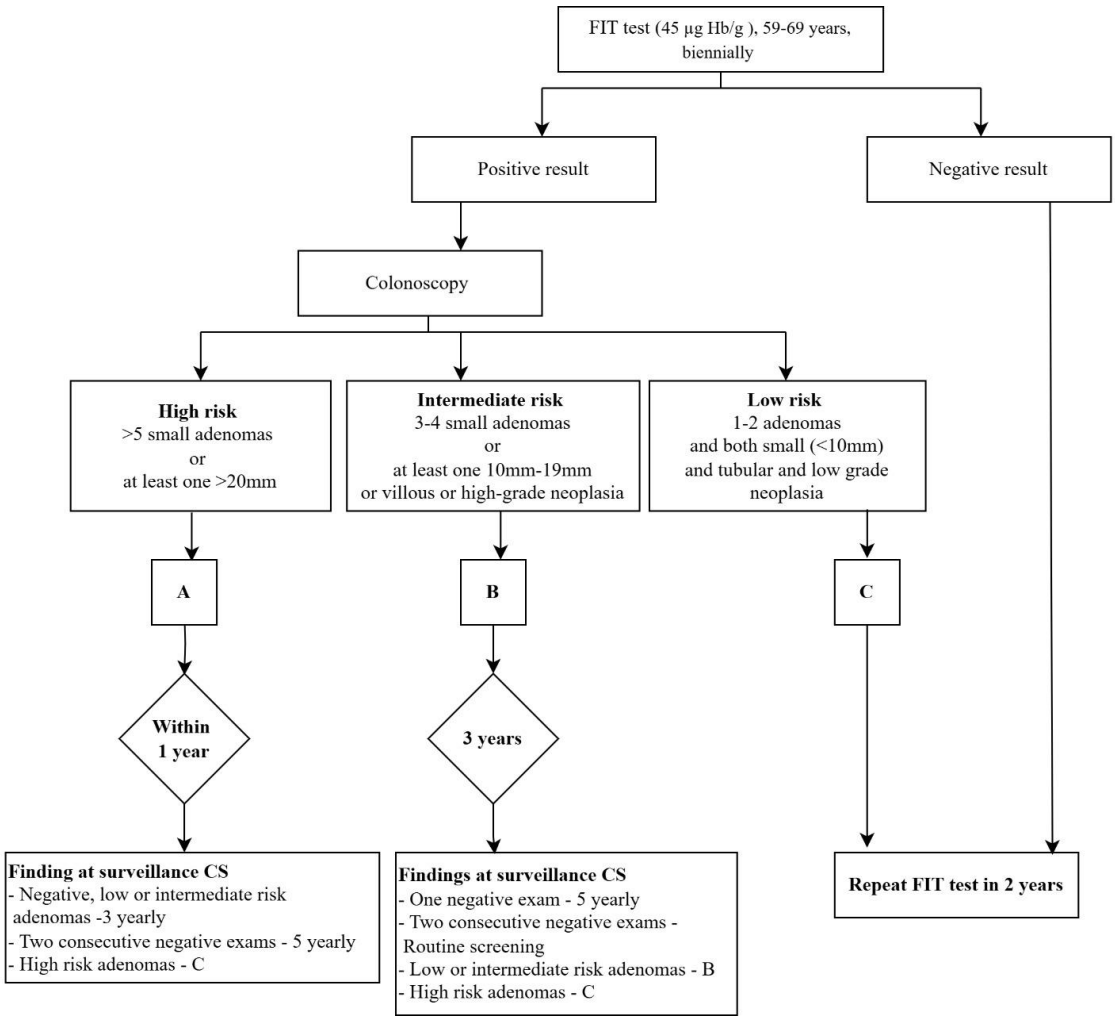


Figure 1-6. Patient pathway through the bowel cancer screening and surveillance process. Adapted from National Bowel Screening Programme [93] and European guidelines for quality assurance in CRC screening and diagnosis [95].

FIT – Faecal Immunochemical Test, CS – Colonoscopy, µg – Microgram, Hb – Haemoglobin, g – gram. Groups A, B and C were defined to stratify patients based on their risk levels after a colonoscopy. It makes it easier to present the follow-up recommendations and surveillance intervals.

National Bowel Screen Programme Key Performance

The NBSP has completed four rounds of implementation. Key indicators of the programme's performance are presented in Table 1-6. Over the four rounds, the uptake rate for primary test has increased to 46.6 percent from 40 percent (Round I, 2012-2015) but still under the programme target of 50 per cent or greater. Similarly, the rate of uptake of follow-up colonoscopy is around 80% across the four rounds which is also below the programme Quality Assurance standard of 85% [50, 96-98]. FIT positive rate and the cancer detection rate were highest in the first round

and lower in subsequent rounds as expected to be in the unscreened population. Adenoma detection rate has been consistently over the programme standard of greater than 45 per cent over the rounds.

Table 1-5 Key performance indicators of the NBSP over four rounds

Round	Individuals invited	Individuals screened	Uptake of FIT test	FIT positive rate	Uptake of colonoscopy	Adenoma detection rate (as proportion of individuals screened)	Cancer detection rate (as proportion of individuals screened)
Round I (2012-2015)	488,628	196,238	40.2%	5%	82.4%	54.2%	2.65/1,000
Round II (2016-2018)	546,767	226,374	41.4%	3.6%	79.5%	56.7%	1.81/1,000
Round III (2018-2019)	534,926	249,112	41.9%	3.3%	78.8%	55.1%	1.36/1,000
Round IV (2020-2021)	299,898	140,063	46.6%	3.4%	81.8%	58.2%	1.49/1,000

Source: NBSP Reports [50, 96-98] FIT- Faecal Immunochemical Test

1.13 Thesis aims and objectives

The aim of this thesis is to answer various policy related questions on CRC screening specifically about the optimal screening strategy, colonoscopy requirement and updated costs of colonoscopy services.

The research objectives include:

1.13.1 Objectives

1. To assess the range of strategies analysed in European cost-effectiveness analyses (CEAs) of colorectal cancer (CRC) screening with respect to the screening intervals, age ranges and test cut-offs used to define positivity, to examine how this might influence what strategies are found to be optimal and compare them with the current screening policies with a focus on the screening interval.
2. To estimate the unit cost of colonoscopy procedure based on intervention and route of referral.
3. To quantify current and future colonoscopy demand for screening and surveillance activities in Ireland

1.13.2 Research questions

The research questions are as follows:

Study 1 Colorectal Cancer (CRC) screening intensity in Europe: A systematic review of Cost-effectiveness Analyses (CEAs) addressing the question of optimal policy choice

What are the intensities used in the European CEAs?

What are the screening policies used in the European countries on population-based screening programmes?

Is the colonoscopy constraint in the health system limiting the choice of optimal cost-effective policy?

Study 2 Micro-costing of the colonoscopy service

What is the unit cost of colonoscopy for the Health Service Executive (HSE)?

What are the costs for clinically and screen indicated colonoscopies?

Study 3 Resource modelling to estimate the colonoscopy requirements for the National Bowel Screen Programme

How many colonoscopies are required for screening and surveillance services over a range of policy alternatives?

What are the colonoscopy related cost implications?

CHAPTER 2 COST EFFECTIVENESS ANALYSES OF COLORECTAL CANCER SCREENING

2.1 INTRODUCTION

2.1.1 The need for economic evaluation in healthcare

Health system resources are limited, and healthcare policymakers face the challenge of allocating them effectively within budgetary constraints. Economic evaluation plays a crucial role in guiding these evidence-based public health decision-making by comparing alternative health technology in terms of both costs and consequences [99]. The primary objective of economic evaluation in healthcare is to optimise population health with the available resources ensuring the best value for money. It includes identifying, measuring, valuing, and comparing the costs and consequences of the alternatives being considered and complements the clinical evidence in aiding the healthcare resource allocation decisions [100]. Economic evaluation can be based on empirical trials, mathematical models, or a combination of both. Many jurisdictions such as the UK [101], Ireland [102], Australia [103], New Zealand [104], and Canada [105] incorporate economic evaluations into their health technology assessment programmes.

2.1.2 Types of economic evaluation

Full economic evaluation explicitly compares the costs and consequences of the health intervention in question to an alternative course of action, known as the comparator. On the other hand, partial economic evaluations do not explicitly compare alternative interventions in terms of both costs and consequences, but they still provide valuable evidence on the economic aspects of interventions. Partial economic evaluations include cost analyses, cost-description studies, and cost-outcome descriptions [106].

The most commonly used types of full economic evaluation in healthcare are cost-effectiveness analysis (CEA), cost-utility analysis (CUA), and cost-benefit analysis (CBA). All these economic evaluations assess costs in monetary terms but approaches to measuring and valuing the consequences of health interventions may differ. CBA express the benefit or consequence of the

health intervention in question in monetary terms. In contrast, CEA measure the health consequences of the health intervention in a single natural unit (such as life-years gained, cases averted, or cases detected), and cost-utility analyses measure the health consequences in terms of preference-based measures of health, such as quality-adjusted life-years, or disability-adjusted life years [100, 107]. The choice of the specific type of economic evaluation to be used depends on the decision problem and the perspective of the decision maker.

In practice, there has been a blurring of the distinctions between CEA and CUA; as a result, literature on CEA often encompasses both these approaches and CUA are often referred to as a CEA [107]. This thesis considers CUA and CEA to be synonymous and uses the latter term.

2.1.3 Cost-effectiveness framework and optimally cost-effective strategy

The results of the CEA models are commonly summarized in a series of incremental cost-effectiveness ratios (ICERs) and presented graphically on the cost-effectiveness plane. ICER is calculated by dividing the incremental cost of an intervention by an incremental change in the effectiveness [108]. The Cost-effectiveness plane consists of a two -dimensional graph where the vertical axis typically represents the costs, and the horizontal axis represents the effects. The origin of the plane typically represents either the current standard of care or the do-nothing option where no intervention is offered. The plane can be defined as four separate quadrants. The CEA estimates in the north-west quadrant and the south-west quadrant are not preferred. The estimate in the north-west quadrant is more costly but results in worse health outcomes. Similarly, the estimate in the south-west quadrant has reduced costs but worse health outcomes. The CEA estimates in the south-east quadrant involve reduced cost and the improved health outcomes and hence are strictly preferred. However, in most of the circumstances, intervention with more effectiveness compared to the alternative strategy also has the higher cost. These kinds of estimates lie in the north-east quadrant [100, 109].

A decision on whether the additional health benefit is worth the additional cost is made based on the CEA threshold which is the predefined maximum amount a jurisdiction is willing to pay for a unit of health outcome. For example, Ireland's cost-effectiveness threshold has previously been

€45,000 per quality-adjusted life-year (QALY) for pharmaceuticals, however, the threshold for non-drug intervention is not explicitly defined [110].

When there are multiple alternative strategies, the cost-effectiveness is determined based on the principle of dominance. Strategies with higher cost and lower effects are strongly dominated by other strategies having both lower costs and greater effects. Further strategies could be extendedly dominated being more costly and less effective than linear combinations of other strategies that can produce greater benefit at lower cost. The remaining non-dominated strategies form set of efficient strategies and the line joining them is called the efficient frontier [100]. From these sets of strategies, incremental cost-effectiveness ratios are calculated by comparing each option with the next more costly and more effective intervention. The optimally cost-effective strategy is the most effective strategy with an ICER within the cost-effectiveness threshold [100, 109].

In Figure 2-1, strategies A, B, D and F form the efficient frontier. Strategy C is dominated by strategy B and strategy E as it is more costly and less effective than their respective dominant strategy. Strategy E is extendedly dominated by strategies D and F. The ICER for each strategy on the efficient frontier is calculated by comparing the cost and effect difference with the next best strategy i.e., ICER for strategy F is calculated comparing with D, D with B and B with A. After calculating the ICER, the optimal cost-effective strategy is identified as the one with the highest effectiveness and the ICER with the CEA threshold. In this example, the strategy with the D is the optimal cost-effective strategy with a decision threshold of €30,000 per QALY.

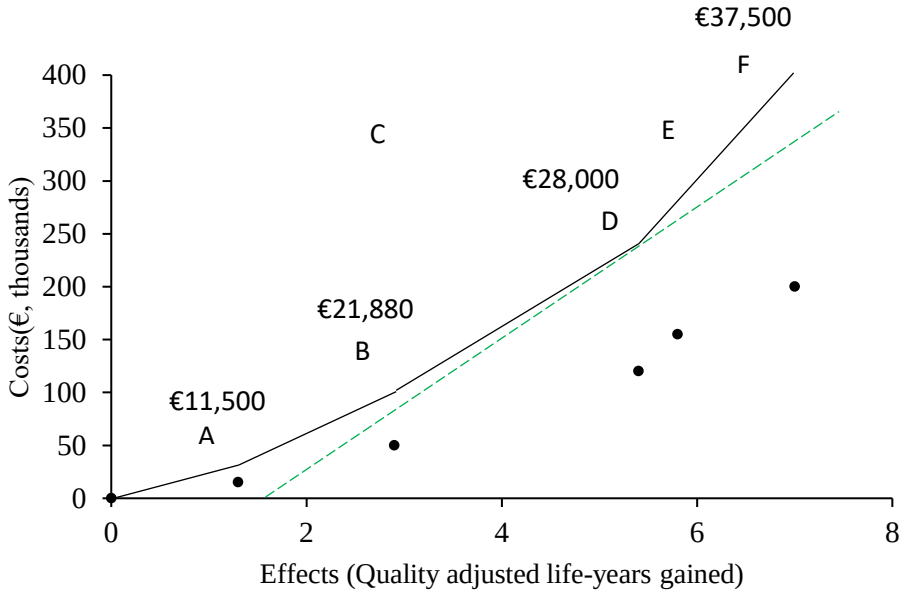


Figure 2- 1 Graphical representation of the CEA plane and the optimal cost-effective strategy

2.1.4 Choice of comparators in Cost Effectiveness Analyses

The selection of comparators in a CEA has implications for the identification of optimally cost-effective strategies and can change the conclusions of the analysis. CEAs should include all relevant comparators, or clearly justify their exclusion [100, 111, 112]. In the CRC screening programme, multiple alternative CRC screening strategies are possible. The intensity of screening can be varied by adjusting the screening interval, screening age range and the threshold to define the positivity rate in the case of quantitative test FIT. In such a situation with variations on the intensity of a programme, each more intense variation should be compared to the next less intense option being considered to calculate the ICER of the options [113]. Thus, in order to find the optimal screening interval, screening age range and the multiple test cut-off options for each should be compared.

Problems can arise if CEAs include insufficient strategies. Any ICER that is estimated based on a comparison set that omits relevant comparisons is not adequate. A study may conclude a given strategy is cost-effective but may have failed to consider other relevant strategies, including those

that are potentially more effective and cost-effective. Thus, when interpreting cost-effectiveness estimates of CRC screening it is important to consider whether analyses included sufficient variation in screening age range, screening intervals, and FIT cut-offs to provide the most useful policy guidance.

The issue of whether sufficient strategies have been included within a CEA has to be considered within the context of the objective of the analysis. While most CEAs may have a broad objective of attempting to find the optimally cost-effective strategy from among all possible strategies, others may have narrower objectives such as assessing the cost-effectiveness of moving from an old test to a new test while holding all other aspects of the screening schedule constant. In the latter case, the exclusion of a range of strategies from a CEA might not be considered problematic given the specific study objectives. Thus, decision context is important in judging the choice of comparators in a CEA.

2.1.5 Cost-effective Colorectal cancer screening strategies

Numerous CRC screening strategies are possible. This is because of multiple available screening tests, the choice of screening start and stop age, screening frequency, and positivity threshold in the case of quantitative stool-based tests. However, there is no consensus on the most optimal cost-effective strategy. The optimal cost-effective strategy might naturally vary between settings due to multiple factors including the health system differences such as differences in screening pathways, care pathways, methodological differences in the conduct of the CEAs such as differences in the discount rates applied, population level differences such as disease incidence etc.

2.1.6 Review of previous systematic reviews on cost-effectiveness of Colorectal cancer screening strategies

A targeted literature search revealed that there are several systematic reviews of CEAs on CRC screening among the average-risk population have been published in different contexts. Below is a summary of the findings from these systematic reviews.

The first systematic review of CEAs of CRCs was published in 2002 for the US Preventive Services Task Force [114]. The authors identified seven original economic evaluations of CRC screening in average-risk populations. The strategies compared in those studies were FOBT annually, FS every 5 years alone or with FOBT, barium enema every 5 years, and colonoscopy every 10 years. The review concluded screening for CRC is cost-effective with any modality compared with no screening, but a single optimal strategy cannot be determined. Further, the review was unable to answer the question of optimal start age and stop age of screening as only two studies varied start and stop ages in individual analyses.

Another systematic review of CEAs of CRC screening conducted by Lansdorp-Vogelaar et.al 2010 [115] also provided similar findings. The review focused on the same set of CRC screening strategies as analysed by the preceding review- annual and biennial FOBT, 5-yearly sigmoidoscopy, the combination of 5-yearly sigmoidoscopy and annual FOBT, and 10-yearly colonoscopy. Based on 32 studies included in the review, the authors concluded that CRC screening is cost-effective or even cost-saving compared to no screening. However, there was no consensus on which screening method was optimally cost effective. Further, the review highlighted that the newly developed screening tests at that time such as stool DNA testing, CTC, and capsule endoscopy were not yet cost-effective compared with the common screening strategies. Unlike the previous systematic review, this review also provided the details of the model used in individual studies.

The systematic review published by Patel et al [116] in 2015 was limited to 17 CEAs conducted in the US. The CRC screening strategies evaluated in the review were those recommended by the US Preventive Task Force. This review reaffirmed the results from previous reviews that any FOBT test, FS, colonoscopy, virtual colonoscopy, or stool DNA test is cost-effective when compared with no screening, but the optimal cost-effective strategy is not agreed upon.

A systematic review by Jeong and Cairns published in 2013 [117] included 68 studies in the review. The paper aimed to provide a critical appraisal of methods used in the model-based economic evaluation of CRC screening and subsequent surveillance. While the review has emphasized the need to evaluate the cost-effectiveness of different combinations or sequences of follow-up strategies for individuals with positive screening, it did not address the same need for primary screening strategies.

Ran et al 2019 [118] conducted a systematic review of CEAs of CRC to provide up-to-date evidence of the cost-effectiveness of CRC screening strategies. In addition to the strategies included in the systematic review conducted by Lansdorp-Vogelaar et.al [115], this review included annual and biennial FIT tests. The review included 33 studies and provided a similar conclusion to that of Lansdorp-Vogelaar et.al. that annual and biennial FOBT, annual and biennial FIT, colonoscopy every 10 years, and flexible sigmoidoscopy every 5 years were cost-effective compared to no screening. Additionally, this review identified CTC every five or 10 years to be cost-effective compared to no screening. The review also highlighted the variation in the cost-effectiveness results according to the regions of analysis and the assumptions used in the models [118]. However, this review did not comment on the difference in cost-effectiveness results of the stool-based tests based on the intervals of screening.

A systematic review conducted by Mendivil et al in 2019 [119] reached similar conclusions to that of preceding reviews that CRC screening is cost-effective compared to no screening with common modalities like colonoscopy, FS, FOBT and FIT. However, due to the heterogeneity in studies' characteristics, the optimal screening strategy cannot be determined. Additionally, the review noted that there is limited economic evidence regarding the use of new technologies such as CTC, faecal DNA (fDNA), multi-target-stool DNA test (MT-sDNA), plasma DNA (pDNA), and methylated septin 9 gene (mSEPT9) test for average-risk individuals screening. The review included 33 CEAs. Unlike earlier systematic reviews, the review emphasized that the studies have neither adequately reported the comparators assessed, including the screening modality and interval, nor provided reasons for their choice.

Zhong G-C, et al. 2019 [120] compared the cost-effectiveness of the FIT test versus colonoscopy in CRC screening. The review included 6 RCTs and 17 cost-effectiveness studies. The review concluded that annual or biennial FIT appears to be very cost-effective, or cost-saving compared with the 10-yearly colonoscopy. However, the review did not evaluate the cost-effectiveness based on the FIT positivity threshold and various start and stop ages.

2.1.6.1 Summary of review of previous systematic reviews on cost-effectiveness of Colorectal cancer screening strategies

We identified seven systematic reviews of model-based CEAs of CRC screening. One review particularly focused on the CEAs published in the US [116]. The reviews included the common screening modalities such as FIT, FOBT, colonoscopy, and sigmoidoscopy available at the time of the review except one which focused on the FIT and colonoscopy only [121]. Earlier reviews have not included the FIT test [114, 115]. The majority of these systematic reviews focused on summarizing the evidence on the CEA of CRC screening and concluded that CRC screening is cost-effective compared to no screening, but the optimal strategy cannot be determined. Two reviews claimed to critically appraise the methods used in the CEAs [119, 122]. Mendivil et al., 2019 [119] evaluated the reporting quality of the CEAs. Jeong et al., 2013 [122] highlighted the unresearched areas in CEAs of CRC screening such as the cost-effectiveness of different combinations or sequences of follow-up strategies for those with positive results in a primary test or identified adenomas.

2.1.7 Rationale

A targeted literature search has revealed that, to our knowledge, the majority of previously published systematic reviews of CRC screening among average-risk populations have not explored methodological aspects of CEAs included in the review. In particular, they have not examined the range of screening intervals included in an analysis for stool-based strategies. As noted above in Section 1.2.4, the choice of screening intervals has implications for identifying optimally cost-effective CRC prevention policies. CEA results may be inaccurate if they exclude relevant strategies. Specifically, in the case of identifying the optimal screening interval, the analyst should use the principle of including all feasible frequencies [113].

RCTs that have assessed annual and biennial screening intervals have found that the annual screening strategy is more effective in reducing CRC incidence and death [123]. However, many CEAs of stool-based tests have recommended biennial screening intervals for CRC screening [118, 119]. Therefore, it is important to consider whether these CEAs have assessed annual screening in their analysis [124]. If CEAs have concluded in favour of biennial CRC screening without including annual screening within their set of compared strategies, then their analyses are incomplete and the resulting policy recommendations are not reliable.

Model-based CEAs have been used in informing the planning and implementation of cancer screening programmes [125, 126]. Broad sets of cancer screening strategies need to be analysed in a CEA to help policymakers choose the optimal policy. Without such broad sets of strategy comparisons, analysts and policymakers cannot appreciate the extent to which a limited set of policy alternatives may fall short of the overall optimal policy. If presented with analyses featuring only a limited range of alternative strategies, it seems likely that policymakers may not readily recognise the implications of a narrow choice set and choose sub-optimal policies.

Given the potential for narrow sets of strategies for comparison to lead to suboptimal policies, there is a clear motivation to examine how well current CEAs of cancer screening inform policymakers regarding optimal policy choices. This need applies to the specific question of the

CEA evidence regarding optimal intervals for stool-based testing in the context of European CRC screening policies. RCTs of stool-based test conducted in European settings have only included a biennial screening interval [52-54, 56, 59, 60]. As RCTs can assess limited set of interventions, model-based studies have the potential to leverage the findings of real-world evidence and evaluate comprehensive set of strategies to well inform the policy makers. Thus, this study aims to assess the screening intervals analysed in the European CEAs and their implications for identifying optimal policy in the context of CRC screening strategies currently applied in European countries.

2.2 METHODOLOGY

Our review was conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines [127]. The protocol was registered on PROSPERO (CRD42021283988), an international register of prospective systematic reviews.

2.2.2 Search strategy

We conducted a systematic search of the PubMed, Web of Science, and Scopus databases on 9th September 2022. We also manually reviewed the reference lists of seven relevant systematic reviews on CEAs of CRC screening [114, 116, 118, 119, 121, 122, 128]. Characteristics of the European screening programmes were identified from recent academic publications and by contacting experts. The full search string is provided in Table 2-1, Table 2-2, and Table 2-3, respectively for Web of Science, Scopus, and PubMed databases. The string was developed with a series of categories for the search, including the studied disease (CRC), intervention (screening), study type (CEA), and study outcomes (cost per QALY or LY gained).

Table 2-1 PubMed search strategy

Search concept	Search string	
Colorectal	colon*	[tiab] OR
	rectal	[tiab] OR
	colorectal	[tiab]
Cancer	cancer*	[tiab] OR
	tumour*	[tiab] OR
	tumor*	[tiab] OR
	neoplasm*	[tiab] OR
	carcinoma*	[tiab] OR
	adenoma*	[tiab] OR
	polyp*	[tiab]
Screening	screen*	[tiab] OR
	faecal occult blood	[tiab] OR
	fecal occult blood	[tiab] OR
	*FOBT	[tiab] OR
	faecal immunochemical test	[tiab] OR
	fecal immunochemical test	[tiab] OR
	FIT	[tiab]
Cost-effectiveness filter	cost-effect*	[tiab] OR
	CEA	[tiab] OR
	cost-utility	[tiab] OR
	CUA	[tiab] OR
	health technology assessment	[tiab] OR
	HTA	[tiab] OR
	health economics	[tiab] OR
	cost	[tiab] OR
	cost-benef*	[tiab] OR
	cost anal*	[tiab]
Cost-effectiveness outcomes	quality-adjusted	[tiab] OR
	QALY*	[tiab] OR
	disability-adjusted	[tiab] OR
	DALY*	[tiab] OR
	LYG	[tiab] OR
	life-year*	[tiab] OR
	life expectancy	[tiab]
1 and 2 and 3 and 4 and 5		
Limit to English language and original articles		

Table 2-2 SCOPUS search strategy

Search concept	Search string	
Colorectal	TITLE-ABS(	
	colon*	OR
	rectal	OR
	colorectal)	
Cancer	TITLE-ABS(	
	cancer*	OR
	tumour*	OR
	tumor*	OR
	neoplasm*	OR
	carcinoma*	OR
	adenoma*	OR
	polyp*)	
Screening	TITLE-ABS (	
	screen*	OR
	"faecal occult blood"	OR
	"fecal occult blood"	OR
	*FOBT	OR
	"faecal immunochemical test"	OR
	"fecal immunochemical test"	OR
	FIT)	
Cost-effectiveness filter	TITLE-ABS (	
	"cost effect*"	OR
	CEA	OR
	"cost utility"	OR
	CUA	OR
	"health technology assessment"	OR
	HTA	OR
	"health economics"	OR
	costs	OR
	"cost benef*"	OR
	"cost anal*")	
Cost-effectiveness outcomes	TITLE-ABS (	
	"quality adjusted"	OR
	QALY*	OR
	"disability adjusted"	OR
	DALY*	OR
	LYG	OR
	"life year*"	OR
	"life expectancy")	
1 and 2 and 3 and 4		
Limit to English language and original articles		

Table 2-3 Web of Science search strategy

Search concept	Search string	
Colorectal	TS=(	
	colon*	OR
	rectal	OR
	colorectal)	
Cancer	TS=(	
	cancer*	OR
	tumour*	OR
	tumor*	OR
	neoplasm*	OR
	carcinoma*	OR
	adenoma*	OR
	polyp*)	
Screening	TS=(	
	screen*	OR
	colonoscop*	OR
	faecal occult blood	OR
	fecal occult blood	OR
	*FOBT	OR
	faecal immunochemical test	OR
	fecal immunochemical test	OR
	FIT)	
Cost-effectiveness filter	TS=(	
	cost effect*	OR
	CEA	OR
	cost utility	OR
	CUA	OR
	health technology assessment	OR
	HTA	OR
	health economics	OR
	costs	OR
	cost benef*	OR
	cost anal*)	
Cost-effectiveness outcomes	TS=(	
	quality adjusted	OR
	QALY*	OR
	disability adjusted	OR
	DALY*	OR
	LYG	OR
	life-year*	OR
	life expectancy)	
1 and 2 and 3 and 4		
Limit to English language and original articles		

2.2.3 Eligibility criteria

We included peer-reviewed CEAs of CRC screening in average-risk populations in the 27 EU member states and the UK (henceforth collectively referred to as Europe). Average risk population includes asymptomatic population without prior diagnosis of CRC, adenomatous polyps, or inflammatory bowel disease; no personal diagnosis or family history of known genetic disorders that predispose them to a high lifetime risk of CRC such as hereditary nonpolyposis CRC (HNPCC or Lynch syndrome) and familial adenomatous polyposis (FAP) [129]. The inclusion criteria were (i) model-based CEA simulations of CRC screening using stool-based tests; (ii) conducted in average-risk populations; (iii) set in Europe. The exclusion criteria were studies: (i) of stool-based tests other than FIT or FOBT such as stool DNA testing; (ii) that did not report quality-adjusted life-years (QALYs) or life-years gained (LYG) or equivalents such as life-years saved; (iii) that did not report costs; (iv) not of a screening intervention; (v) not written in English; and (vii) reviews, conference abstracts, editorials and notes.

2.2.4 Study selection

The titles and abstracts of studies from the database searches and other sources were recorded in Microsoft Excel (version 2108) and duplicates were removed. Records were independently screened by two reviewers (RP and YL). A third reviewer (JOM) was consulted in case of a disagreement. Full text of studies that met the inclusion criteria were exported to the Mendeley reference management software (version 2.57) and examined in full. RP, YL, EM and JOM assessed the studies based on the quality assessment checklist described below.

2.2.5 Data extraction

For each individual study included in the study, two reviewers (RP and YL) individually extracted the study publication year, authors, country setting, details of the simulated strategies such as screening start and stop ages, intervals between screens, test modality, costs, estimated QALYs or LYG, reported incremental cost-effectiveness ratio (ICER) and cost-effectiveness threshold (if stated). As not all studies report a threshold, we used the threshold reported in other studies from

the same setting as a proxy. Where there were multiple studies from the same setting that reported different thresholds, we used the highest as the proxy threshold. We interpret the optimally cost-effective strategy in the conventional way as being the most effective strategy with an ICER within the cost-effectiveness threshold. A third reviewer (JOM) checked a random 20% of the extracts for verification.

2.2.6 Assessment of quality of studies

A quality assessment checklist was developed based on Drummond's 10-item checklist [17], with adjustments corresponding to our study aims. We omitted certain sub-questions within the checklist that were not applicable to our study. The adjusted checklist is presented in Table 2-4. The adjusted Drummond checklist was used to assess the quality of the reviewed studies. We use the same 10 topic areas as the original Drummond checklist but omitted 9 of the 33 specific sub-questions as they did not apply to the studies considered here. Each study was graded on the 10 topic areas, with a 1 and 0.5 being awarded where the study fully or partially satisfied the checklist questions respectively and 0 where the questions were not satisfied. Grades were totalled to generate a summary score.

Table 2-4 Critical appraisal checklist for economic evaluations (Adapted from Drummond et al [100])

Checklist
1. Was a well-defined question posed in answerable form? 1.1 Did the study examine both costs and effects of the service(s) or programme(s) over an appropriate time horizon? 1.2 Did the study involve a comparison of alternatives? 1.3 Was a perspective for the analysis stated and was the study placed in any particular decision-making context? 1.4 Were the patient population and any relevant subgroups adequately defined?
2. Was a comprehensive description of the competing alternatives given (i.e. can you tell who did what to whom, where, and how often)? 2.1 Were any relevant alternatives omitted? 2.2 Was (should) a 'do nothing' alternative (be) considered?
3. Was the effectiveness of the programme or services established? 3.1 Was this done through a randomized controlled clinical trial? If so, did the trial protocol reflect what would happen in regular practice? 3.2 Were effectiveness data collected and summarized through a systematic overview of clinical studies? If so, were the search strategy and rules for inclusion or exclusion outlined? 3.3 Were observational data or assumptions used to establish effectiveness? If so, were any potential biases recognized?
4. Were all the important and relevant costs and consequences for each alternative identified?

	4.2 Did it cover all relevant perspectives? (Possible perspectives include those of patients and third-party payers; other perspectives may also be relevant depending on the particular analysis.)
5.	Were costs and consequences measured accurately in appropriate physical units (e.g. hours of nursing time, number of physician visits, lost work-days, gained life years)? 5.1 Were the sources of resource utilization described and justified? 5.2 Were any of the identified items omitted from measurement? If so, does this mean that they carried no weight in the subsequent analysis?
6.	Were the cost and consequences valued credibly? 6.1 Were the sources of all values clearly identified? (Possible sources include market values, patient or client preferences and views, policymakers' views, and health professionals' judgements.) 6.4 Was the valuation of consequences appropriate for the question posed (i.e. has the appropriate type or types of analysis—cost-effectiveness, cost–benefit—been selected)?
7.	Were costs and consequences adjusted for differential timing? 7.1 Were costs and consequences that occur in the future 'discounted' to their present values? 7.2 Was any justification given for the discount rate(s) used?

8. Was an incremental analysis of costs and consequences of alternatives performed? 8.1 Were the additional (incremental) costs generated by one alternative over another compared to the additional effects, benefits, or utilities generated?
9. Was allowance made for uncertainty in the estimates of costs and consequences? 9.2 If a sensitivity analysis was employed, was justification provided for the form(s) of sensitivity analysis employed and the ranges or distributions of values (for key study parameters)? 9.3 Were the conclusions of the study sensitive to the uncertainty in the results, as quantified by the statistical and/or sensitivity analysis?
10. Did the presentation and discussion of study results include all issues of concern to users? 10.1 Were the conclusions of the analysis based on some overall index or ratio of costs to consequences (e.g. cost-effectiveness ratio)? If so, was the index interpreted intelligently or in a mechanistic fashion? 10.2 Were the results compared with those of others who have investigated the same question? If so, were allowances made for potential differences in study methodology? 10.4 Did the study allude to, or take account of, other important factors in the choice or decision under consideration (e.g. distribution of costs and consequences, or relevant ethical issues)? 10.5 Did the study discuss issues of implementation, such as the feasibility of adopting the 'preferred' programme given existing financial or other constraints, and whether any freed resources could be redeployed to other worthwhile programmes?

10.6 Were the implications of uncertainty for decision-making, including the need for future research, explored?

Sub-questions from the original Drummond checklist that were omitted in our application are as follows:

2.3 Were relevant alternatives identified for the patient subgroups?

4.1 Was the range wide enough for the research question at hand?

4.3 Were capital costs, as well as operating costs, included?

5.3 Were there any special circumstances (e.g. joint use of resources) that made measurement difficult? Were these circumstances handled appropriately?

6.2 Were market values employed for changes involving resources gained or depleted?

6.3 Where market values were absent (e.g. volunteer labour), or market values did not reflect actual values (e.g. clinic space donated at a reduced rate), were adjustments made to approximate market values?

9.1 If patient-level data on costs or consequences were available, were appropriate statistical analyses performed?

9.4 Was heterogeneity in the patient population recognized, for example by presenting study results for relevant subgroups?

10.3 Did the study discuss the generalizability of the results to other settings and patient/client groups?

2.3 RESULTS

Our search identified 984 studies yielding 430 unique studies after removing duplicates. Following title and abstract screening 382 studies were excluded. We assessed the full texts of the remaining 56 studies and 7 additional studies identified from manual reference checking. A total of 39 studies were ultimately included [125, 130-167]. A PRISMA flow diagram is presented in Figure 2-2.

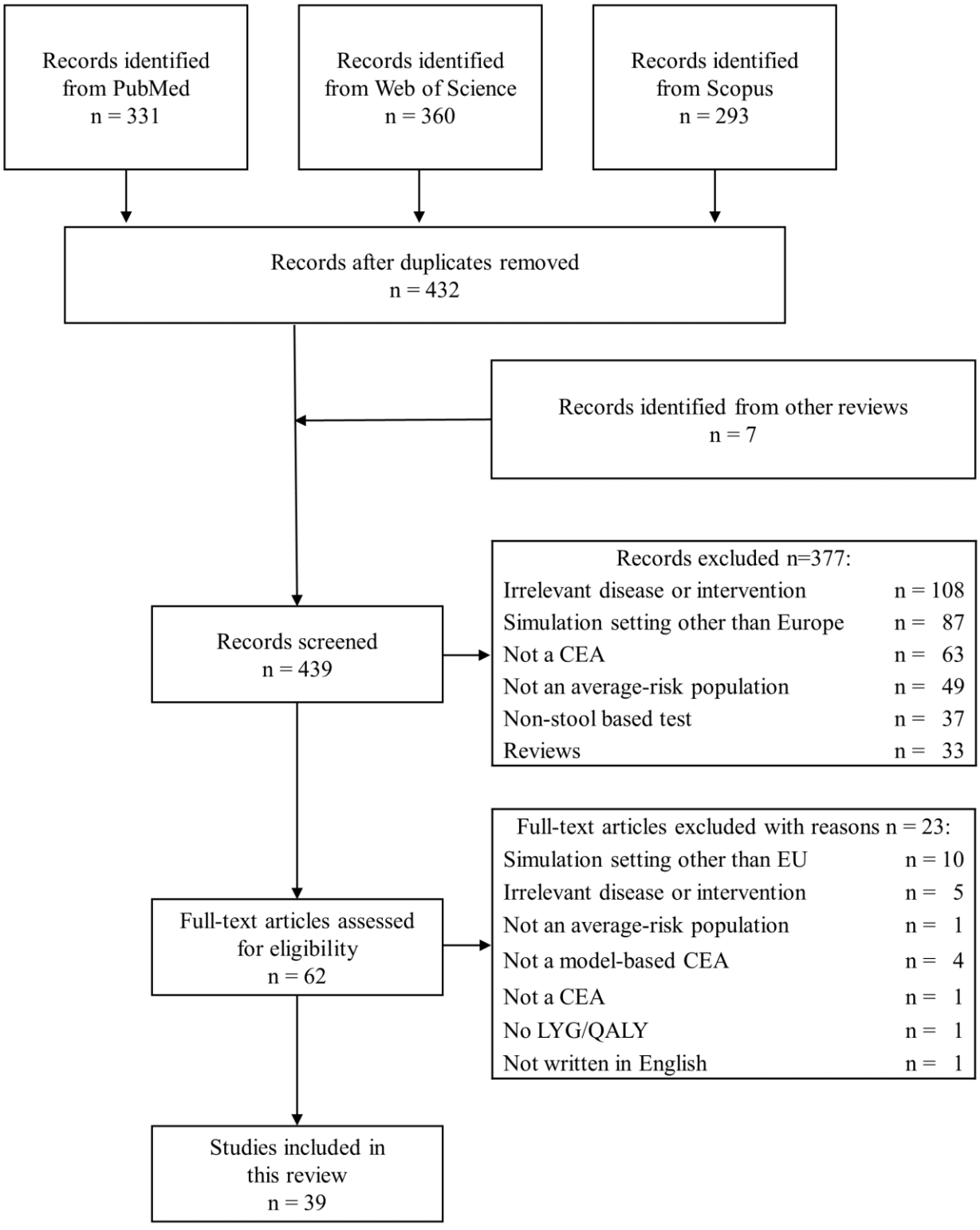


Figure 2- 2. PRISMA flow diagram. CEA – cost effectiveness analysis, EU – European Union, LYG – Life Years Gained, QALY – Quality Adjusted Life Years

2.3.1 Characteristics of Cost Effectiveness Analyses conducted in Europe

As detailed in Table 2-5, CEAs of stool-based tests were simulated in 14 different countries; France, the Netherlands, and the UK were the most frequent source countries with 9, 7 and 7 studies respectively. Slovakia is the only country within the sample from Central and Eastern Europe as defined by the Organisation of Economic Cooperation and Development [168]. Most studies (n=33, 85%) were conducted after 2010. Of the 39 studies, 37 studies (95%) were published after the European Council's 2003 recommendations. Of the 39 studies, 11 had narrow analysis objectives while the remaining 28 corresponded to the broad CEA objective of seeking optimally cost-effective strategies (Appendix 7). Of those studies that had narrow objective, 7 focused on screening tests alone or in combination with age range and cut-offs [134, 137, 150-152, 157, 158] 2 focused on assessing specific policies [138, 146], 1 on a change to the screening interval [131] and 1 on changes to the age range and cut-off [160].

Of the 39 CEAs, 22 (56%) exclusively analysed stool-based tests while 17 (44%) also assessed image-based primary screening modalities. Of those that exclusively simulated stool-based tests, 12 assessed FIT only, three assessed FOBT only and six assessed both FIT and FOBT, and one assessed a biomarker test. Nearly all studies assessed strategies in which recipients receive the same modality over the entire screening programme. One exception was set in Germany, in which younger screening eligible population start with stool-based testing but later switch to image-based testing [148].

While most studies included some variation of screening strategies regarding the screening age range, interval or FIT cut-off, the level of variation was limited. There were 25 (64%) studies that only simulated five strategies or fewer. Nine out of those 25 studies were from the set with narrow objectives.

Figure 3-2 illustrates the screening intervals considered by the reviewed studies. Regarding the screening interval, 14 studies (36%) examined more than one screening interval. Biennial screening was the most frequently simulated interval which was assessed in 37 (95%) studies of which 23 (59%) considered no other interval, assessing only biennial screening. The 11 studies

addressing narrow objective are shown with grey markers in Figure 3-2, eight of which only considered biennial screening. Whilst annual screening was assessed in only 13 (33%) studies, the majority of these (n=12) also considered other intervals.

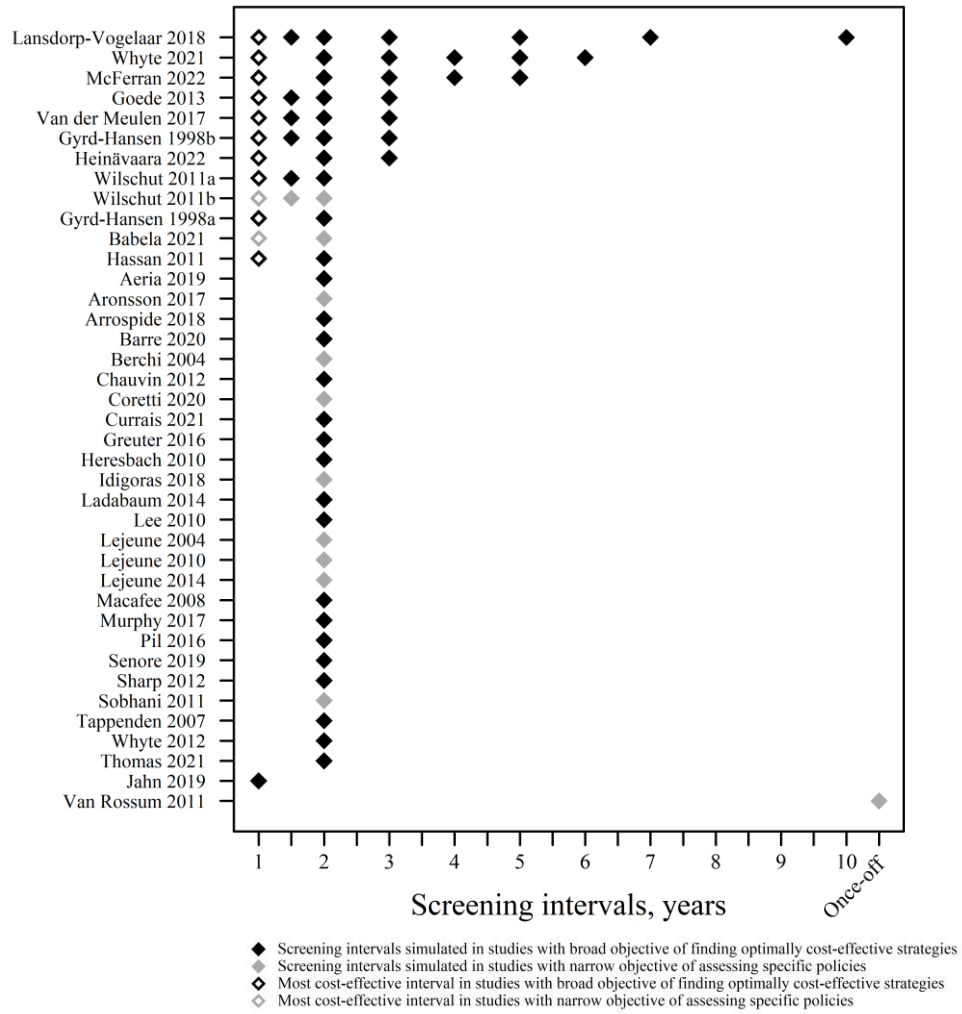


Figure 2- 3. Screening interval simulated in studies

Figure 2-3 uses a white diamond to highlight the intervals found to be optimally cost-effective in those studies which considered multiple intervals. All 13 studies that assessed annual screening intervals found it to be optimally cost-effective. That is, annual screening was the most effective strategy with an ICER within the CEA threshold in all cases. Naturally, that annual screening was always found to be optimally cost-effective does not imply that all strategies featuring annual screening are cost-effective. Four studies that varied the screening age range and FIT cut-offs found some strategies featuring annual screening with ICERs above the threshold [140, 142, 164,

169]. Regarding the age ranges simulated, there was wide variation in the ranges examined by the studies as depicted in Figure 2-4. Of the 39 studies, 27 (69%) did not consider alternative age ranges. The 11 studies with narrow objectives are depicted with the white hatching, 9 of which only considered a single age range. Ages 50-74 years was the most commonly analysed range, which was assessed in 11 (28%) studies followed by 50-75 years used in 9 (23%). Only seven (18%) included start ages below 50 years and 12 (31%) analysed stop ages above 75 years. Figure 3 uses white diamonds to indicate the start and stop age of those age ranges found to be optimal within those studies that did consider alternative age ranges. All such studies found starting and stopping between 45-50 years and 74-80 years respectively to be optimal. In the sensitivity analysis using the lowest CEA threshold where more than one is available, we found a policy change in one study. In the study, the start age of 50 years was found optimal instead of 45 years [140].

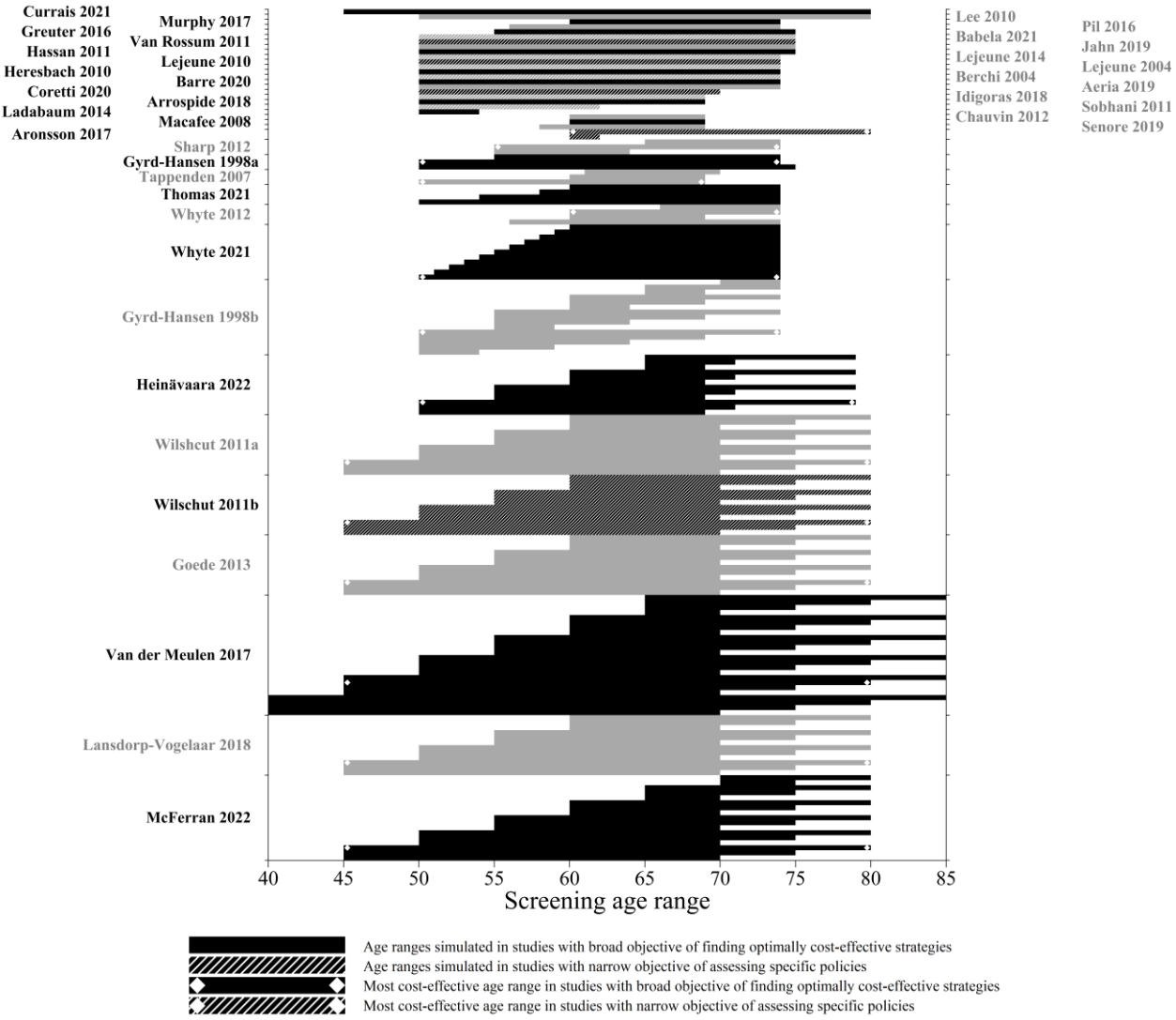


Figure 2- 4. Screening age range simulated in studies

The FIT cut-off was reported in 26 of the 34 studies (77%) examining FIT-based strategies. Figure 2-5 presents the FIT cut-offs considered. The most common cut-offs used were 20 and 10 µg Hb/g of faeces with 18 and 10 studies respectively (53% and 29%). Multiple cut-offs were examined in 11 (28%) studies. Of these, nine found lower cut-offs dominated, the exceptions being studies from the UK and France [132, 152]. There were eight studies with narrow objectives with FIT cut-offs to report. These are shown in Figure 4 with the grey markers. Of these eight, five considered one cut-off alone.

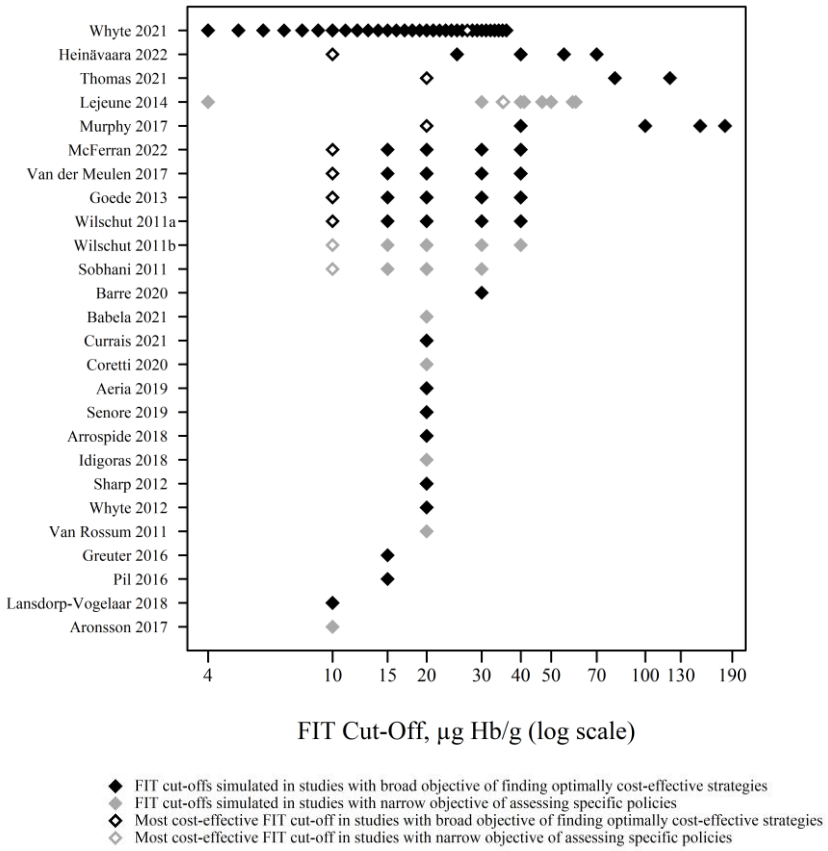


Figure 2- 5. FIT cut offs analysed in studies

2.3.2 Endoscopy capacity constraints

The potential for endoscopy capacity to constrain the feasibility of screening strategies has been recognised by several studies. Colonoscopy capacity is mentioned as an important consideration by 20 studies (48%) [125, 132, 134, 135, 138, 140, 146, 149, 152, 154, 159-166, 169, 170]. Of these, four studies actively considered strategies under capacity constraints within their analyses [132, 160, 162, 169]. Those studies found annual screening was not optimally cost-effective in constrained analyses but was optimal in analyses without capacity constraints.

2.3.3 European Colorectal cancer screening provision

Table 2-6 summarises aspects of CRC screening in the European nations considered. Population-based screening is implemented in 22 of 28 European countries at national and regional levels [125, 131, 133, 136, 138, 146, 171-186]. Cyprus and Estonia have pilot programmes [175]. The countries without population-based programmes are Romania, Bulgaria, Greece, Latvia [175].

Most countries use stool-based primary testing except Poland [175] and the Austrian region of Vorarlberg [176] which both use primary colonoscopy (Table 2-6). All countries using stool-based testing employ FIT except Croatia [175], where FOBT test is used. Colonoscopy is used as triage in all countries with stool-based primary testing

Among the 26 countries with stool-based screening including pilot programmes, 23 screen biennially. The three exceptions are Austria region of Burgenland [176], which screens annually, and Germany [178] and the Czech Republic [184], which reduce screening frequency with age. Germany screens annually between ages 50-54 years and then switches to biennial screening. Similarly, the Czech programme screens annually between 50-54 years and participants are then offered biennial FIT or 10-yearly colonoscopy.

Screening start and stop ages also vary. Vorarlberg (in Austria) [176] starts at 40 years; 14 countries start at 50 years and seven programmes start at 60 years. Estonia [175], Finland [183], Ireland [125], Spain [146] and Sweden [182] had the narrowest population age range covered of 60-69 years. Sex-specific start ages apply in Germany [178] at 50 years and 55 years for males and females respectively.

There is considerable variation in the FIT cut-off used across the EU. All countries use defined FIT thresholds except Malta [175], which uses a range of 16-20 µg Hb/g. Germany [178] and Lithuania [180] use different cut-offs depending on the test manufacturer [178, 180]. Programmes using higher cut-offs are Ireland [125] and the Netherlands [179] with 45 and 47 µg Hb/g respectively and the constituent countries of the UK [171-173, 181, 187], where 80-150 µg Hb/g is used. Programmes using lower cut-offs are Germany and Lithuania. The most common cut-off is 20 µg Hb/g which is used in six programmes. Sex-specific cut-offs are used in Finland [183] and Sweden [182].

2.3.4 Comparison of policy to Cost-effectiveness Analysis evidence

The most apparent overall observation when comparing the CEA estimates with European screening policies is that although studies that compared annual and biennial clearly indicate

annual screening is optimally cost-effective when using FIT many screening programmes use biennial screening in practice, which is both less effective and less cost-effective. Studies indicating the superiority of annual screening have been published in the setting of the Netherlands [149, 160, 161, 164], France [144], Denmark [142, 143] and Austria [147]. In practice, while Burgenland (Austria) uses annual screening, it has done so since 2002, long before the Austrian CEA was published [147]. In the Netherlands, several CEAs were conducted prior to the implementation of organised screening in 2014 [140, 160, 161, 164]. All of those that assessed annual screening found it cost-effective, yet the programme has employed biennial screening since its introduction, likely reflecting colonoscopy capacity constraints. Similarly, in France, while eight of nine CEAs only considered biennial screening [133, 136, 137, 139, 145, 150-152] one study did include annual screening and found it to be cost-effective [144]. Despite this, France has used biennial screening since 2002.

Regarding screening age ranges, CEA estimates suggest start ages of 50 years or lower to be optimal. In practice, 19 of 33 programmes feature screening start ages of 50 years or below [133, 136, 138, 173-178, 180, 185, 186] (Table 2-6). Six programmes use a screening start age of 60 years despite no CEA evidence which indicates it to be optimal [125, 146, 172, 175, 181-183, 187]. Ten programmes are using a stop age of 70 years or below [125, 133, 138, 146, 174, 175, 182, 183, 188] contrary to the CEA evidence of a stop age between 74 to 80 years being optimal.

Regarding the FIT cut-off, while most simulation estimates indicate 10 µg Hb/g to be optimal (Table 2-5) only Burgenland [176] uses such a low threshold. Germany [178] and Lithuania [180] both feature cut-offs as low as 4 µg Hb/g, but not on a programme-wide basis as there is variation in the cut-offs used within these systems. All Dutch CEA [149, 160, 161, 164, 180] estimates report 20 µg Hb/g or lower to be optimal, but the Dutch programme [179] uses a higher cut-off of 47 µg Hb/g.

2.3.5 Quality appraisal of the studies included in the review

The quality appraisal checklist findings are reported in Appendix 8. Of the 39 studies, two achieved positive answers to all ten checklist questions, and the remaining studies recorded 7.5/10

or higher overall. Principal areas of weakness were the comprehensive description of the competing alternatives and presentation and the description of the study results. Studies performed well on the remaining items.

Table 2- 5 Characteristics of CEAs conducted in Europe

Authors, Year of Publication n= 39	**Simulation setting**	**Stool-based tests included**	**Screening interval (years)**	**FIT cut-off (µg Hb/g)**	**Screening start and stop ages (years)**	**Number of stool-based strategies**	**CEA Cost-effectiveness threshold reported (/QALY)**	**Optimally cost-effective stool-based strategy (Test name, interval, FIT cut-off, age range)**
Areia et al, 2019 [170]	Portugal	FIT	2	20	50-74	2	€39,760	FIT, biennial, 20, 50-74
Aronsson et al, 2017 [134]	Sweden	FIT	2, twice in lifetime	10	60-62/80	2	€10,000	FIT, biennial, 60-80
Arrospide et al, 2018 [135]	Spain	FIT	2	20	50-69	1	€30,000* [58]	FIT, biennial, 20, 50-69
Babela et al, 2021 [131]	Slovakia	FIT	1,2	20	50-75	2	$50,000	FIT, annual, 20, 50-75
Barre et al, 2020 [136]	France	FIT	2	30	50-74	3	€40,000	FIT, biennial, 30, 50-74
Berchi et al, 2004 [137]	France	FIT, FOBT	2	NR	50-74	4	€50,000* [46]	FIT, biennial, NG, 50-74
Chauvin et al, 2012 [139]	France	FIT, FOBT	2	Not given	50-80	2	€50,000* [46]	FIT, biennial
Coretti et al, 2020 [138]	Italy	FIT	2	20	50-70	1	€30,000	FIT, biennial, NG, 50-70
Currais et al, 2021 [133]	Portugal	FIT	2	20	45 onwards	1	€39,760	None

Authors, Year of Publication n= 39	Simulation setting	Stool-based tests included	Screening interval (years)	FIT cut-off (µg Hb/g)	Screening start and stop ages (years)	Number of stool-based strategies	CEA Cost-effectiveness threshold reported (/QALY)	Optimally cost-effective stool-based strategy (Test name, interval, FIT cut-off, age range)
Goede et al, 2013 [140]	The Netherlands	FIT	1, 1.5, 2 ,3	10,15,20, 30,40	45/ 50/ 55/ 60 -70/75/80	960	€50,000* [37]	FIT, annual, 10, 45-80
Greuter et al, 2016 [141]	The Netherlands	FIT	2	15	55-75	1	€50,000* [37]	FIT, biennial, 15, 55-75
Gyrd Hansen et al, 1998a [143]	Denmark	FIT, FOBT	2,1	Not given	50/55-74	5	DKK 88,000* [59]	FOBT, annual, NA, 50-74
Gyrd Hansen et al, 1998b [142]	Denmark	FOBT	3,2,1.5,1	NA	50/55/60/65/ 70- 54/59/64/69/ 74	60	DKK 88,000* [59]	FOBT, annual, NA, 50-74
Hassan et al, 2011 [144]	France	FIT, FOBT	1, 2	Not given	50-75	4	$50,000	FIT, annual, NG, 50-75
Heinävaara et al, 2022 [166]	Finland	FIT	1,2,3	10,25,40, 55,70	50/55/60/65-69/71/79	362	€10,000	FIT, annual, 25,50-79 (m),10, 55-69 (w)
Heresbach et al, 2010 [145]	France	FIT, FOBT	2	Not given	50-74	2	€10,000 & 20,000	FIT, biennial, NG, 50-74
Idigoras et al, 2018 [146]	Spain	FIT	2	20	50-69	1	€30,000* [58]	FIT, biennial,20, 50-69
Jahn et al, 2019 [147]	Austria	FIT, FOBT	1	Not given	50-75	2	€15,000	FIT, annual, NG, 50-75

Authors, Year of Publication n= 39	Simulation setting	Stool-based tests included	Screening interval (years)	FIT cut-off (µg Hb/g)	Screening start and stop ages (years)	Number of stool-based strategies	CEA Cost-effectiveness threshold reported (/QALY)	Optimally cost-effective stool-based strategy (Test name, interval, FIT cut-off, age range)
Ladabaum et al, 2014 [148]	Germany	FIT, FOBT	1, 2	Not given	50-54, once at 50 and 60	5	€25,000 & 50,000	FIT, annual (50-54) followed by biennial up to 75
Lansdorp-Vogelaar et al, 2018 [149]	The Netherlands	FIT	1,1.5,2,3,5,7, 10	10	40/50/55/60-70/75/80	84	€50,000	FIT, annual, 10, 45-80
Lee et al, 2010 [167]	The UK	FOBT	2	NA	60-69	1	£30 000	†
Lejeune et al, 2004 [150]	France	FOBT	2	NA	50-74	2	$20,000	FOBT, biennial, NA, 50-74
Lejeune et al, 2010 [151]	France	FIT, FOBT	2	Not given	50-74	2	£20,000	FIT, biennial, NG, 50-74
Lejeune et al, 2014 [152]	France	FIT, FOBT	2	4,30,35,35.2,40,41,46.8,50,58.6,60,70.4	50-74	15	£20,000–30,000	FIT (2 samples), biennial, 35.2, 50-74
Macafee et al, 2008 [153]	The UK	FOBT	2	NA	60-69	1	£20,000* [18]	FOBT, biennial, NA, 60-69
McFerran et al, 2022 [189]	Ireland	FIT	1,2,3,4,5	10,15,20,30,40	45/50/55/60/65/70-70/75/80	525	€20,000	FIT, annual, 10, 50-80

Authors, Year of Publication n= 39	Simulation setting	Stool-based tests included	Screening interval (years)	FIT cut-off (µg Hb/g)	Screening start and stop ages (years)	Number of stool-based strategies	CEA Cost-effectiveness threshold reported (/QALY)	Optimally cost-effective stool-based strategy (Test name, interval, FIT cut-off, age range)
Murphy et al, 2017 [154]	The UK	FIT, FOBT	2	20, 40, 100, 150, 180	60-74	6	£20,000	FIT, biennial, 20, 60-74
Pil et al, 2016 [155]	Belgium	FIT	2	15	56-74	4	€35,000	FIT, biennial, NG, 55-74
Senore et al, 2019 [156]	Italy	FIT	2	20	58-69	1	$50,000	FS at age 58 +biennial FIT for all non-attendees to FS
Sharp et al, 2012 [125]	Ireland	FIT, FOBT	2	20	55/65-64/74	6	€45,000	FIT, biennial, 20, 55-74
Sobhani et al, 2011 [157]	France	FIT, FOBT	2	10,15,20, 30	50-62	2	£30,000	FIT (3 sample), biennial, 10, 50-62
Tappenden et al, 2007 [165]	The UK	FOBT	2	NA	50/60/61-69/70/74	5	£20,000* [18]	FS age 60, FOBT, biennial, NA, 61-70
Thomas et al, 2021 [162]	The UK	FIT	2	20,80,120	50/54/58/60-74	25	£20,000	FIT, biennial, 120, 56(m)/60(w)-74
Van der Meulen et al, 2017 [164]	The Netherlands	FIT	1,1.5,2,3	10,15,20, 30,40	40/45/50/55/60/65-70/75/80/85	480	€20,000	FIT, annual, 10, 45-80
Van Rossum et al, 2011 [158]	The Netherlands	FIT, FOBT	Once in lifetime	20	50-75	2	€25,000-100,000	FIT, once in a lifetime, 20, 50-75

Authors, Year of Publication n= 39	Simulation setting	Stool-based tests included	Screening interval (years)	FIT cut-off (µg Hb/g)	Screening start and stop ages (years)	Number of stool-based strategies	CEA Cost-effectiveness threshold reported (/QALY)	Optimally cost-effective stool-based strategy (Test name, interval, FIT cut-off, age range)
Whyte et al, 2012 [159]	The UK	FIT, FOBT	2	20	56/60/66-69/74	9	£20,000	FS age 55, FIT, biennial, 20, 56–74
Whyte et al, 2022 [132]	The UK	FIT	1,2,3,4,5,6	4-36	50/51/52/53/54/55/56/57/58/59/60-74	60,221	£20,000	FIT, annual, 27-32.8, 50/51-71/74
Wilschut et al, 2011a [161]	The Netherlands	FIT	1,1.5,2	10,15,20,30,40	45/50/55/60-70/75/80	48	€20,000	FIT, annual, 10, 45-80
Wilschut et al, 2011b [160]	The Netherlands	FIT, FOBT	1,1.5,2	10,15,20,30,40	45/50/55/60-70/75/80	48	€50,000* [37]	FIT, annual, 10, 45-80

FIT- Fecal Immunochemical Test, FOBT- Fecal Occult Blood Test, FS-Flexible Sigmoidoscopy, CTC- Computed Tomography Colonoscopy QALY- Quality Adjusted Life Years, *- CEA threshold cited in other literature from the same country, NA-Not Applicable, NG- Not Given, µg Hb/g- Microgram haemoglobin per gram, DKK-Danish krone, †-Insufficient information to define the optimally cost-effective stool-based strategy

Table 2- 6 European CRC screening programmes characteristics

Country	Screening programme type	Start year	Primary test	Screening interval (years)	FIT cut off (µg Hb/g)	Screening start & stop age (years)	Triage test	References
Austria Burgenland	Organised	2003	FIT	1	10	40-80	Colonoscopy	[176]
Austria Vorarlberg	Organised	2007	Colonoscopy	10	NA	50+		[176]
Belgium Flanders	Organised	2013	FIT	2	15	50-74	Colonoscopy	[186]
Belgium Wallonia	Organised	2009	FIT	2	15	50-74	Colonoscopy	[177]
Bulgaria	Opportunistic	NA	NA	NA	NA	NA	NA	[175]
Croatia	Organised	2007	FOBT	2	NA	50-74	Colonoscopy	[175]
Cyprus (pilot/planned)	Organised	2013	FIT	2	Not given	50-69		[175]
Czech Republic	Organised	2000	FIT TC	1 or 2*	15	50+	Colonoscopy	[184]
Denmark	Organised	2014	FIT	2	20	50-74	Colonoscopy	[175]
Estonia (pilot/planned)	Organised	2016	FIT	2	Not given	60-69		[175]
Finland	Organised	2009	FIT	2	25 (females), 70 (males)	60-69	Colonoscopy	[183]
France	Organised	2009	FIT	2	30 µg/ml	50-74	Colonoscopy	[136]
Germany	Organised	1971	FIT/TC	1 or 2*	4,6,8,10,15,17,25 µg/ml	50 (males), 55 (females)	Colonoscopy	[178]
Greece	Opportunistic	NA	NA	NA	NA	NA	NA	[175]
Hungary	Organised	2018	FIT	2	20	50-70	Colonoscopy	[174]

Ireland	Organised	2012	FIT	2	45	60-69	Colonoscopy	[125]
Italy	Organised	1982	FIT/FS	2	20	50-69	Colonoscopy	[138]
Latvia	Opportunistic	NA	NA	NA	NA	NA	NA	[175]
Lithuania	Organised	2014	FIT	2	6/40 µg Hb/g or 20 µg Hb/ml	50-74	Colonoscopy	[180]
Luxembourg	Organised	2016	FIT TC	2	Not given	55-74	Colonoscopy	[175]
Malta	Organised	2013	FIT	2	16-20	55-66	Colonoscopy	[175]
The Netherlands	Organised	2014	FIT	2	47	55-75	Colonoscopy	[179]
Poland	Organised	2012	Colonoscopy	Once in a lifetime	n/a	55-64		[175]
Portugal	Organised	2009	FIT	2	20	50-70		[133, 175]
Romania	NA	NA	FIT	2	NG	NA	NA	[175]
Slovakia	Organised	2019	NA	NA	NA	NA	NA	[131]
Slovenia	Organised	2009	FIT	2	20	50-74	Colonoscopy	[185]
Spain Basque	Organised	2008	FIT	2	20	60-69	Colonoscopy	[146]
Sweden (Stockholm/Gotland County)	Organised	2008	FIT	2	40 (females), 80 (males)	60-69	Colonoscopy	[182]
UK-England	Organised	2006	FIT	2	120	60-74	Colonoscopy	[181, 187]
UK-Wales	Organised	2007	FIT	2	150	55-74	Colonoscopy	[171]
UK-Scotland	Organised	2008	FIT	2	80	50-74	Colonoscopy	[173]

UK-Northern Ireland	Organised	2010	FIT	2	150	60-74	Colonoscopy	[172]

*50-54-annual, 55- biennial, FIT- Faecal Immunochemical Test, FOBT- Faecal Occult Blood Test, FS-Flexible Sigmoidoscopy, TC- Total Colonoscopy, µg Hb/g- Microgram haemoglobin per gram, µg Hb/ml- Microgram haemoglobin per millilitre, NA – Not Available,

4.1 DISCUSSION

Our review assessed the screening intensities analysed by European CEAs of stool-based CRC screening and compared that with current screening policies in Europe. We found that nearly all CEAs examined biennial screening while only a minority considered annual screening. Every study that assessed both intervals found annual screening to be both more effective and cost-effective. Despite this, most European screening programmes currently use biennial screening. This indicates the widely adopted biennial screening interval in Europe is likely of sub-optimal intensity. That many studies omitted what appears to be the optimal screening interval from their analyses may have led policymakers across Europe to adopt an insufficiently intensive screening frequency.

Although in some cases the choice of only simulating biennial screening can be explained by a narrow study objective, this does not explain why CEA analysts have simply chosen to simulate biennial screening rather than consider broader options is unclear in all cases. The 2003 European Council recommendation to adopt colorectal screening did not specify a particular interval [190]. The three European randomised controlled trials (RCTs) of FOBT published at that time had all examined a biennial interval [191-193]. It is possible that health economists simply reflected the trialled intervals in their analyses. Despite this, a US trial completed in 1992 included both annual and biennial screening and found the former more efficacious [123]. Indeed, North American RCTs and CEAs assessing stool-based testing have mostly analysed annual screening [114, 116]. Furthermore, annual testing is typically recommended by North American guidelines when stool-based testing is employed [83]. Existing CEA methods guidance strongly encourages modellers to simulate as broad a range of strategies as possible in order to correctly identify optimally cost-effective strategies [8]. Indeed, it has long been recognised that considering a broad range of strategies is of particular relevance to CEAs of cancer screening [112]. Furthermore, one of the motivating rationales of simulation modelling is that it permits the comparison of additional strategies not assessed in trials [194]. Moreover, it is noteworthy that the two earliest studies

within our review by Gyrd-Hansen from 1998 examined a range of intervals including annual screening [142, 143]. In summary, the omission of annual screening by many studies [125, 134-139, 141, 146, 154, 170] is, despite relevant trial evidence, well-established methods guidelines and one early simulation study indicating annual screening is relevant for policy consideration.

Another possible explanation of why many modellers restricted their analysis to biennial screening could be tacit acceptance of colonoscopy constraints, not explicitly explored in their analyses. The Netherlands, UK, Finland and Ireland have faced colonoscopy capacity constraints and have been transparent in modifying aspects of screening provisions to operate within available capacity [125, 132, 140, 195]. It is possible that analysts only considered biennial intervals as they anticipated there would be insufficient endoscopy capacity for annual screening. We believe; however, it is good practice to simulate a broad range of strategies to correctly estimate the optimal strategy, with and without constraints. Such analyses have been published [132, 189], allowing modellers to demonstrate the shortcomings imposed by constraints and ensure policymakers are aware of the benefits of alleviating them. However, colonoscopy capacity is not the sole basis determining the policy decisions on CRC screening. Other factors such as budget impact, acceptability of a frequent screening strategy among the eligible population also play important roles in policy decisions.

The quality appraisal of the included CEAs revealed the scope for improvement in the description of strategies and the presentation and description of results. Given that a wide range of screening strategies are possible in CRC screening context, the studies should describe possible alternate strategies. The description of results should acknowledge the limit of the analysis if studies have analysed a limited number of strategies.

The primary focus of this review has been the optimal interval, motivated in part by recent findings quantifying the potential QALY gains from an increase in colonoscopy capacity that would facilitate an increase in screening frequency [189]. That study conducted in Irish setting estimated gains in QALYs of 167% compared to the current policy if colonoscopy capacity was expanded to permit intensifying the screening interval as well as broadening the age range and

lowering the FIT cut-off [189]. From the studies reviewed here it is quite clear that annual screening seems preferable. Analogous findings also apply regarding the screening age range and FIT cut-off, though the conclusions may be less definitive. CEAs that varied the screening age range generally find that broader age ranges are preferable. Similarly, many but not all studies that vary the FIT cut-off found lower cut-offs preferable. Accordingly, the conclusions regarding the need for strategy variation apply to age range and cut-off parameters also. The feasibility of optimising screening depends, in part, on available colonoscopy capacity. Moving from biennial to annual screening will increase colonoscopy demand, as will broadening the screening age range and reducing FIT cut-offs [140]. Our review shows that the simulation of restricted sets of policy alternatives is not merely a theoretical consideration but may have meaningful policy significance. That many studies have assessed an insufficient range of alternatives has resulted in incomplete cost-effectiveness evidence that may have misled decision-makers leading to inadvertently adopting sup-optimal policies and failing to highlight how long-term capacity expansion should be prioritised in healthcare planning. If health systems can increase screening capacity to offer annual screening and populations chose to participate at that frequency, then it seems that many CRC related deaths could be prevented across Europe.

Our conclusions are naturally subject to caveats. Whether the simulation of a broader range of strategies results in more effective CRC screening is naturally contingent on factors beyond the control of CEA modellers. Even if CEA modellers assess a comprehensive range of strategies, it not necessarily the case that policy maker will implement optimally cost-effective strategies. A full consideration of the limits of CEA evidence on policy is beyond the scope of this manuscript but there are several points to consider. Policy makers may have priorities other than cost-effectiveness and we should not presume that decision makers seek to optimise cost-effectiveness. As mentioned above, colonoscopy capacity constraints may prevent policy makers from expanding screening services in the short to medium run, as might budget constraints. Indeed, our review finds four Dutch studies have indicated that annual screening would be optimal in the

Netherlands [140, 149, 160, 161], yet only biennial screening is offered due to well-documented colonoscopy capacity constraints.

Even if policy makers do not or cannot offer the screening strategies that CEAs indicate to be optimal, we still believe it is important that CEAs simulate a broad range of strategies. The only way policy makers can appreciate the consequences of limiting the set of strategies under consideration or the impact of capacity constraints is with reference to simulation model estimates. Simulating a broad range of strategies may not always be feasible considering time and capacity constraints. In such situations, an iterative approach of finding the optimal strategy could be applied. In this approach, CEA analysts run a simulation with a manageable number of strategies selected from a broad range of relevant strategies. Based on the partial CEA results of the first simulation, the strategies likely to be cost-effective are identified by observing the CEA plane. The second simulation is rerun with expanded set of strategies. The process is continued until the strategies with characteristics of being a high chance to be cost-effective have been exhausted or other pragmatic considerations [196].

A further important caveat to our analysis is that the sample of studies from which there were CEAs to examine are drawn from Western Europe and thus predominately from wealthier European states. Moreover, the 13 studies within our sample that considered annual screening were from seven wealthy European countries (Austria, Denmark, France, Finland, Ireland and the Netherlands and the UK). Furthermore, all five Dutch studies employed the same model. It is open to question whether annual screening would remain cost-effective when assessed among less wealthy countries, including those in Central and Eastern Europe.

Our review differs from previous systematic reviews of CEAs on CRC screening as those studies did not focus on the methodological consideration of the adequacy of the range of strategies. We focused on a specific question of the CEA evidence regarding optimal intervals for stool-based testing in the context of European screening policies. Thus, our review is limited compared to prior reviews in terms of the screening modalities examined and the context of simulations [114, 116, 118, 119, 121, 122, 128].

Our findings are based on reviewing the outcomes of modelling studies. We appreciate the uncertainty of simulation analyses. There may be scope for further RCTs to reduce uncertainties regarding the benefits of intensified screening, especially as there has been only one RCT comparing the biennial and annual intervals [123]. The same applies regarding extending screening ages and lowering FIT cut-offs.

Limitations

Our study has several limitations. First, not all screening programmes clearly document screening strategy employed, especially the FIT cut-off used. Accordingly, we cannot be definitive about screening practices in all programmes. Second, we did not examine the model types or assumptions used in studies which might have played a role in the optimal strategy recommendations. Further we did not consider issues of transferability of the CEA evidence across settings, which could differ according to discount rates, perspectives and different thresholds. Despite possible differences all relevant studies consistently found annual screening to be more effective and cost-effective than biennial screening. It seems likely the results would still apply even if a more nuanced assessment of the evidence transferability was conducted. Third, we limited our analysis to stool-based based tests and did not consider image-based screening modalities or a combination of stool and image-based modalities. Fourth, we limited our analysis to papers written in English.

CHAPTER 3 DIRECT COST OF COLONOSCOPY: A MICRO-COSTING EXERCISE

3.1 INTRODUCTION:

With the advancements in medical knowledge and technology, the number and variety of treatment options in healthcare have rapidly been increasing. Consequently, healthcare budgets are increasingly under pressure and value-based policy and practice are preferred. Thus, cost estimates are needed for clinical and policy decision-making [197]. Economic evaluations provide a standard, well-accepted methodological approach for judging whether a health and medical service provides value [198]. In order to do so, economic evaluations need precise cost estimates of health technology.

3.1.1 Type of costing methodologies in healthcare

Costing methodology involves the identification, valuation, and measurement of resource costs. Broadly, the costing methodologies used in health care can be divided into two groups- 1) micro-costing, and 2) gross-costing. Based on the identification and valuation of resource use, they could further be divided as top-down and bottom-up approaches. Table 3-1 describes various types of costing methodologies.

Table 3- 1. Description of costing methodologies

	Level and type of data collected		
Level of identification of resource use items		Expenditure data collected at organisational level	Resource use data collected for each individual patient and then multiplied by unit cost to estimate the expenditure
	Highly detailed resource use items are identified	Top-down micro-costing	Bottom-up micro-costing
	Aggregate resource use items are identified	Top-down gross-costing	Bottom-up gross-costing

Source: Adapted from Špacírová et al, 2019 [199]

Micro-costing method

In micro-costing each component of resource use is identified at a detailed level and a unit cost is derived for each [100]. In top-down micro-costing, all relevant cost components are identified but valued for average patients by separating the relevant cost from comprehensive sources such as annual accounts. Whereas in bottom-up micro-costing cost components are valued by identifying resource use directly employed for a patient, resulting in patient-specific unit costs [200].

In economic evaluations, bottom-up micro-costing is generally considered to be the gold standard because it allows for the calculation of actual cost per individual patient or sub-population [100, 200]. Insight in patient subgroups is important because particular patient subgroups might have a great share in the total costs and ignoring this might mislead the total cost estimate. Bottom-up micro-costing allows statistical analyses for the detection of cost differences between patients in a single or combination of cost components as the cost incurred by individual patients is recorded. However, micro-costing is a time-consuming process and might not always be feasible to conduct because resource use and unit costs are often not available or inaccurately registered [200, 201]. Another limitation of the micro-costing studies is the difficulty of translating results in another context as these studies are typically conducted at a single centre or a few centres due to substantial resources and coordination required to collect detailed data [202].

The top-down micro-costing methodology is more feasible compared to the bottom-up micro-costing, the disadvantage of the approach is that it fails to trace costs directly to the specific patients who incur that cost. Therefore, statistical analyses of costs cannot be performed and differences between patients cannot be detected [203, 204]. Activity-based costing is a form of top-down micro-costing [199].

Gross-costing method

In the gross-costing method, cost components of health services or healthcare interventions are identified at a highly aggregated level. Gross-costing approaches usually rely on large, aggregated secondary data sources, as a result, it is inevitably based on the assumption that there is only a small variation between patients and/or providers. Generally, gross costing is more feasible

compared with micro-costing because it identifies only one (or few) cost component which is large relative to the healthcare service being analysed [198]. Bottom-up gross costing values the cost component for each individual patient. Top-down gross costing values the cost component per average patient by separating out costs from comprehensive sources and is therefore considered to be the least accurate costing methodology [199].

The advantages of gross-costing methods are that they are simple and transparent. The results could be externally valid. The costing is usually faster and cheaper than micro-costing. The main drawback of gross costing is that it may be less accurate. This is because it measures large resource units such as one hospital episode, inpatient hospital stays and fails to trace costs directly to specific cost components such as single procedure or activity performed during the hospital stay [205]. Gross-costing should be considered when the cost estimates are conducted for a short term or when the data is not available. However, gross-costing should always be interpreted with caution [200]. Figure 3-1 displays the level of accuracy in resource identification and valuation across different costing methodologies.

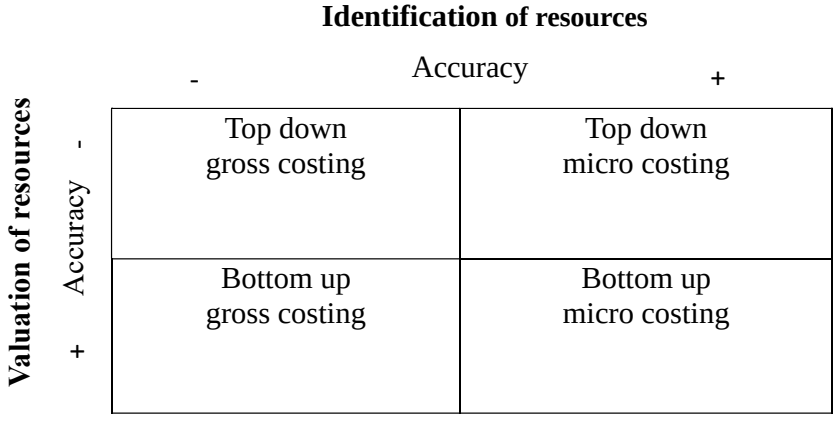


Figure 3-1. Level of accuracy in resource identification and valuation across different costing methodologies. Adapted from Drummond et al [100]

3.1.2 Steps involved in a micro-costing study

In general, there are 5 key steps in conducting a micro-costing study (Figure 3-2). Each of the steps are described in detail below.

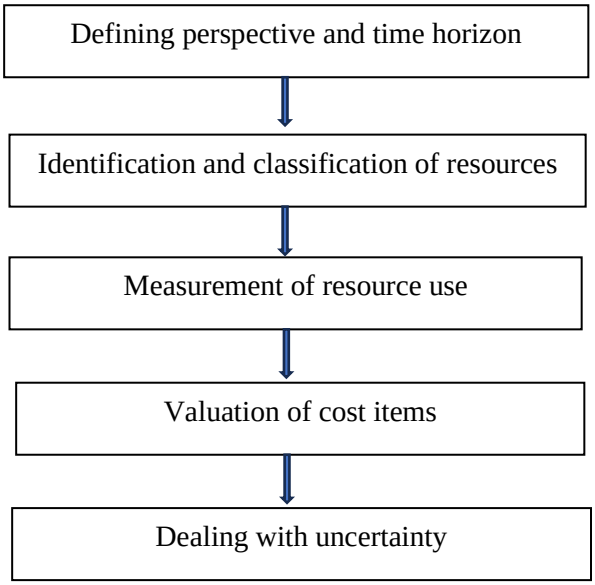


Figure 3-2. Steps involved in a micro-costing study

Step 1 Defining scope of the study

The costing study should define the health service under consideration, the perspective, time horizon as these determine the range of cost elements to be included and excluded [201, 205, 206]. The definition of health service should include all the essential and common elements of the service such as content, scope, settings, institutional arrangement, financial / payment systems, standards, quality, and unique characteristics of the services [205]. The perspective of a study could be broad (societal) or narrow(payer). The societal perspective aims to provide a wide of costs regardless of who bears them. The healthcare sector perspective includes formal healthcare sector (medical) costs borne by third-party payers or paid for out-of-pocket by patients. Unlike the societal perspective, the healthcare sector perspective does not include patient and family costs and time, and costs in other sectors. In general, stakeholders take narrower perspectives in particular decision contexts and in light of specific resource constraints [188]. Similarly, costing studies should be explicit about the time horizon during which the study has taken place as it can impact the cost of services in several ways including the cost behaviour over time, practice changes, technological variation, and comparability issues. Most textbooks and guidelines agree

that a costing study should be completed in one year. However, if the time span exceeds one year, costs should be discounted and expressed in present value [205].

Step 2: Identification and classification of cost items

All the relevant resource used in the delivery of health services needs to be identified. Each healthcare service activity comprises different cost items such as staff, equipment, consumables, and drugs, overhead. Developing a detailed description of a clinical pathway or a flowchart could help identify cost items. This could be developed based on clinical guidelines or literature reviews or via focus group discussions, interviews and individual consultation with experts/health professionals or a combination of both approaches. It is also important to identify if any resource is shared with other services and include only the proportional cost to the health services being analysed. After the identification of the cost components, they can be classified as direct and indirect costs or fixed and variable costs. As the names suggests, direct costs are the costs directly related to the delivering of the health service such as medicines and consumables used in the procedure whereas indirect costs are those indirectly related to the health service such as overhead and capital costs. Similarly, variable costs are those that depend on the quantity of output and the fixed costs remain the same regardless of the quantity [202].

Step 3: Measurement of cost items

All the identified resource items should be measured in physical or natural units. For example, hours spent by staff delivering the service, number of gloves used, etc. Careful consideration should be given to accurately measure those resource items that are likely to form the largest components of the total cost also known as cost drivers. In general, micro-costing approaches take representative samples of a particular service (and/or patient) and measure most of the resource use at the service (patient or cost object) level [205]. In addition, the opinions of experts, health professionals, and the patients as well as the carers can also be utilized. Common methods for measuring cost items are participant-recorded activity logs, surveys or interviews of health care

providers, time and motion techniques, review of medical case records, expert panels, and direct observation [202, 205]. These methods can be used individually or in combination.

Step 4: Valuation of cost items

This involves placing a monetary value on each of the resources identified. For this, patient resource utilization data is multiplied by unit prices which results in cost estimates for individual patients. Possible data sources to obtain unit prices for micro-costing studies are standard unit costs, fees, charges or market prices, and estimates/extrapolation based on previous research. A direct measurement method is used when these data sources are insufficient to estimate the monetary value of a particular service. Activity-based funding is an example of the direct cost measurement approach which divides a patient's care process necessary to deliver a particular service into discrete activities.

Step 5: Dealing with uncertainty

All cost estimates inherently have some level of uncertainty associated with them. The robustness of cost estimate results can be addressed by sensitivity analysis and statistical tests [205]. Statistical methods such as non-parametric test, log-norm parametric test and bootstrapping should be used to address the skewed distribution of the cost data [205].

A key source of uncertainty is parameter uncertainty, which arises from variability around the estimates of input variables and the assumptions used. The impact of parameter uncertainty should be evaluated using deterministic univariate or multivariate sensitivity analyses. In univariate sensitivity analyses, one parameter is changed at a time while in multivariate sensitivity analysis more parameters are varied simultaneously. Cost estimate parameters can be varied with a fixed percentage or uncertainty ranges such as standard deviations [206].

3.1.3 Description of colonoscopy procedure

As briefly discussed above in the screening tests section, colonoscopy is an endoscopic procedure that visualizes the colon and rectum and allows the removal of abnormal growth of cells known as adenomas or polyps. It is also employed in the investigations of GI symptoms, and surveillance of high-risk populations, including those previously treated for CRC.

Colonoscopies are typically conducted on an outpatient basis in a hospital's gastroenterology department. During the procedure, an endoscopist inserts a flexible camera-equipped tube through the rectum to visually examine the colon. Prior to the examination, patients are instructed to take laxatives to ensure the bowels are empty for a clear view [207]. Sedatives and analgesics are commonly used to enhance patient comfort and improve examination quality [208]. During a colonoscopy, adenomas or polyps can be removed (polypectomy), tissue samples may be collected for biopsy, or both could be conducted. Various polypectomy techniques are used. Typically, cold forceps and cold snares are used for smaller polyps, while hot snares are used for larger polyps [209]. Pathology (including biopsy and/ or relevant blood tests) is necessary to categorise adenomas removed during colonoscopy and to stage the cancers detected.

Colonoscopy is widely used in the screening, diagnosis, and treatment of various gastrointestinal (GI) diseases. Within CRC screening programmes, it can be employed either as a primary test or as a follow-up to stool-based primary testing. In Ireland, it is used as follow-up test after a positive FIT test and for surveillance activities.

The Irish healthcare system is a complex mix of public and private [210]. The system is predominantly tax-financed however, private health insurance and out-of-pocket payments are also used to finance significant amounts of healthcare expenditure. All citizens are entitled to free or subsidised public health services with modest copayments, which is managed by the Health Service Executive (HSE) [211]. Under the screening programme, colonoscopy services are offered free of charge at the point of service. Hospitals are reimbursed by the HSE based on activity-based funding prices.

3.1.4 Review of previous micro-costing studies on colonoscopy

A targeted literature search has revealed that, to our knowledge, there are only a few studies that estimated the cost of colonoscopy from the micro-costing approach. We focused on the methods reported, colonoscopy procedure time, cost components included, and cost differentiation based on intervention in each study.

Henry et al, 2007 [212] performed a cost analysis of colonoscopy using micro-costing and time-and-motion techniques to determine the total societal cost of colonoscopy at a Veterans' Affairs Medical Centre and University Hospital in the Southeastern US between July 2001 and June 2002. The study identified a comprehensive list of resources consumed while obtaining colonoscopy service through direct observation, interviews with clinical personnel and consultation with experts. A nurse accompanied all 276 participants included in the study to record the duration of all transactions involved in the procedure and resources used in each transaction. The cost components included for the estimation of the direct cost of colonoscopy were staff costs, equipment costs, medicines costs, overhead costs e.g., utilities, administrative costs, and building costs. The labour costs were calculated by multiplying the employee time for each procedure by per minute rate which was adjusted for administrative overhead rate (of 30% and 44% for respective hospitals) and capital utilization rate. The direct colonoscopy cost was found to vary significantly between procedures. The total direct cost was $358 for screening, $366 for diagnostic, $385 with biopsy and $445 with polypectomy. The total societal cost rose to $904 for screening, $899 for diagnostic, $929 with biopsy, and $982 with polypectomy which included direct non-health care costs and costs related to patients' time. The study found that labour related costs were the largest contributors to the direct cost that constituted approximately 66% of the total cost of which physician time and nursing time accounted for 29% and 25% of the direct health care costs. Fixed and capital costs constituted approximately 24% which includes direct health care costs as well as direct non-health care costs and costs related to patients' time.

Sharara et al, 2008 [213] conducted a micro-costing study of colonoscopy in the Montreal General Hospital in Montreal, Quebec to estimate the direct hospital costs of both diagnostic and therapeutic (polypectomy) colonoscopy from a third-party payer perspective in 2006. Based on

the patient pathway, the study identified every cost component of the procedure and a corresponding unit price. The cost components included were equipment costs, equipment and repair costs, labour costs, department-specific overhead costs, and hospital institutional overhead costs. The study reported a large proportion of the total cost was attributed to physician fees. The total cost of colonoscopy without physician fees was CAD157 compared to CAD352 with physicians' fee. Additionally, there was substantial cost variation between diagnostic and therapeutic colonoscopy. The total cost for colonoscopy without polypectomy was CAD199 compared to CAD467 for colonoscopy with polypectomy. The study highlighted the importance of improving hospital accounting systems to better allocate overall hospital overhead costs to medical departments and units, and ultimately to individual procedures as these overhead costs are an important component in the estimation of the overall total cost of the procedure.

Monakova et al, 2019 [214] conducted a micro-costing study of colonoscopy procedure in Ontario, Canada. The study established the best practice of performing colonoscopy based on clinical experts and then determined the costs associated with it using a micro-costing approach supported by hospital financial and administrative data from fiscal years 2014–2015 to 2015–2016 and input from 3 working groups of endoscopic unit nurses, endoscopists and endoscopy unit administrators. These working groups defined the patient pathway and advised on nursing activities, time, and staffing ratios, average procedure duration and average use and cost for supplies, sundries, and equipment required to perform the select procedures. The final resulting funding rate for colonoscopy was CAD161.8 and for colonoscopy biopsy it was CAD16.06. The majority of the cost was contributed by the total nursing costs (46%). The study excluded physician costs, costs outside of the endoscopy unit (laboratory and pathology, pharmacy, imaging, and so on) and overhead costs (equipment reprocessing, hospital administration, and so on).

Loras et al, 2018 [215] estimated the direct cost of various techniques of advanced endoscopy procedures and based the analysis on the cost of basic procedure including colonoscopy. The study was carried out in Hospital Universitari Mutua Terrassa, Spain. The study excluded costs of

support personnel involved in appointments and admission, cleaning of the facilities, equipment repair, communication, miscellaneous costs, as well as the structural costs of the hospital such as finance and accounting, human resources, information systems, information technology and communications, finance control, and the hospital management. The study calculated the direct standard cost based on time, equipment, inventoriable material, consumables, medications, and stent devices used in each procedure. The study reported the direct cost of colonoscopy with polypectomy as €1109.61. The consumables cost was the highest contributor to the total cost followed by personnel cost.

Larsen et al, 2019 [216] estimated the cost of colonoscopy based on the micro-costing approach in the US. The study included capital costs and costs associated with reprocessing, personnel, maintenance, repair, and postprocedural hospitalisation due to infection. The study differentiated the cost of colonoscopy between high-volume and low-volume centre. At a high-volume centre performing 3000 annual procedures on average, the direct cost of colonoscopy was US$188 whereas, at a low-volume centre performing an average of 1000 annual procedures, the cost was US$501. The study excluded the overhead cost as well as costs related to initial and recurring training, personnel education, time spent on repair documentation. The study did not provide details of measuring personnel cost and consumable cost. It noted that the total cost would be higher if reprocessing and equipment costs are considered such as additional reprocessing after 7 days of storage, cost of disposing single-use accessories, conducting internal audits, water and electricity, etc). In facilities with many colonoscopes available, the cost of additional reprocessing after seven days could be substantial due to low usage per colonoscope. The study suggested that disposable colonoscopes might be more cost-effective for low-volume facilities and patients with high infection risk.

1.3.4.1 Summary of review of previous micro-costing studies on colonoscopy

Literature on micro-costing studies on colonoscopy is scant. Most of the studies on the micro-costing of colonoscopies are from North America and there is only one study conducted in a European setting. There was substantial variation in the details of the methods reported and

applied. Four out of five studies employed interview techniques or expert opinions to identify and value resources, whereas only one study utilized a prospective approach to observe patients and associated resources [212]. Further, there was substantial variation in the cost components included in the study. Overhead cost and structural cost of hospital and support personnel cost were excluded by some studies [214-216]. Only two studies disaggregated the cost of colonoscopy with and without polypectomy [212, 217].

3.1.5 Rationale

Cost estimates of colonoscopy are useful for several reasons. First, they inform the resource allocation within the health system and help identify where cost reductions may be obtained. Second, they assist in the planning and health economic evaluation of CRC screening programmes. Micro-costing is considered a more reliable and accurate method than top-down approaches to estimate the cost of an intervention and is recommended by several economic evaluation guidelines as one of the preferred methods to determine health costs [100, 218, 219]. A full bottom-up methodology is especially suitable for healthcare services based on complex organisational arrangements with a large component of labour or overheads [220]. Further, the top-down approach is not suitable for estimating the cost of colonoscopy as this approach assumes an equal distribution of resources between patients, which is not accurate for this procedure.

Based on our targeted literature review, the existing micro-costing literature focused specifically on colonoscopy is extremely limited. Only four North American studies and one European study have published detailed micro-costing analyses of colonoscopy reporting the cost range €304-€605 for no additional intervention and €334-€791 for polypectomy (updated to 2023/2024 prices converted to Euro) [212-214]. However, the European study bundled the colonoscopy costs together with another intervention and the disaggregated cost of colonoscopy alone was not reported. Additionally, one of these studies disaggregated estimates according to whether the colonoscopy was for screening or some other indication. European CEAs of CRC screening have

not used micro-costing to inform the costs of colonoscopies in their analyses and have primarily relied on reimbursement rates for the procedure [131, 132, 134, 144, 170]. These may not necessarily correspond with the true cost. Thus, there is a need for additional micro-costing studies, especially in a European context.

Currently, the NBSP plans to expand the age range to cover 55-74 years old. Further there is evidence that Irish CRC screening would remain sub-optimal [189] and there is a rationale for further expansion even beyond current plans. Therefore, there is a rationale to cost current policy plans and further possible proposals.

Our study will fill the gap in the literature by estimating the cost of conducting a colonoscopy comprehensively using a full micro-costing approach. To our knowledge, this is the first investigation of the cost of colonoscopy using the micro-costing approach within the Irish healthcare setting. Our cost estimate may contribute to the updating of CEA of CRC screening in Ireland. Further, understanding the unit cost of colonoscopy is important for the NBSP as it plans to extend coverage to the recommended age. The unit cost will aid in assessing the feasibility of service expansion and effective budget planning.

3.2 METHODOLOGY

This section describes the methods used in the micro-costing of direct cost of colonoscopy.

3.2.1 Study design

We conducted a prospective observational study to enumerate the direct cost of all resources used for a patient in a colonoscopy procedure. We used a micro-costing approach from a health system perspective to assess costs.

3.2.2 Setting

The study was conducted in a teaching hospital, the Mater Misericordiae University Hospital (MMUH), based in Dublin Ireland. The Irish healthcare system is a complex mix of public and private. The system is predominantly tax-financed however, private health insurance and out-of-pocket payments are also used to finance significant amounts of healthcare expenditure. All citizens are entitled to free or subsidised public health services with modest copayments, which is managed by the Health Service Executive (HSE) [210].

The GI unit at the MMUH is a national referral centre for the National Bowel Screen Programme (NBSP). The unit provides colonoscopy to the patients referred from the NBSP as well as patients referred by general practitioners (GP) or consultants from within the hospitals or other hospitals. There is no charge to the patient for either primary screening of follow up colonoscopy. The MMUH performs approximately 3000 colonoscopies annually, including one third of the procedures from the NBSP [98, 221].

3.2.3 Ethics statement

We secured ethics approval from both the MMUH and Trinity College Dublin for this research (Appendix 3). Further, we obtained informed consent from staff interviewed. Participant information leaflet was provided before obtaining the consent.

3.2.4 Resource use data collection

We collected data from the MMUH gastroenterology department for colonoscopy in May 2023. The data collection involved structured interviews, direct observations and consultation with clinical experts. The details of these instruments are provided in Appendix 4. We conducted two structured interviews with clinical and managerial staff of the gastroenterology department from which we developed an event pathway for patients from admission to discharge. We identified resource use in the patient pathway across four categories: i) medication; ii) equipment/device including maintenance; iii) staff; and iv) consumables. In addition, we observed the colonoscopy procedure confirming the staff involved, equipment, consumables and medication used. Furthermore, we identified four main outcomes of the colonoscopy procedure i) colonoscopy with no intervention ii) colonoscopy with biopsy iii) colonoscopy with polypectomy iv) colonoscopy with polypectomy and biopsy.

To obtain a representative sample, we monitored all procedures performed between Monday and Friday over the course of one week. The sampled week was deliberately selected to avoid atypical low-volume periods such as summer and Christmas weeks. The study included all day case patients registered for colonoscopy in that week. No patient identifiable data was collected as part of this study. The observer (RP) recorded the timings of interactions with a stopwatch over rounds of observation and recorded if the colonoscopy was conducted with any intervention such as polypectomy and biopsy. The observer did not attend the colonoscopy procedure room during procedures. We recorded the proportion of cases who are sedated and unsedated and whether the colonoscopy was for screening or another indication.

We obtained the hospital unit costs of the consumables and medications from the managerial staff of the gastroenterology department and the finance team. We did not observe certain pre-procedure activities, including patient triage by the consultant and appointment scheduling by the secretary. Additionally, we did not observe the consultation time with patients before their discharge and the duration of the disinfection process on the procedure day. We also did not observe the time required by the pathologist for the laboratory analysis. We estimated the costs of

these aspects of colonoscopy according to experts' opinion on time used and an appropriate unit cost.

3.2.5 Cost estimation

All costs were recorded in euro for the year 2023. Costs from prior years such as machinery purchases were adjusted to 2023 values using the health Consumer Price Index [222].

We calculated staff costs according to Irish health economic appraisal guidance that includes gross salaries, pay-related social insurance (PRSI), pension contributions and overheads [219]. We used consolidated salary scales available from the Health Service Executive (HSE) [223]. For each relevant salary grade, we determined the average salary cost by taking the midpoint between the minimum and maximum amounts. We obtained the employer PRSI rates from the Department of Social Protection which is calculated at 4% of gross weekly earnings [224]. The per minute staff cost was derived from annual salaries by dividing by the number of workable minutes per year assuming 48 working weeks per year and 35 working hours per week. This assumption is based on a prior micro-costing study in Ireland [225]. Per procedure staff costs were calculated by multiplying per minute rates with the time taken by each procedure. We assumed one nurse per patient in the admission room and the recovery room.

Equipment expenses including purchase and maintenance costs were annualized using an equivalent annual cost method [100]. This method distributes the total cost equally over the equipment lifespan. We used discount rate of 4% and an equipment lifespan of 8 years to determine the annuity factor [100, 219]. Per minute equipment costs were derived by dividing the annual cost by the total workable minutes per year by assuming 50 working weeks per year and 40 working hours per week based on a previous Irish study. The equipment was assumed to work to full capacity. Per procedure costs were calculated by multiplying per minute equipment rate with time required for the colonoscopy. For equipment that is shared for other procedures, the proportion of colonoscopy-specific use was used in the time calculations. For consumables and medicines, the public list price provided by a clinical manager was used in the cost calculation.

We calculated the unit price of consumables and medicines by dividing the purchase price with quantities used per procedure. Value Added Tax (VAT) was excluded from cost calculations for medicines and consumables in accordance with national guidelines [219].

3.2.6 Data analysis

We documented the analysis using Microsoft® Excel® 2011. For each resource type, we calculated the total cost by multiplying unit costs with the quantities used. The total cost of colonoscopy per patient was calculated by summing all the resource variables. We used 1000-replicate bootstrap of the original time and cost data to obtain the mean values and standard deviations (SD). Further, we investigated the statistically significant differences in comparisons using the two-sample t-test. The bootstrap method involves randomly sampling data with replacement from the original dataset and does not rely on parametric assumptions about the data distribution. This technique is widely acknowledged as a reliable approach for analysing skewed cost data [226]. Bootstrapping was conducted in R studio (version 2023.06.1) [227].

We conducted one-way deterministic sensitivity analysis with a range of costs from identified main cost domains. The ranges of the input values were informed by a pragmatic literature search and consultation with clinical experts.

2.2.7 Data search

In order to provide context to our estimate we sought previously published estimates of the cost of colonoscopy. We did a targeted literature search for the cost of colonoscopy from European studies. We examined the costs reported in European CEAs within a recent systematic review [49]. We conducted a supplementary literature search to find additional cost estimates. The reported cost estimates were converted to euro using currency exchange rates [228] and updated to 2023 prices by using consumer price index published by Central Statistics Office [229]. The Consumer Price Index is the official measure of inflation in Ireland. We also retrieve recent reimbursed costs for colonoscopy from the Irish public health system.

3.3 RESULTS

We observed 58 patients undergoing colonoscopy over one week. Two cases were incomplete due to poor bowel preparation, and we excluded these in the calculation.

3.3.1 Patients' demographics

Table 3-3 describes the patient demographics. The mean (SD) patient age was 60.3 (11.2) years. Most patients (39.7%) were aged 60-69 years. Of the 58 patients, 55.2% were females. The majority

(75.9%) were referred by a GP or by a consultant, either within the hospital or from other hospitals. The remaining 24.1% patients were referred from the NBSP.

Table 3- 2 Patient Demographics. SD- Standard deviation, Other includes referral from GP or

Characteristics (n=58)	Number of patients (%)	Mean Age (±SD) years
Age		60.3 (11.2)
<40	4 (6.9)	31.5 (5.7)
40-49	8 (13.8)	45.5 (3.5)
50-59	9 (15.5)	54.0 (2.6)
60-69	23 (39.7)	63.6 (2.7)
70+	14 (24.1)	74.4 (4.0)
Sex		
Males	26 (44.8)	60.0 (10.1)
Females	32 (55.2)	60.5 (12.2)
Referral routes		
Screening programme	14 (24.1)	64.9 (4.0)
Other	44 (75.9)	58.6 (14.1)

consultants within the hospital or other hospitals of patients

3.3.2 Patient pathway

Figure 3-3. shows the identified patient pathway, indicating each step of the process recorded. Prior to the procedure, a consultant triages the referrals based on clinical priority, and appointments are scheduled by the secretary either by phone or email. During the procedure day, patients move through several areas, including the waiting area, admission room, procedure room, and recovery area. They are attended to by a variety of staff including secretaries, porters, doctors, nurses, and catering staff. Additionally, pathologists and endoscopic operators are central to the procedure but do not have face-to-face interactions with the patients.

On average, patients spent 197 minutes in the gastroenterology department for a colonoscopy. They spent 23 minutes in the waiting area before admission and 70, 40 and 64 minutes in the admission, procedure and recovery rooms respectively.

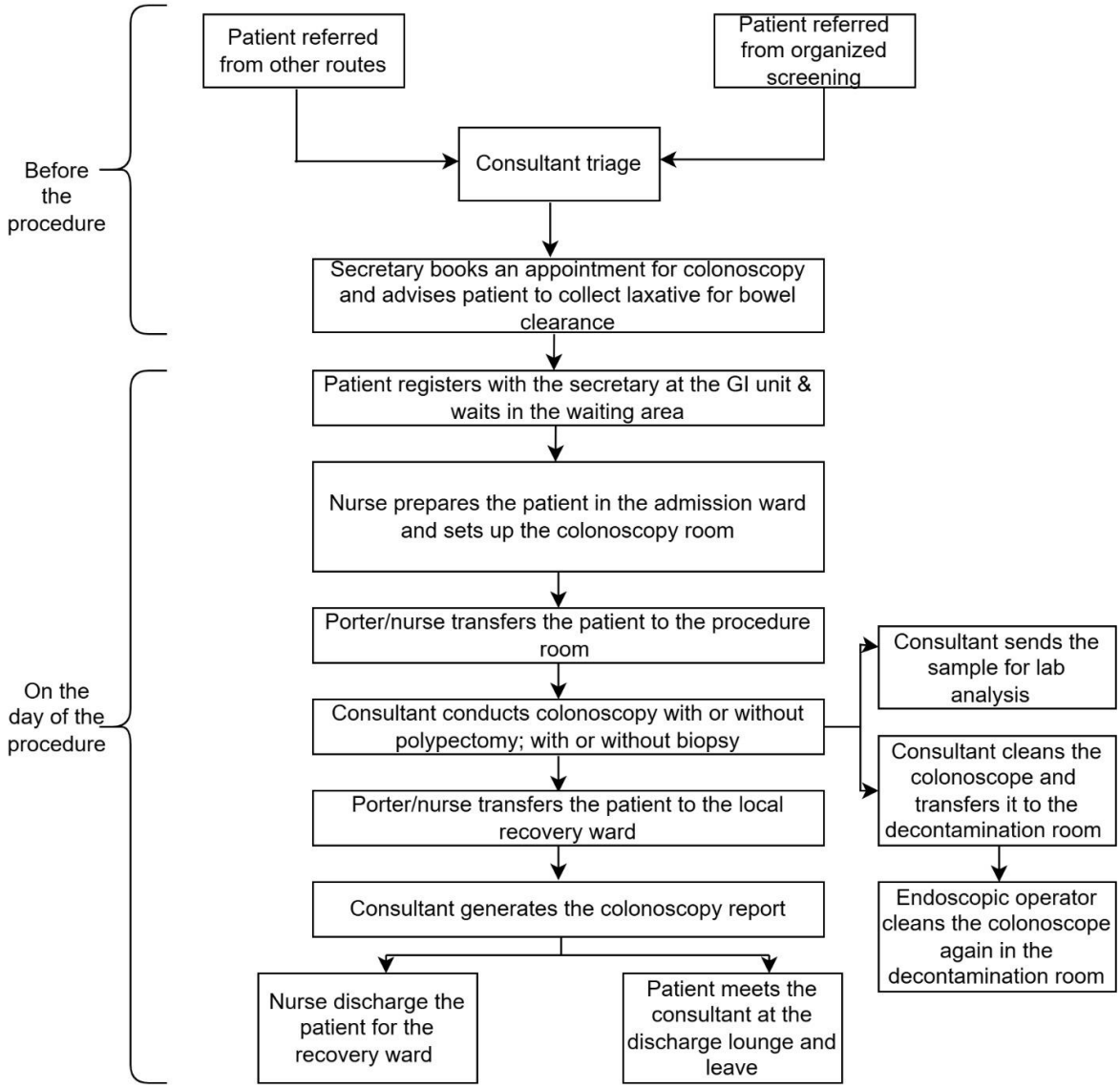


Figure 3-3. Patient pathway, GI- Gastrointestinal Unit, GP- General Practitioner, NBSP- National Bowel Screen Programme

3.3.3 Cost outcomes

The overall average direct cost of colonoscopy is estimated as €571. We observe significant differences in the procedure time based on referral route and whether interventions were conducted, resulting in substantial difference in the overall cost.

Table 3-3. Unit cost of the resources used in colonoscopy procedure. Cost estimates were calculated via data obtained from primary data collection at the MMUH.

Intervention Type	**Cost category**	**Description**	**No/No of units/Quantity per patient**	**Cost per minute (Euro)/Cost per unit**	**Time spent in the procedure (min)**	**Cost per procedure (Euro)**	**Note**
No intervention	**Staff**	Secretary	2	0.55	5, 2 (Time for scheduling the appointment, time for receiving the patient)	3.92	
		Nurse	5	0.58	70.45, 39.91, 64.25, 5 (Time for admission, procedure, recovery and discharge)	127.32	2 nurses for procedure; 1 for admission, 1 for recovery area and 1 for discharge, this may be the same person or different
		Consultant	2	2.75	5, 39.91 (Time for patient triage and procedure)	123.50	This may be the same person or different
		Porter	1	0.42	7	2.98	
		Kitchen operator	1	0.41	5	2.05	
		Endoscopic operator	1	0.48	40	19.14	
		Pathologist	1	0.54	60	32.69	
		Posi flush	1	0.01	-	0.01	

	Medicines and pharmacy supply	IV Midazolam	1-2mcg	1.19	-	1.19	
		IV Flumazenil	200mcg-1000mcg	27.39	-	27.39	
		IV Naloxone	200mcg-10mg	7.48	-	7.48	
		IV Fentanyl	25-50 mcg	0.30	-	0.30	
		IV Pethidine	25-50mg	0.35	-	0.35	
		IV Buscopan	10-20ml	0.34	-	0.34	
		Gelofusion	50ml	6.24	-	0.60	
		Plenvu	1	2.75	-	2.75	
		Gauze	20	1.09	-	0.54	
		Gel	1/4	1.56	-	3.12	
		Bottle of Sterile water	2	0.01	-	0.01	
	Consumables	**Routine tests**					
		Water sample test	Test conducted biweekly	0.08		0.08	
		Protein test consumables	Test conducted weekly				
		Paramyl		0.02		0.02	
		Brushes		0.06		0.06	

		ATP test	Test conducted biennially				
		Endoswab		0.001		0.001	
		Ultraswab		0.001		0.001	
		Nursing Assessment Booklet	1	0.45	-	0.45	
		Drug Kardex	1	0.08	-	0.08	
		Consent form	1	0.22	-	0.22	
		IV Cannula	1	0.80	-	0.80	
		IV Cannula Dressing	1	0.32	-	0.32	
		Alcohol wipe	2	0.04	-	0.04	
		IV Bung Cannula	1	0.80	-	0.80	
		Temperature Ear probe	2	0.10	-	0.10	
		Disposable pants	1	0.74	-	0.74	
		Nasal Cannula	1	0.29	-	0.29	
		Incontinent Sheet	2	0.38	-	0.38	
		Gauze	15pcs	0.15	-	0.15	
		Enzyme Scope Cleaner	1	1.51	-	1.51	
		Gloves	14	1.40	-	1.40	

		Apron	3	0.09	-	0.09	
		Kidney Dish	1	0.07	-	0.07	
		Posiflush 10ml saline	2	1.00	-	1.00	
		Syringes	2	0.54	-	0.54	
		Blunt needles	2	0.08	-	0.08	
		Drug labels	2	0.14	-	0.14	
		Sharps Bin	1	0.008	-	0.008	
		Suction Liner (Stack)	1	0.07	-	0.07	
		Suction Tubing (Stack)	1	0.78	-	0.78	
		Irrigator Tubing	1 per day	1.75	-	1.75	
		CO2/Air/Water Tubing	1 per day	1.10	-	1.10	Per patient cost was calculated by dividing the cost by per day volume which is 30 on average
		Bacterial Filter (stack)	1 per week	0.18	-	0.18	
		Valve Basket (Decon)	1	1.06	-	1.06	
		Scope Brushes	1	1.18	-	1.18	

		PAA Detergent	6 Bottles/3AERs/week	4.77	-	4.77	
		Endohigh Detergent	6 Bottles/3AERs/week	6.67	-	6.67	
		Mediclean Detergent	4 Bottles/week/2sinks	1.06	-	1.06	
	Capital	Bed	1	215.95		0.31, 0.35, 0.360 0.44	Cost per procedure for no intervention, biopsy, polypectomy and both interventions based on usage time
		OBS machine	1	1089.49		0.24, 0.40, 0.43, 0.37	Cost per procedure for no intervention, biopsy, polypectomy and both interventions based on usage time
		Endoscopic stack	1	14053.756		3.09,5.16,5.56,4.85	Cost per procedure for no intervention, biopsy, polypectomy and both interventions based on usage time
		Monitor	1	391.53		0.08,0.14,0.15,0.13	Cost per procedure for no intervention, biopsy, polypectomy and both interventions based on usage time

		Procedure trolley	1	1532.10		0.33, 0.56, 0.60,0.53	Cost per procedure for no intervention, biopsy, polypectomy and both interventions based on usage time
		Scope guide	1	5741.11		1.26, 2.11, 2.27, 1.98	Cost per procedure for no intervention, biopsy, polypectomy and both interventions based on usage time
		Printer	1	99.46		0.001	
		PC	3	170.23		0.007	
		Colonoscope	1	6515.49		1.43, 2.39, 2.58, 2.25	Cost per procedure for no intervention, biopsy, polypectomy and both interventions based on usage time
		BP monitor	1	420.19		0.17, 0.23, 0.24, 0.27	(BP monitor cost per procedure for no intervention, biopsy, polypectomy and both intervention)
		Oxy port	1	23.83		0.01, 0.01, 0.01, 0.01	(Oxy port cost per procedure for no intervention, biopsy, polypectomy and both intervention)
		Automated endoscopic processor	1	12562.36		4.18	Same usage for all intervention

		Adenosine triphosphate (ATP) measurement machine	1	42.28		0.002	
		Leak test machine	1	51.48		0.002	
		Scanner	1	66.68		0.003	
		Scope buddy	1	425.58		0.142	
		Drying cabinet	1	4523.74		6.78	
		Storage tray	1	170.23		0.02	
		Storage cart	1	62.99		0.02	
		Thermometer	1	61.00		0.006	
Polypectomy (additional to no intervention)	**Staff**	Post procedure consultation	10	3.02		30.27	
		Pathologist	60	0.54		32.69	
	Consumables	ERBE Plate (Diathermy)	1	1.53		1.53	
		Hot Snares	1	12.54		15.54	
		Cold Snares	1	22.34		22.34	
		Colonic Biopsy Forceps	1	6.00		6.00	
		Retrieval Net	1	39.00		39.00	
		Polyp Trap	1	9.40		9.40	

		Injector Needle	1	26.40		26.40	
		Clips	As required	43.00		43.00	
		Proctoscope	1	5.70		5.70	
		Haemorrhoidal Bander	1	34.00		34.00	
	Medicines and pharmacy supply	Methylene blue	1 amp	109.62		109.62	
		Adrenalinex3amps (1:1000)	3 amps	0.39		1.17	
		Adrenaline 1:10000	3 amps	12.18		36.54	
		Tattoo	1 tube	31.73		31.73	
Biopsy (additional to no intervention)	**Staff**	Consultant post procedure	10	3.02		30.27	
		Pathologist	60	0.54		32.69	
	Consumables	Biopsy forceps	1	6		6	
		Biopsy button	1	1.290		1.29	
		Histology pot	1	0.03		0.03	

ATP- Adenosine Triphosphate, PC – Computer, BP – Blood Pressure, IV – Intravenous, mcg – micrograms, Co2 -Carbon Dioxide, PAA – Detergent, OBS – Observation, ERBE – Electrophysiology electrodes

For the purpose of our analysis, we categorised the colonoscopy cases where there was either no additional intervention; polypectomy; biopsy; or both polypectomy and biopsy. On average, there was 18 minutes difference in procedure time between the colonoscopies with interventions versus those without (independent sample t-test, p value 0.001, confidence interval- 8.00-29.89) (Table 3-4). However, there was no significant difference in procedure time between polypectomy and biopsy interventions. We also investigated the difference in the procedure time based on the referral route i.e., the screening route and the other referral route. The procedure time for the cases referred from the bowel screening programme was 29 minutes while it was 44 minutes for the other referral cases, the difference was statistically significant (independent sample t-test, p value 0.006, confidence interval-4.37-24.91) (Table 3-4).

Table 3-4 Average procedure time based on the intervention and referral route

Outcome	**Total volume, n**	**Average procedure time, minutes**	**p-value (Confidence interval) of difference in means of procedure time, independent sample t-test**	**Average cost in Euros (SD)**	**p-value (Confidence interval) of difference in cost, independent sample t-test**
Colonoscopy without additional intervention	16	26.37	<0.001(18.64-19.32)	276.91(±14.17)	<0.001(408.73-413.27)
Colonoscopy with additional intervention	40	45.32		687.82(±35.09)	
Colonoscopy referred from organized screening	14	28.94	<0.001(14.23-14.84)	521.98((±60.67)	<0.001(54.32-63.65)
Colonoscopy from other routes	42	43.59		587.00(±42.86)	

The average direct cost of colonoscopy without any intervention (€276.91) was significantly different to the average cost of colonoscopy with any intervention (€688) (independent sample t-test, $p<0.001$, 95% CI of the difference 306.67-532.03,). Further disaggregation of the observed costs by type of intervention are shown in Table 3-4. The average direct cost of colonoscopy for screening indicated cases was €522 and other referrals was €587. The difference was also statistically significant. (Table 3-4)

Table 3-5 presents cost estimates disaggregated by category in terms of staff, overheads, consumables, medicines and equipment. Within the intervention group, polypectomy is the largest driver in cost differences. Staff cost was the largest contributor to the total cost contributing to 34-60% of the total cost followed by consumables. The details of the unit cost of resources are presented in the supplementary file.

Table 3-5 Cost distribution in capital, labour, consumables and medicines based on the intervention per patient (€, year 2023 values).

Type	**Colonoscopy without additional intervention Mean (%)**	**Colonoscopy with biopsy Mean (%)**	**Colonoscopy with polypectomy Mean (%)**	**Colonoscopy with biopsy & polypectomy Mean (%)**
Capital	18.13 (7)	22.55 (5)	23.41(3)	22.04 (3)
Labour	166.61 (60)	267.92 (63)	277.12 (34)	282.18 (34)
Overheads	55.39 (20)	89.31 (21)	92.37 (11)	94.06 (11)
Consumables	26.84 (10)	35.43 (8)	230.92 (28)	238.24 (29)
Medicines	9.21 (3)	9.21 (2)	188.27 (23)	188.27 (23)
Total	276.91	424.42	812.09	824.80

The original cost data sample was parameterised normally by bootstrapping the original sample with 1000 subsamples.

We conducted a comparative analysis of our cost estimates with previous estimates, reimbursement rates and private service provider's prices in Ireland. In a 2009 Health Technology

Assessment (HTA) of colorectal screening in Ireland by Health Information Quality Authority (HIQA), the average cost of colonoscopy was reported as €650 in 2008 prices which equates to €780 when adjusted for inflation to 2023 prices.

+8941

Reimbursement for public hospitals in Ireland is based on ABF which sets price based on the average cost of providing care for diagnoses and procedures. The ABF price list for the years 2020, 2022, and 2023 indicates a rising cost for colonoscopy, with prices set at €818, €896, and €994, respectively. These prices do not differentiate between different types of colonoscopy procedures based on interventions [49, 230-232] (Table 3-6).

For private healthcare services, we found a fee of €1375 for a day case colonoscopy at the Bon Secours Hospital Dublin which reports itself to be the largest private endoscopy unit in Ireland in 2023 [233].

Two studies conducted in North America before 2010 reported similar direct cost of colonoscopy: CAD340 (€605.92 in 2023) and USD358 (€ 540.22 in 2023) without polypectomy, and CAD 413 (€791.04 in 2023) and USD445 (€671.51 in 2023) with polypectomy [212, 217]. Similarly, a 2019 Canadian study estimated the cost of colonoscopy and biopsy colonoscopy as CAD161.18 (€ 304.43 in 2023) and CAD177.24 (€ 334.76 in 2023) respectively, excluding polypectomy costs [214].

As reported in table 3-7, the cost of colonoscopy varied widely in Europe. For colonoscopy without intervention, the cost ranged from €136.94 in Slovakia to €879.62 in the Netherlands. Similarly, for polypectomy the cost ranged from €165.24 in Slovakia to €1137.71in the Netherlands. The difference in the cost of colonoscopy with and without polypectomy was substantial in Ireland compared to other countries.

Table 3-6 Comparison of the cost of colonoscopy

			Cost of colonoscopy
Current analysis	**Based on intervention**	Without additional intervention	€277.00
		With intervention	€682.00
	Based on referral route	Screening Programme	€522.00
		Others	€587.00
	Overall average		€571.00
	Cost used in HTA of CRC screening (inflation adjusted to 2023 prices)		€780.00
	Current reimbursement rates		
	Activity based funding price 2020		€818 .00
	Activity based funding price 2022		€896.00
	Activity based funding price 2023		€994.00
	Cost estimates from other micro-costing studies (inflation adjusted 2023)		
	Sharara, 2008		€605.92, €791.04 (p)
	Henry, 2007		€540.22, €671.51(p)
	Monakova, 2019		€304.43, € 334.76 (b)

(p) - cost with polypectomy, (b) - cost with biopsy

Table 3- 7 Cost of colonoscopy in European countries

Country	**Cost estimates (€)**	**Cost in 2023 (€)**	**Source**
Portugal	397.00	469.50	Areia et al, 2019 [170], Currais et al, 2021 [133]
Sweden	650.00	784.01	Aronsson et al, 2017 [134]
Spain	281.30, 461.30(p)	336.95, 552.56(p)	Arrospide et al, 2018 [135]
Slovakia	121.00, 146.00 (p)	136.94, 165.24(p)	Babela et al, 2021 [131]
France	526.00, 641.00 (p)	660.73, 805.18(p)	Leujene et al, 2010 [151]
Italy	142.20, 288.60 (p)	173.77, 352.67(p)	Cesare et al, 2007 [234]
The Netherlands	729.26, 943.24 (p)	879.62, 1137.71(p)	Greuter et al, 2017
Austria	352.00, 450.00 (p)	416.28, 532.18(p)	Jahn et al, 2019 [147]
Germany	276.23	333.18	Rathmayer et al, 2017 [235]
The UK	594.97, 677.28 (p)*	611.74, 708.28(p)	Whyte et al, 2022 [132]
Ireland		276.91, 824.80 (p)	From current study

(P) Polypectomy

3.3.4 Sensitivity analysis

In sensitivity analyses we varied equipment life span, procedure time, the number of nurses required per procedure and overhead cost in a univariate manner.

We varied the equipment life span to 5 years and 10 years, from the base case of 8 years. The cost of colonoscopy increased to €582 (1.93%) for a 5-year life span and decreased to €567(0.70%) for a 10-year life span compared to the base case cost of €571. Similarly, the cost of colonoscopy decreased with reduction in the procedure time compared to the base case and increased with the increment in the procedure time. The cost of colonoscopy decreased to €532 (6.83%) and €562 (1.58%) for 30 minutes and 35 minutes procedure time respectively. The cost increased by 3.5% reaching €591 when the procedure time was increased to 45 minutes compared to the base case cost of €571. Further, we varied the overhead cost as 40% of the staff salary as reported in another study [225]. The cost of colonoscopy increased to €596 (4.38%) compared to 25% in the base case. The cost of colonoscopy decreased to €548 when we changed the number of nurses to 1 in the sensitivity analysis compared to 2 nurse per procedure in the base case.

3.4 DISCUSSION

We estimated the cost of colonoscopy using bottom-up micro-costing in an Irish tertiary hospital that serves as one of the national referral centres for the NBSP. Our analysis disaggregates costs estimates according to the indication for colonoscopy and whether any additional diagnostic procedures are conducted.

Cost Estimates based on referral route and intervention

We found that colonoscopy procedures with no additional diagnostic or therapeutic intervention take less time and so costs less to perform. In addition to the procedure time, the differences were attributed to the post procedure consultation time, consumables, and pathologist time to analyse the biopsy and polyp samples.

Regarding the referral route to colonoscopy, we found a significant difference in the procedure time and the cost between the screen indicated cases and the other referrals. Previous micro-

costing studies focusing on colonoscopy have not explored time and cost variances based on referral route, highlighting a gap in the existing literature. The cost discrepancies have important implications for their use. If screen-indicated procedures cost less than other colonoscopies, then CEAs that use costings not derived from screen-specific activity are likely to underestimate the cost-effectiveness of screening. However, we do not have a sufficiently large sample size to fully explore such potentially lower costs in the NBSP context. Thus, obvious extension for future research is to increase the sample for a comprehensive analysis of the observed time and cost variations based on referral route. The cost differentiation is also important for the NBSP's expansion plans. Additionally, including younger age groups in the programme's expansion could result in different cost estimates due to varying risk levels among age groups.

In general, it would be desirable for the CEAs of CRC screening to use the cost of screening colonoscopy. However, the number of screen-indicated colonoscopies in our study was small. A larger sample size would permit examination of the factors influencing the difference in cost for the screen-indicated and the referral colonoscopy and enhance the certainty of this finding. Patient characteristics including their sex, age and prior screening history might contribute to the differences in cost which we were not able to examine due to the small number of screen-indicated colonoscopies in our study.

Comparison of colonoscopy cost

We found our estimates were broadly consistent with previous estimates and lower than currently reimbursed prices in Ireland. To date there has been no study conducted to address the colonoscopy cost in Ireland using micro-costing. A HTA of CRC cancer screening published by HIQA in 2009 utilised colonoscopy cost derived from the Diagnostic Related Group case mix [219].

Our estimate is somewhat below current reimbursement rates for colonoscopy used in the Irish health system. However, the comparison is challenging as the components included in the ABF costing is not known. If there is an explicit basis for the items costed for in the ABF and these would be made available, then further examination could be possible. The lower cost estimates for

the colonoscopy service from our study may stimulate a discussion regarding potential opportunities for efficiency gains and cost containment within the current colonoscopy service system. However, the generalizability of our study finding is limited as this is a single centre study. Any revision to the current funding based on our study findings might lead to underfunding of the service. Therefore, caution should be exercised when considering adjustments to the current funding model. The government also purchases the colonoscopy service from private providers through a national treatment purchase fund (NTPF) initiative [233]. The NTPF reimbursement rates are negotiated individually with hospitals but are not publicly disclosed. Similarly, the private service charges are not readily publicly available. One private service cost that we were able to find was considerably higher than our estimate. The higher cost in the private sector can be attributed to various factors. The administrative and overhead expenses are higher in the private sector. Being profit-driven, private hospital need to generate sufficient revenue to sustain their operations and investments. Consequently, these elevated expenses are reflected in the pricing of health services.

Internationally, there is limited research employing micro-costing method to examine the cost of colonoscopy. We identified four North American studies that utilized micro-costing methods to estimate the cost of colonoscopy [212, 214, 217]. The lower cost of colonoscopy in a 2019 Canadian study is because it excluded costs of physician time, overheads, cost outside the endoscopy unit such as laboratory and pathology, pharmacy [214]. Additionally, we found a Spanish study that estimated the cost of colonoscopy using micro-costing methodology [215]. This study reported the cost of colonoscopy in conjunction with other procedures in such a way that disaggregating the costs of the procedure is not possible. Similar to our study finding, the staff cost was the greatest proportional cost.

The cost of colonoscopy is reported in various other studies that have not performed micro costing. These include values used with published CEAs. Most of these cost estimations of colonoscopy were either from costing studies or the application of those studies in CEAs. The cost of colonoscopy was the second highest in Europe, after the Netherlands. The higher cost of

colonoscopy in Ireland compared to the EU countries could be because of its expensive health system. Irish wages are high relative to those across Europe [236]. The salaries constitute a major portion of the colonoscopy cost.

Reflection on methodology

In addition to studies that cite colonoscopy cost, there are a few costing studies using top-down costing methods that estimated the cost of colonoscopy [131, 134, 135, 144, 147, 151, 159, 164, 170, 235]. Such methods take the total procedure cost without detailing individual components. While easy to implement due to their simplicity and less intensive data requirements, such approaches cannot identify cost drivers. In contrast, bottom-up micro-costing precisely documents granular cost details and identifies areas for potential cost reduction. However, bottom-up micro-costing is not widely used in assessing the costs of healthcare services as it is time-consuming, especially where administrative data cannot provide sufficient detail [205]. More generally, standardised methods and reporting guidelines and evaluation tools for micro-costing have yet to be established, further limiting its application [197].

No standardised guideline for micro-costing studies

Current micro-costing guidelines do not provide sufficient detail for conducting, appraising or reporting micro-costing studies. A review that critically appraised micro-costing methods used in health and medicine discussed that despite the increasing use of micro-costing analysis in healthcare literature there is a large variation in the quality of conducting and reporting micro-costing data [197]. Studies often lacked sufficient detail in explaining the study design and lacked providing granular details regarding the measurement of resource utilization quantity and unit costs. Furthermore, the study identified considerable variability in the terminology to describe their method across the studies. These findings support that there is an imminent need to develop robust guidelines to help standardize the conduct and reporting of micro-costing studies. While there are a few checklists that are to be used for full economic evaluation including cost-effectiveness analysis [99, 100, 111, 237], such checklists are not tailored to micro-costing methods and hence are not applicable. Similarly, the country-specific guidelines on economic

evaluations including that from Ireland are very broad [219]. Therefore, there is also an urgent need to develop checklists that are suitable for micro-costing studies particularly including items such as detailed enumeration of resource utilization, quantity and unit costs [238]. These particular items are not available in currently available checklists for economic evaluation. Furthermore, the inconsistent use of study methods makes it hard to compare across studies and understand the transparency of the study. Therefore, until the new guidelines and checklists are available, the users of such cost estimates need to pay closer attention to the design and reporting of micro-costing studies. In addition, it is advised that the professional organizations such as International Society for Pharmacoeconomics and Outcomes Research (ISPOR) and Society of Medical Decision Making (SMDM) give special consideration to the quality standards of reported studies.

Strengths and limitations of our study

Our study provides critical economic evidence to inform resource allocation and policy decisions regarding colonoscopy in Ireland. We reported the cost components, unit costs of each resource used in the colonoscopy procedure and all the assumptions about the resource utilization. This transparency in our reporting provides a clear framework for presenting a micro-costing study and enhances the reproducibility and transferability of our results to different settings. Further we precisely measured the time dedicated by each category of staff in the colonoscopy procedure unlike in other micro costing study [214]. This provides the better estimate of the staff time unlike gross costing method.

Our study has some limitations. Even though our overall sample for this study is reflective of the standard sample size used in micro-costing studies [239], the number of screening colonoscopies was small. A stratified sampling approach could be used to select more screening colonoscopies. This would help better understand differences in resource use and costs by indication. The study was conducted at a single centre tertiary hospital. Thus, the costs are reflective of colonoscopy service at this establishment and may not be directly generalisable to other settings. Further, overhead costs were allocated as a proportion of labour costs, while in accordance with Irish

health economic analysis guidelines this may not accurately reflect the true overhead expenses at different facilities which might artificially inflate labour intensive parts of the procedure. Additionally, we did not include costs associated with colonoscopy complications. However, the rate of complications in colonoscopy is low in Ireland and we did not observe any complications within our sample [98]. Lastly, the use of purchase price for medicines may not precisely reflect their economic costs.

CHAPTER 4 RESOURCE MODELLING FOR COLORECTAL CANCER SCREENING

4.1 INTRODUCTION

4.1.1 The need for modelling to inform Colorectal cancer screening policies

Decision-analytic modelling (DAM) has been increasingly used to aid decision-making in healthcare [240]. The International Society for Pharmacoeconomics and Outcomes Research (ISPOR) Task Force on Good Research Practices–Modelling Studies defines a health-care evaluation model as "an analytic methodology that accounts for events over time and across populations, that is based on data drawn from primary and/or secondary sources, and whose purpose is to estimate the effects of an intervention on valued health consequences and costs" [241]. These models can be used to guide public health research and priorities, and they can aid in the development of optimal cancer control strategies.

In the policy question of resource requirement for CRC screening, decision modelling is important due to various factors. First, this kind of analysis requires a variety of data such as data on the natural disease processes, epidemiological data, demographic data, cost-effectiveness data, behavioural data, test performance data, and policy data. It is not possible to gather all these data from a single source. Such data needs to be derived from RCTs, observational studies, model calibration, and cancer registries. The structure of a decision model provides a means by which empirical observations from different data sources and different study populations can be combined and directed at a specific decision problem of addressing resource requirement policy question [100, 109].

Second, RCTs and observational studies can only evaluate a limited number of policies at a time and are expensive and time-consuming. Whereas in the screening context, numerous options are possible with variations in different screening tests, age ranges, and positivity thresholds for follow-up testing. Such variations are impossible to be evaluated in a single RCT or an observational study. Third, decision models allow for the evaluation of many different screening

strategies and results can be generated in a short time frame. RCTs cannot provide evidence of the incremental benefits relative to other screening strategies unless those alternatives have also been trialled [194].

Fourth, lifetime health effects and costs are necessary to determine the cost-effectiveness of effectiveness of screening policy. Empirical studies are unable to do so due to their limited follow-up years. This can be achieved through decision models through extrapolation of evidence from empirical studies. Fifth, RCTs and observational studies are conducted within a specific context. Important parameters that drive the effectiveness of screening programmes can be very different from setting to setting. Decision models can be adjusted to reflect the setting of interest, taking into account CRC risk, life expectancy, and population preference.

4.1.2 Types of decision analytical models

The most common decision models used in health care are decision tree model, state transition model and discrete event simulation model.

A decision tree is a simple form of decision model that schematically provides a logical structure for a decision and possible events as they unfold over time [109]. A decision tree starts with a decision node for mutually exclusive available choices followed by all possible events that could occur following a decision or a previous event known as chance nodes which are represented as branches and assigned their respective probabilities. A terminal node represents the end points of each complete branch, and the outcome associated with it.

Decision trees can be used when the outcomes evaluated are relatively short-term (a short time horizon), and the long-term effects (survival) are assumed to be unchanged by the treatment [241]. Thus, decision trees are not suitable for addressing complex health services decisions as the tree format easily becomes unwieldy [242]. Estimating colonoscopy volume needs to reflect a large number of possible consequences over multiple rounds of screening making a decision tree unfit for the purpose.

The limitation of the decision tree model can be overcome by the state transition model (STM). Instead of possible consequences over time being modelled as a large number of possible pathways as in a decision tree, STM uses mutually exclusive finite health states. So, STM can accommodate recurrent events and long-time horizons. Based on the transition probabilities, individuals or cohorts' membership change over a series of discrete time period called cycles. Length of the cycle is chosen based on the clinical significance e.g., one month or one year. During a cycle, the individuals or cohorts can make only one transition. In time-homogenous Markov models, transition probabilities are constant over time, whereas in the time-inhomogeneous models they can depend on the time since the start of the model [243]. The model outputs are calculated based on the average number of cycles spent in each state [244]. Such models have been used in the evaluation of screening programmes, diagnostic technologies, and therapeutic interventions [242].

Although STM provides greater flexibility than a decision tree, it also has some important restrictions in the context of structuring complex prognoses. The primary disadvantage of STM is its underlying assumption that the probability of moving from one health state to another depends only on the initial state ignoring past states and duration spent in those. This 'memoryless' limitation of STM can be addressed by adding additional states to the model and incorporating time dependency into transition probabilities [242]. However, incorporating all relevant history for a clinical problem can exponentially increase the number of states, leading to a model that becomes excessively large and often unmanageable [109].

The key advantages of discrete event simulation (DES) models are their flexibility for modelling the disease process and interventions and their ability to overcome many of the limitations inherent in state transition models [109]. The term "discrete" indicates that DES progresses through time in distinct intervals, jumping from one event to the next, and these events are mutually exclusive. In DES, individuals can be given attributes, such as age, sex, and disease history, which influence their route through the simulation and the length of time between events [244]. So, there is no need for a complex set of health states to be defined and is not restricted to

the use of equal time periods or the Markov assumption. These factors give DES the flexibility and efficiency to be used over a very wide range of problems including a complex decision question however, more time and expertise is generally required to implement such models [245].

4.1.3 MISCAN-Colon model

In this thesis, we have used the Microsimulation Screening Analysis-Colon (MISCAN-Colon) model to estimate the colonoscopy volume for the NBSP Ireland. MISCAN-Colon model is a well-established microsimulation model for CRC developed at the Department of Public Health, Erasmus University Medical Center in Rotterdam, the Netherlands. It is part of Cancer Intervention and Surveillance Modelling Network (CISNET), a consortium of cancer decision modelers sponsored by the National Cancer Institute (NCI) of the US [246]. MISCAN-Colon model is considered a useful tool to support decision making on CRC screening. CEAs of CRC screening have extensively used the MISCAN-Colon model [247, 248]. MISCAN-Colon model is used to inform the Dutch CRC screening program and United States Preventive Services Task Force guidelines [247]. The model has been applied in several jurisdictions outside the US and the Netherlands such as in Spain and Switzerland [135, 249].

The MISCAN-Colon model's structure, underlying assumptions, and calibration have been described in previous publications [126, 248]. Briefly, the model simulates colorectal disease progression in a large population of individuals from birth to death. The model consists of three parts - demography part, natural history part, and screening part [250]. MISCAN–Colon model first generates a series of individual life histories in the demography part to form a population according to the demography parameters (e.g., the life table). Each person in the population has a date of birth and a date of death from causes other than CRC. Subsequently the natural history component of MISCAN–Colon model simulates CRC histories (natural histories) for each individual life history separately. As each individual ages, there is a chance that an adenomatous polyp – a benign precursor lesion that leads to CRC– develops. One or more adenomas can occur in any individual and each can independently develop into CRC. In the third part of the programme, screening for CRC is simulated. The introduction of screening potentially alters the

simulated life histories through the detection and removal of adenomas or through detection of CRC at earlier stages. The life history of each person is altered according to the natural history that is simulated for that person. If they die from CRC before they die from other causes, their death age is adjusted accordingly.

MISCAN-Colon model uses demography assumptions, natural history assumptions, and screening assumptions. Where possible these assumptions are derived from literature, however, some natural history and screening assumptions are not readily available or are uncertain. When this is the case, model calibration is required to estimate these parameters or to reduce uncertainty.

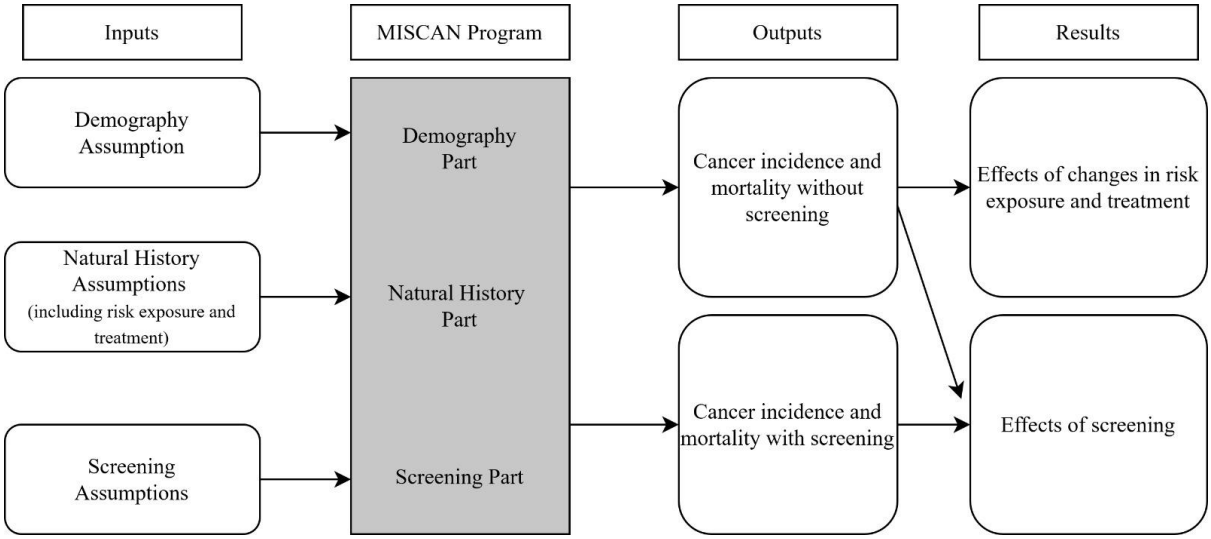


Figure 4 - 1. MISCAN-Colon model structure. Adapted from: Cancer Intervention and Surveillance Modelling Network [246].

4.1.4 Model validation and calibration

An important part of model development is to check that the predictions of the model are consistent with other data sources describing the model outputs, such as disease prevalence and mortality rates [251]. Validation is a set of methods for judging a model's accuracy in making relevant predictions. That information can be used by decision-makers to determine the results' applicability to their decision [252]. Sensitivity analysis is an important complement to validation. Sensitivity analysis can be used to explore how a model's results change upon variation in inputs. MISCAN-Colon model has been validated with trials data [247, 248, 253].

Models require plausible parameter values for its credibility and usefulness. However, some model parameters are not directly observable or are unavailable from the observed data. Examples of such parameters include adenoma dwell time, and mean duration of preclinical stage. Such parameters need to be calibrated based on observed data [247]. Calibration is a method to obtain parameter estimates such that the outcomes of a model using the parameter estimations fit the observed data. This involves comparing model outputs with empirical data, known as calibration targets (e.g. disease prevalence rate), and exploring variations (within a priori plausible bounds) of the input parameter values of the model to identify combinations that provide a better fit to the data [251].

Calibration reporting should include the target, goodness-of-fit metric, search algorithm, acceptance criteria, and stopping rule [252]. Vanni et al [251] has described seven steps in the calibration process as described below:

Step 1 Identify parameters

The first step in the calibration process is to identify the parameters. These are commonly the unobservable parameters that are allowed to vary in the model [251]. For example, the preclinical duration of CRC is not observable [253].

Step 2 Identify calibration targets

The second step is the selection of calibration targets. Calibration targets should be well representative of the population for which the decision is being made and should be derived from studies with sufficient sample size and no or limited study biases [251]. Examples of calibration targets are age-specific incidence rate, and stage distribution at the time of cancer diagnosis.

Step 3 Goodness of fit

The next step in the calibration process is to evaluate how close the model predictions are to the target data also known as goodness of fit (GOF) measures. This can be done qualitatively by visually comparing the model predicted and observed data. However, this is considered a subjective GOF and quantitative FOF is preferred [254]. The most commonly used quantitative

measures of GOF criteria in cancer screening models are the sum of squared errors (SSE), the Pearson chi-square and a likelihood-based approach [255].

Step 4 Parameter search strategy

Next step in the calibration process is to search for parameter values or sets of values that produce model outputs that match specified calibration targets most closely. This is known as ‘parameter search strategy’, ‘search algorithm’, or ‘optimization method’. There is no ideal optimization method. Analysts should choose the most appropriate method for the problem and compare results using different methods [251]. The MISCAN-Colon model has used Nelder-Mead Simplex method for calibration [250].

Step 5 Convergence criteria

The next step in the calibration process is to define acceptable sets of input parameter values. This is known as convergence criteria or acceptance criteria. There are different approaches to define acceptable sets of input parameter values. Analysts frequently set goodness-of-fit (GOF) thresholds based on a subjective assessment of "plausible" visual fit to the data. They plot the outputs from many potential parameter sets, and then arbitrarily define the poorest-fitting parameter set that is still considered acceptable. The GOF score of this borderline parameter set is then used as the threshold, and all parameter sets producing a better GOF than this threshold are deemed acceptable during the calibration process. An alternative to subjective visual thresholds is to define target ranges based on the data underlying the calibration targets. Parameter sets producing model outputs within those target ranges are then considered acceptable. Another approach is to establish a confidence interval around the goodness-of-fit (GOF) score of the best-fit parameter set. All parameter sets with GOF estimates within that confidence interval are considered acceptable.

Step 6 The stopping rule

The stopping rule defines when the iterative parameter search process is complete. There are two common approaches used as the stopping rule- 1) continuing the calibration until at least one

parameter set produces model outputs within the 95% CI of the calibration targets 2) stopping the calibration process after completion of a specific number of iterations.

Step 7 Integrate results

The last step of the process is to integrate the results of the model calibration within the full model. The simplest approach is to use the point estimates derived from the best-fitting set of calibrated input parameters.

4.1.5 Colonoscopy volume for Colorectal cancer screening programme

Colonoscopy capacity within a health system contributes to the success of population- level CRC screening programmes. The implementation of the screening programme generates a significant demand of colonoscopy services. Within CRC screening programmes, it can be employed either as a primary test or as a follow-up to stool-based primary testing. Further, it is used for the surveillance of patients found to be at higher risk after the procedure. Besides this, additional colonoscopy procedure may be needed for many reasons such as incomplete first colonoscopy because of poor bowel preparation, patient tolerance to the first procedure, necessary to have a second colonoscopy to site-check, or a clinical decision to perform colonoscopy over two visits instead of surgery [50, 96-98].

The volume of the colonoscopy requirement depends on the choice of the screening test, characteristics of screening strategy such as screening start and the stop age, positivity threshold of the primary test, screening interval. Compared with FOBT, FIT would approximately double colonoscopy demand [256]. The requirement is higher with the intensive strategies covering broad age range, frequent intervals. Similarly, the test positivity threshold strongly affects positivity rates and ensuing burden on colonoscopy services. Lower the test positivity threshold higher the positivity rates and referral to colonoscopy. Colonoscopy volume is higher when it is used as primary screening test compared to when it is used as diagnostic tests.

The volume of colonoscopy also depends on the uptake rate, population demographics and disease prevalence. The uptake rate of the primary test determines the colonoscopy referral.

Similarly, demographic ageing of the population means both a higher proportion of individuals within screening age range and a higher disease prevalence, resulting in more colonoscopy demand compared to a younger population structure. Certain population may have higher disease prevalence because of dietary and lifestyle risk factors or genetic factors. Screening such population would also result in higher colonoscopy demand.

Successive rounds of screening programmes are, however, expected to reduce the disease prevalence in the population or shift the diagnosis at the earlier stage. This has the potential to reduce the overall cancer resource requirements in the future including the colonoscopy demand.

4.1.6 Colonoscopy capacity in the Irish health system

Ireland has a mix of public and private care [210]. While there is universal access to most public health services, subject to some copayments for those without complete public entitlements under the Medical Card scheme, roughly 40% of the population purchases private health insurance to access privately provided care [257]. Moreover, the public health system sometimes purchases care from private providers for public patients. This public and private mix of provisions is relevant to colonoscopy capacity. In 2019, there were 34 public hospitals and 10 private hospitals providing endoscopic services under the National Endoscopic Quality Improvement Programme [258]. Screening programmes operate within the general symptomatic service. In 2021, there were 14 participating hospitals in the screening programme. The list of the participating hospitals is given in Appendix 2.

Nationally, colonoscopy capacity is constrained by the short supply of endoscopists with an appropriate level of skill [50, 96-98]. The hospital waiting list figures published by the National Treatment Purchase Fund (NTPF) in March 2024 show 9,285 people are waiting for more than 12 weeks for a GI scope across the hospitals in Ireland exceeding the Sláintecare target [259]. Within the screening programme substantial number of individuals have to wait for more than 6 weeks for index colonoscopy. This is not in accordance with the standards set by the HSE and the NSS, that greater than 85% of patients scheduled for surveillance colonoscopy should have their

procedure within three months of their indicative date. At the end of March 2019, the Irish Cancer Society published that there were 5,371 patients waiting longer than 3 months for a colonoscopy [260].

There is a steady increase in the total number of colonoscopies conducted annually. In 2019, 104,989 colonoscopies were performed nationally compared to 79,039 in 2016, 87,560 in 2017, and 97,864 in 2018. Approximately 5% of the colonoscopies were indicated following screening. Surveillance colonoscopies comprise a large proportion of colonoscopy volume, with the numbers increasing as the programme matures [50, 96-98].

Table 4-1 shows the screening colonoscopies and surveillance colonoscopies conducted as part of the NBSP and their waiting times.

Table 4-1 Screening and surveillance colonoscopy conducted by the National Bowel Screening Programme and their waiting times

Round	Screening colonoscopy, n	Surveillance colonoscopy, n	Additional planned colonoscopy	Colonoscopy waiting times for screening colonoscopy after positive FIT results		
				Within 4 weeks	Within 4-6 weeks	More than 6 weeks
Round I [50]	8,062	1,353		47%	25%	28%
Round II [97]	6,523	1,702	783	63%	20%	16%
Round III [98]	5,826	2,817	742	69%	15%	16%
Round IV [96]	3,878	3,233	802	83%*	14%	3%

*Because of COVID-19 related restrictions, invitations were paused from March 2020 to July 2020. Only 61% of individuals on the register were invited during this reporting period [96]. FIT– Faecal Immunochemical Test

4.1.7 Review of previous studies estimating colonoscopy volume for screening and surveillance activities

A targeted literature search has revealed that, there are several studies that have estimated the volume of colonoscopy for screening and surveillance activities. Below are the findings from key previous studies. In each study, we focused on the type of model used, assumptions regarding positivity threshold of FIT test, sensitivity and specificity of FIT test, sensitivity and specificity of colonoscopy, adherence to primary test, colonoscopy uptake (as primary modality, triage test) and surveillance uptake, surveillance guidelines and surveillance stop age and volume of colonoscopy reported for screening and surveillance activities for various screening strategies considered involving FIT test and colonoscopy.

Two studies conducted in the Irish setting have estimated the colonoscopy volume required for the CRC screening. Sharp et al [92] as part of a health technology assessment (HTA) of population-based CRC screening in Ireland estimated the resource requirement for the first decade of programme implementation. Using a Markov state transition model with a cross-sectional population simulation approach, they estimated the resource requirements for three scenarios including biennial FIT at 55–74 years to the actual target population in Ireland. For the FIT test, the base-case sensitivity values were considered to be 21% for adenomas and 71% for CRC. The specificity for CRC and adenoma was considered to be 95%. The uptake of FIT test was assumed to be 53%. The study did not evaluate FIT at different cut-off values. The compliance with screening colonoscopy and surveillance colonoscopy was assumed to be equal to 86%. The surveillance interval used was one yearly for high-risk group and three yearly for intermediate risk group.

The study estimated FIT-based screening at a cut-off of 100 ng Hb/mL will generate demand for 11,095 (year one) to 14,820 (year ten) additional colonoscopies annually in Ireland for diagnosis of screen positive cases and surveillance of individuals with screen detected adenomas. At year 1ten, 16% of these colonoscopies will be for surveillance and the rest would be diagnostic. The

study suggested a staggered age-based roll-out of FIT-based screening to allow time to increase colonoscopy capacity and meet the demand.

The second study addressing colonoscopy volumes in an Irish setting is a CEA that estimated colonoscopy volume generated under a broad range of different screening scenarios [189] [McFerran 2021]. The study aimed to identify alternative feasible policies that are more effective and cost-effective under the current colonoscopy capacity constraint. The MISCAN-Colon model was used to simulate 525 strategies varying 3 key screening parameters -screening intervals, age ranges, and FIT cutoffs. The model parameters were sourced from the published literature. The FIT sensitivity for adenomas 5mm or smaller was assumed to be 0% for all FIT cut-offs. For 6-9mm adenomas, the FIT sensitivity values ranged from 2.5% to 9.6% as the cut-off increased from 10 to 40 µg Hb/g respectively. For adenomas, larger than 10mm, the FIT sensitivity was 10.3% to 16.1% across the cut-offs. For early-stage CRC, the FIT sensitivity was 50-65%, increasing as the cut-off decreased. For late-stage CRC, the FIT sensitivity was 82.5-90%, again higher at lower cut-offs. The FIT specificity ranged from 95.97% to 98.7% as the cut-off increased from 10 to 40 µg Hb/g. Colonoscopy sensitivity was assumed to be 75% for adenomas smaller than 5mm, 85% 6-9mm, 95% for adenomas more than 10mm as well as for early and late-stage CRC. Colonoscopy specificity was assumed to be 100%. Surveillance was assumed to be annual for high-risk individuals and three-yearly for intermediate-risk individuals, up to age 80 years. Considering 100% adherence rate, the study has estimated the colonoscopy volume required for various policy options in Ireland. For age range 55-75 years, with biennial screenings using a FIT cut-off of 20µg Hb/g, the colonoscopy volume required was 1017 per 1000 people. For age range 60-70 years, with biennial screenings using a FIT cut-off of 20µg Hb/g, the colonoscopy volume required was 662 per 1000 people. For age range 60-70 years, with biennial screenings using a FIT cut-off of 40µg Hb/g, the colonoscopy volume required was 464 per 1000 people. For the age range 55-75 years, with biennial screenings using a FIT cut-off of 40µg Hb/g, the colonoscopy volume required was 735 per 1000 people. The paper only considered the total volume of lifetime colonoscopies and didn't disaggregate when they occurred or for what specific

indication (triage, surveillance, symptomatic). The model used wasn't adapted for Irish population structure or CRC incidence.

Other European studies that estimated the colonoscopy volume for organised screening programmes are from Germany, the Netherlands, Spain and the UK. Heisser et al [163] estimated colonoscopy volume for Germany under different scenarios using a muti-state Markov model for a hypothetical cohort of perfectly adherent 100,000 males and females aged 50-75 years under perfect adherence. They estimated colonoscopy volume under current screening offers in Germany i.e., annual FIT from ages 50 to 54 years followed by screening colonoscopies at age 55 and 65 years, annual FIT from ages 50 to 54 years followed by biennial FIT from ages 55-75 years and screening colonoscopies at ages 50 and 60 years (males only) and other potential alternative strategies. Sex-specific FIT sensitivity was assumed. For males, the FIT sensitivity was assumed to be 15.7% for non-advanced adenoma, 31.3% for advanced adenoma and 80.6% for preclinical CRC. For females, the FIT sensitivity was assumed to be 10.7% for non-advanced adenoma, 26.3% for advanced adenoma and 75.6% for preclinical cancer. The FIT test specificity was assumed to be 91.2% for males and 96.2% for females. Colonoscopy sensitivity was assumed to be 75% for non-advanced adenoma, 95% for advanced adenoma and preclinical cancer. Surveillance frequency was assumed to be 10 years up to age 75 years with non-advanced adenomas and 3 years with advanced adenomas up to age 85 years. For males, using the current screening offer strategies, the number of estimated colonoscopies per 1000 population ranged from 2187 to 2868. For females, the number of estimated colonoscopies for the current screening offer strategies ranged from 1457 to 2530. For males, around 460 additional colonoscopies were required for annual FIT (2448 per 1000 screened population) screening compared to biennial FIT (1987 per 1000 screened population). For females, around 420 additional colonoscopies were required for annual FIT (1730 per 1000) screening compared to biennial FIT (1309 per 1000).

Two Dutch studies have estimated colonoscopy volume for screening and surveillance [141, 160]. Greuter et al [141] conducted microsimulation using the ASCCA (Adenoma and Serrated pathway to Colorectal CAncer) model to estimate colonoscopy demand associated with screening

at surveillance at different intervals. The screening participation was assumed to be 72.6% and adherence to triage and surveillance colonoscopy was assumed to be 92%. Sex specific FIT positivity rate per adenoma and serrated lesion was assumed. For males, FIT positivity rate was 0.004 per diminutive adenoma, 0.12 per small adenoma, 0.30 per large adenoma, 0.004 per serrated lesion, 0.50 for early-stage CRC and 0.85 for late-stage CRC. For females, FIT positivity rate was 0.0003 per diminutive adenoma, 0.10 per small adenoma, 0.28 per large adenoma, 0.003 per serrated lesion, 0.50 for early-stage CRC and 0.85 for late-stage CRC. The surveillance was assumed to be conducted based on the Dutch guideline. The guideline uses a risk score based on size, number, morphology, location of colorectal lesions to categorize patients on low, intermediate and high-risk group. Patients with risk score 0 are considered low risk and are referred back to screening after 10 years. The intermediate risk group (risk score of 1 to 2) and high-risk group (risk score ≥ 3) are offered surveillance at 3 yearly and 5 yearly basis. Further, surveillance is stopped when the patient reached 75 years or when the patient had two negative results on surveillance colonoscopy in combination with risk scores less than 3 points. The model estimated that screening 55 to 75 years biennially without surveillance requires 335 colonoscopies per 1000 average-risk persons. The number increased to 543 for FIT screening with surveillance. The colonoscopy demand decreased to 376 when all surveillance intervals were increased to 10 years.

Wilschut et al [160] estimated colonoscopy volume of different screening strategies using FOBT or FIT test at various cutoff levels, surveillance strategies, and age ranges using the MISCAN-Colon microsimulation model. The estimated colonoscopy volume to screen 45-80-year-olds annually with FIT positivity threshold of 50 ng Hb/mL was 49 colonoscopies per 1000 individuals. This was under the assumption that unlimited colonoscopy capacity was available. The adherence was assumed to be 60% for the FIT test, 85% for diagnostic colonoscopy and 80% for surveillance colonoscopy. The FIT sensitivity at 50 ng Hb/mL was assumed to be 0 for adenomas less than or equal to 5mm, 8.4 for adenomas between 6 to 9mm, 16.7 for adenomas more than or equal to 10mm, 61 for all CRC stages before diagnosis in the absence of screening

and 88 for CRC stages at diagnosis in the absence of screening. Surveillance was assumed to stop at 80 years. Surveillance was modelled according to the Dutch guidelines; individuals with 2 to 3 adenomas removed were offered surveillance at 6 years interval and those with 3 or more adenomas removed at 3 years interval.

Rodríguez-Moranta et al [261] estimated endoscopic requirements for different CRC screening in an average-risk population aged 50-74 years for both screening and surveillance activities in Spain using a Markov model. The study estimated the colonoscopy volume for screening and surveillance activities at adherence rates of 20%, 40% and 60%. The frequency of surveillance was five-yearly if an adenoma was found and initial three yearly followed by five yearly in patients developing CRC until the age of 74 years. For both screening and surveillance activities, the mean number of annual colonoscopies were 149, 285 and 404 per 100,000 for annual FOBT at adherence rate of 20%, 40% and 60% respectively. Similarly for biennial FOBT the annual requirements were 111, 213 and 302 per 100,000 at adherence rates of 20%, 40% and 60% respectively. For five-yearly sigmoidoscopy the annual volumes were 498, 953, 1355 per 100,000 at adherence rate of 20%, 40%, 60% respectively. For ten-yearly colonoscopy, the annual estimated colonoscopy (screening and surveillance) volumes were 1287, 2466 and 3496 per 100,000 respectively.

Comas et al, 2016 estimated the long-term need for colonoscopies for screening and surveillance activities in Spain. Using a discrete event simulation method, the study predicted the number of colonoscopies needed to screen individuals aged 50-69 years biennially with a FIT test followed by a diagnostic colonoscopy. Surveillance was modelled according to European guidelines for Quality Assurance in CRC Screening and Diagnostics, with surveillance stopping at age 80 years. The study predicted 1200 colonoscopies per 100,000 population in the first year of programme, increasing to 1400 colonoscopies per 100,000 population by the 20th year.

Three studies have estimated colonoscopy volume for CRC screening programme in England at different time period using a Markov model. Nnoaham and Lines [262] predicted colonoscopy capacity required for CRC screening programme using biennial FOBT and colonoscopy, for

people aged 60–74 years from 2008 to 2023. The study assumed the screening uptake rate of 53%. The surveillance frequency used was one yearly and 3 yearly for high risk and intermediate risk population respectively and compliance with the surveillance colonoscopy was 83%. The annual colonoscopy required for screening and surveillance was 323 (94% screening colonoscopies) in the first year and 581(64% screening colonoscopies) in the 16th year.

Murphy et al, 2017 [154] estimated the colonoscopy volume required for CRC screening using FOBT and FIT test at various positivity threshold for average risk individuals aged 60-74 years. The screening uptake for FIT test assumed was based on age- 63.71% among 60-64 years age group, 68.88% among 65-69 years age group and 67.57% among 70-74 years age group. The colonoscopy uptake after a positive test was assumed to be 86.2%. The model assumed a simplified assumption for surveillance where both high risk and intermediate-risk patients undergo the same surveillance schedule of 12 months initially, followed by a colonoscopy every three years. Patients are returned to screening if they have two consecutive three yearly colonoscopies with no high-risks adenomas detected. The study estimated the 157 colonoscopies per 1000 people using FOBT and 189 using FIT at positivity threshold of 180µg Hb/g faeces. The number (cost) of additional colonoscopies with FIT compared with FOBT over the 40year time horizon ranges from 31,314 (£9 640 198) for FIT 150µg Hb/g faeces to 244, 999 (£57 903 423) for FIT 20µg Hb/g faeces.

Whyte et al, 2021 estimated colonoscopy volume required in the UK for the implementation of various cost-effective optimal strategies under colonoscopy capacity constraint. The study used School of Health and Related Research (ScHARR) state transition bowel cancer screening model. The uptake rate for the FIT test was assumed to be 65%, and colonoscopy surveillance compliance was assumed to be 83%. Surveillance was modelled according to the British Society of Gastroenterology guidelines which recommend annual surveillance for high-risk group, three yearly for intermediate-risk group and no surveillance for low-risk group or 5 yearly based on other considerations. A range of FIT sensitivity and specificity values at cut-off ranging from 20 to 180µg Hb/g for low risk and high-risk adenoma and cancer were simulated. Using a single

cohort of 50 years old (N=785,955), the study predicted screening referral colonoscopies for 50-74 years old undergoing biennial FIT screening at 124µg Hb/g and 105 µg Hb/g faeces to be 5.8 per 1000 persons and 8 per 1000 persons respectively.

Few US and a Canadian study have also estimated colonoscopy volume for a national and regional screening programme. Joseph et al, 2016 [263] used the MISCAN-Colon model to estimate colonoscopy demand in the USA for 2014 to 2040 resulting from the implementation of a national screening programme in 2014. The study assumed an uptake rate of 80% for a screening strategy of annual FIT for population aged 50-75 years. The assumed FIT sensitivities were 5% for adenomas 5mm or smaller, 10% for adenomas 6-9mm, 22% for adenomas 10mm or larger and 70% for cancer. For colonoscopy, the sensitivities were 75% for adenomas 5mm or smaller, 85% for adenomas 6-9mm, and 95% for both adenomas 10mm or larger and cancer. Specificities were 95% for FIT test and 90% for colonoscopy. Surveillance intervals ranged from three to five years dependent on the number and size of the adenomas detected. The study found that over a ten-year period (from 2014 to 2024), approximately 5.1 million colonoscopies would be required annually if FIT was used as a primary screening test. In contrast, using colonoscopy as the primary test screening test would necessitate approximately 11-13 million colonoscopies annually, with 57% being performed for screening and 43% for surveillance. They estimated that this figure will stay consistent at least until the year 2030. In the sensitivity analysis they found that the 100% adherence to primary test FIT would require 14.3 million colonoscopies in the initial year of 2014 and 6.9 million colonoscopies annually by 2030. Similarly, the 100% adherence to colonoscopy would require 14.1 million colonoscopies in 2014 and 17 million colonoscopies annually by 2030.

Cenin et al [264] estimated the colonoscopy demand for Australia's National Bowel Cancer Screening Programme under different implementation scenarios for 50-74 years old starting in 2006. The participation assumed were 38.1% for the first screening attendance followed by 80% for those who attended previously and 15% for those who did not attend previously. Similarly,

participation rates for follow up colonoscopy and surveillance were assumed to be 74% and 80% respectively. The specificity was assumed to be 95% for FIT and the sensitivity was assumed to be 0% for adenomas smaller than 5mm, 9% for 6-9mm adenomas, 32% for adenomas equal to or larger than 10mm, 36.5% for early preclinical stage and 72.8% for late preclinical stage. Similarly, sensitivity assumed for colonoscopy was 75% for adenomas smaller than 5mm, 85% for 6-9mm adenomas, 95% for adenomas equal to or larger than 10mm and preclinical cancer. Surveillance was modelled following National Health and Medical Research Council (NHMRC) guidelines which recommends surveillance interval of 3-5 years based on the number, type and size of adenomas. Surveillance was assumed to stop at 75 years of age. The colonoscopy volume for the current scenario using FIT test for 55 to 65 years from 2006 adding 50 years from 2008 and 70 years from 2015, was estimated 2, 275, 054 from 2015 to 2055. For the scenario assuming full implementation achieved by 2035 adding one age cohorts every 2 years, the total volume was assumed to be 4,218,449 for calendar years 2015 to 2055 and for the scenario assuming the full implementation in 2020 the colonoscopy volume was assumed to be 4 919,566 for calendar years 2015 to 2055.

4.1.7.1 Summary of review of previous studies estimating colonoscopy volume

Studies have used either cohort state transition models or microsimulation to generate the colonoscopy volume from the screening and surveillance activities. Only one study considered the role of the serrated pathway in CRC development [265]. Majority of the studies used single cohort for simulation except one study that used multi-cohorts [92]. Studies used various test performances, assumptions and differing estimates of uptake of primary, triage and surveillance testing. Two studies used sex-specific FIT test sensitivity [163] [265]. Some studies have not varied the FIT positivity cut-off in the analysis [92]. Surveillance interval modelled were more frequent for Ireland [92] and the UK [132] compared to the US [263], Australia [264] and other European countries [261, 265].

4.1.8 Rationale

The demand for the colonoscopy has seen a pronounced rise with the implementation of population-based screening programmes. In programmes that use colonoscopy as primary screening modality, there is substantial and continuous rise in the demand for colonoscopy after the implementation of screening programme. Similarly, in screening programmes utilising colonoscopy as follow test after positive primary test, the initial rise in the volume is driven by the need to rule out the positive cases and subsequently due to surveillance activities as the programme matures.

Quantifying the demand for colonoscopy and its cost impact over the years of screening programme implementation is crucial for effective service planning and resource allocation. Further, there are implications on the colonoscopy demand based on the choice of test, disease and population factors such as population size, uptake of screening and surveillance colonoscopy. Understanding these implications is critical for establishing and maintaining a successful screening programme. This can be achieved through simulation modelling.

CEAs of CRC screening also typically report the colonoscopy volume required for different scenarios. Models commonly assume perfect adherence to screening programmes and provide estimates over a long period of time without disaggregation year by year. Further, most CEAs of CRC screening do not consider the binding colonoscopy capacity constraints that likely apply in practice. The estimation from these models may overestimate the colonoscopy volume required or fail to identify what is feasible for adoption. While colonoscopy demand reported by CEAs can be helpful, policy makers ideally need analyses based on realistic adherence rates. Moreover, they need to be able to understand how demand estimates vary with other factors, such as disease incidence, test performance and screening and surveillance intervals, all of which typically vary between settings.

CRC screening programmes involve multiple rounds of screening for eligible populations which comprise multiple birth cohorts. Hence, the multiple birth cohort approach, also known as population-based approach, that considers multiple concurrent cohorts for analysis more accurately represents actual implementation [266]. Unlike the cohort approach which follows a

group of people over their lifetime and does not allow the addition of new individuals, the population approach allows the addition of new individuals into the model (incident cohorts) as time progress.

Several countries have struggled in meeting the demand of colonoscopy with the implementation of screening programmes. There is potential for unintended harms from population screening in the face of inadequate colonoscopy resources [132, 160, 189]. These include the harms of long waiting time for colonoscopy such as psychological impact on patients, higher incidence of CRC and diagnosis at advanced stage, reduced effectiveness and cost-effectiveness of CRC screening. Thus, understanding the yield from screening activities is essential to planning for adequate colonoscopy services.

Previous study that estimated colonoscopy volume for Ireland only considered the total volume of lifetime colonoscopies and did not disaggregate when they occurred or for what specific indication (triage, surveillance, symptomatic) have not used model adapted for Irish population structure or CRC incidence [189] and used a single cohort approach. Another Irish study that estimated colonoscopy volume have not considered the demand generated by current screening strategy of the NBSP nor the study has considered implementation scenarios using various FIT cut-offs.

Our study provides estimates of colonoscopy required for screening and surveillance activities for the next decade in Ireland using a validated and recalibrated model for various screening scenarios. We used a population approach. Additionally, we also utilised the adherence rates observed in the national screening programme in Ireland.

Furthermore, we provide a yearly budget implication corresponding to various scenarios, including the current screening strategy and planned expansions. This information is crucial for the NBSP as it plans to extend the programme to the recommended age group. Thus, our study aims to support effective planning and resource allocation for the successful expansion of CRC screening in Ireland.

4.2 METHODOLOGY

This section describes the development of the decision analytic model to estimate colonoscopy demand over multiple cohorts over a ten-year period for alternative CRC screening policies for Ireland. The model employs natural history estimates of CRC development upon which estimates of screening effectiveness are imposed. The natural history is drawn from an existing model of CRC model that was recalibrated for Irish CRC incidence.

4.2.1 Model

We substantially adapted an existing simulation model to estimate the colonoscopy volume for different screening scenarios. The model does not neatly fall under the category of Markov model or the microsimulation model. We used the outputs from the natural history of the MISCAN-Colon model which is a micro-simulation model. For the simulation of the screening scenarios, we built a de novo discrete event simulation model which processes events on an annual basis. While the underlying MISCAN-Colon natural history model has semi-Markov features, the de novo screening model cannot be considered Markov as it retains the history of each individual such as the participation in earlier round, adenoma detection and removal.

Figure 4-2. shows the structure of the de novo discrete event simulation model which was informed by the current screening pathway of the National Bowel Screening Programme.

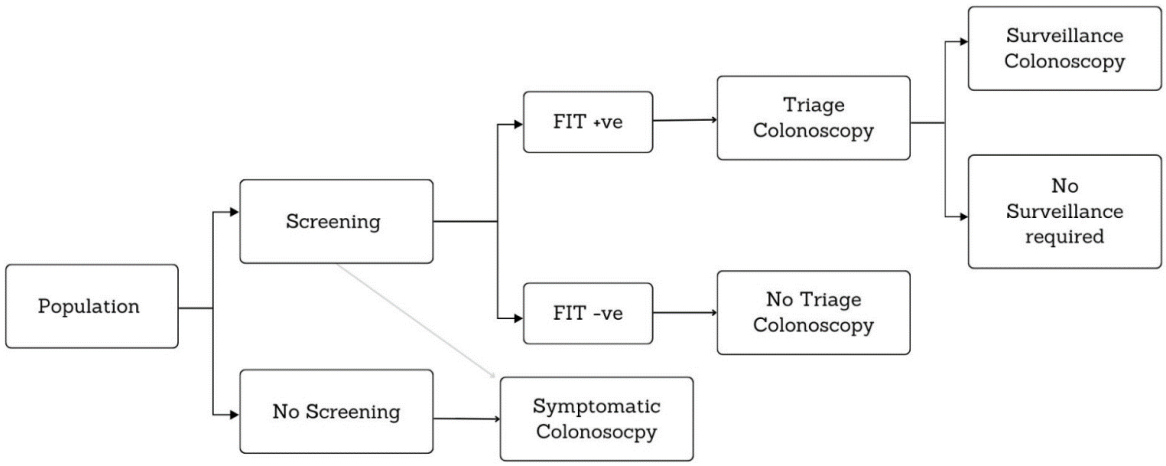


Figure 4-2 Model structure of the de novo discrete event simulation model

The model simulates demographically representative cohorts of males and females from the inception of CRC screening in Ireland from 2013 onward to a series of alternative screening strategies which are assumed to be adopted in beginning of 2025. We assess their consequences for the ten-year period from 2025 to 2034 inclusive. While the NBSP began in late 2012 we model the programme as beginning in 2013 as a pragmatic approach.

The model considers outcomes for those who do and do not participate in screening. Those who do not participate in screening can still develop symptomatic disease and generate colonoscopies for symptom investigation. For those who do participate in screening and have adenomas detected, screening is then suspended, and those individuals enter into a surveillance programme based on their risk according to the number and size of adenomas detected. The population continue to receive surveillance until age 80 years or before if they die before age 80 years.

The colonoscopies generated by the model are triage colonoscopy, surveillance colonoscopy and clinically-indicated colonoscopy arising from symptomatic presentation of CRC. Surveillance for the screen detected adenomas was modelled according to the nationally adopted guidelines for surveillance colonoscopies in Ireland which is based on the European Guidelines for quality assurance in CRC screening and diagnosis [95]. People with low-risk adenomas or normal colonoscopy are returned to the routine screening and do not contribute to numbers of surveillance colonoscopies. For people with high-risk adenomas removed (five or more small adenomas or at least one big adenoma 20mm), surveillance colonoscopy is conducted every year. If there are two consecutive negative findings on surveillance colonoscopy of high-risk group, the surveillance interval is extended to three years. For people with intermediate risk adenomas removed (three to four small adenomas or an adenoma 10 mm or larger)- surveillance colonoscopy is conducted at three years interval. If there are two consecutive negative findings on surveillance colonoscopy of intermediate risk group, the surveillance interval is extended to three years.

The de novo screening model was developed in R programming language R studio version 2023.06.1. The details of the model code are provided in Appendix 5.

4.2.3 Base-case scenario

The base case uses the current bowel screening programme screening strategy i.e., population aged 59-69 years are invited to participate in stool based primary test (FIT with positivity threshold at 225ng Hb/mL) every two years followed by colonoscopy in case of positive FIT test. For the period 2013-2023, the model simulates the screening age range of 60-68 years, which applied until late 2023 when the NBSP lowered the screening start age to 59 years. As a pragmatic approach, we assume that the switch from screening between 60-68 years to 59-69 years occurred in 2024. The model uses the FIT cut-off value of 100 ng Hb/mL in the first year i.e., 2013 then switches to 225ng Hb/mL, corresponding to that as implemented by the NBSP [50, 96-98].

4.2.4 Alternative scenarios

We compared the estimates of base case scenario (scenario i) with various alternative screening scenarios. As the aim of this study was to inform policy makers on the resulting colonoscopy volume for screening and surveillance activities, we chose the alternative scenarios based on the current strategy and the planned strategy of NBSP. We included different strategies intensifying the of current strategy such as reducing the screening interval, expanding the eligible age group for screening, and reducing the FIT cut-off threshold. We simulated the planned NBSP strategy as is that is biennial FIT screening among age group 50-74 years and diagnostic colonoscopy after a positive FIT result at a cut-off of 225ng/Hb/mL [93]. Additionally, we included a strategy found to be optimal in a recent study conducted in an Irish setting [189]. The CEA conducted in the Irish setting simulated a comprehensive set of strategies and provided recommendations on the optimal CRC screening.

The alternative scenarios simulated were:

ii. Biennial FIT screening among age group 59-69 years and diagnostic colonoscopy after a positive FIT result at a cut-off of 50ng Hb/mL (an intensification of current screening strategy [93] by reducing the FIT cut-off)

iii. Annual FIT screening among age group 59-69 years and diagnostic colonoscopy after a positive FIT result at a cut-off of 100ng Hb/mL (an intensification of current screening strategy [93] by reducing the screening interval and FIT cut-off)

iv. Annual FIT screening among age group 59-69 years and diagnostic colonoscopy after a positive FIT result at a cut-off of 100ng Hb/mL (an intensification of current screening strategy [93] by reducing the screening interval and FIT cut-off)

v. Biennial FIT screening among age group 55-74 years and diagnostic colonoscopy after a positive FIT result at a cut-off of 225ng Hb/mL (currently planned NBSP screening strategy [93])

vi. Annual FIT screening among age group 55-74 years and diagnostic colonoscopy after a positive FIT result at a cut-off of 100ng Hb/mL (an intensification of planned NBSP strategy [93] by reducing the screening interval)

vii. Annual FIT screening among age group 55-74 years and diagnostic colonoscopy after a positive FIT result at a cut-off of 50ng Hb/mL (an intensification of planned NBSP strategy [93] by reducing the screening interval and FIT cut-off)

viii. Annual FIT screening among age group 45-80 years and diagnostic colonoscopy after a positive FIT result at a cut-off of 50ng Hb/mL (optimal strategy recommended by recent research in the Irish context [189])

4.2.5 Cohorts simulated

We used a multi-cohort approach in the simulation. We identified which cohorts would be potentially eligible candidate recipients for a range of alternative screening scenarios. The model considers each of 51 birth cohorts for both males and females separately. The oldest cohort in the model is that born in 1945 and eligible to receive a screen at age 68 years in the NBSP first full year of operation in 2013 [50]. We determined the size of each birth year by sex in the year 2025 in accordance with CSO population projections [267]. We used CSO lifetables to estimate the size

of each birth cohort required at birth to yield the projected 2025 population. In order to generate the life histories, including the natural history of CRC development from initial adenomas to preclinical and clinical CRC, we randomly sampled from a previously defined population derived from the natural history model (described below) in proportion to the size of the cohorts at the birth year.

Figures 4-3, 4-4, 4-5 illustrate multiple cohorts under different screening scenarios. These figures are the broad representations of alternative policies, different cohorts and how they might be classified with respect to periods of observation in the model. The figures are slight simplifications of strategies considered in our analysis.

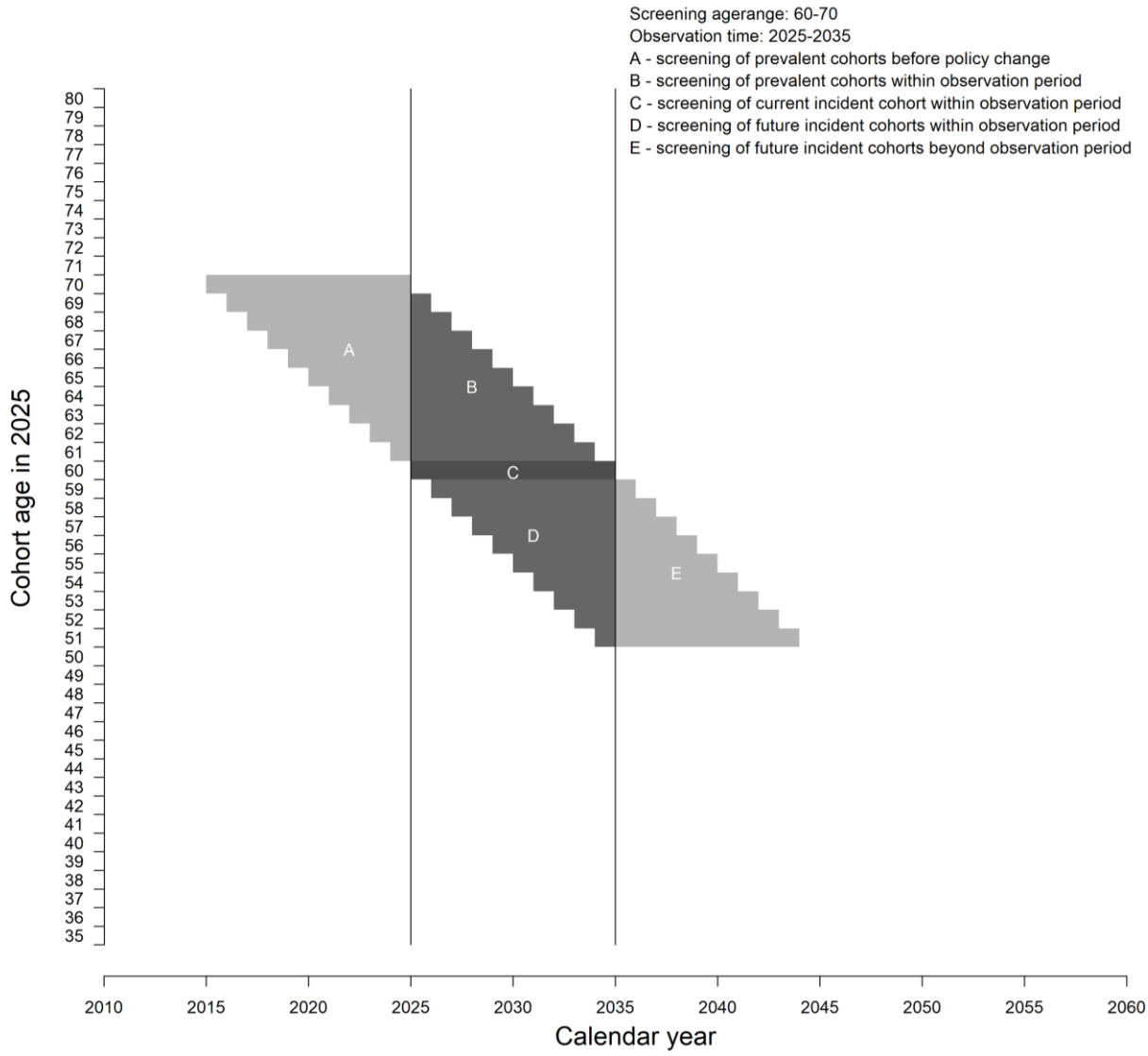


Figure 4-3. Details of birth cohorts for screening strategy covering age group of 60-70 years

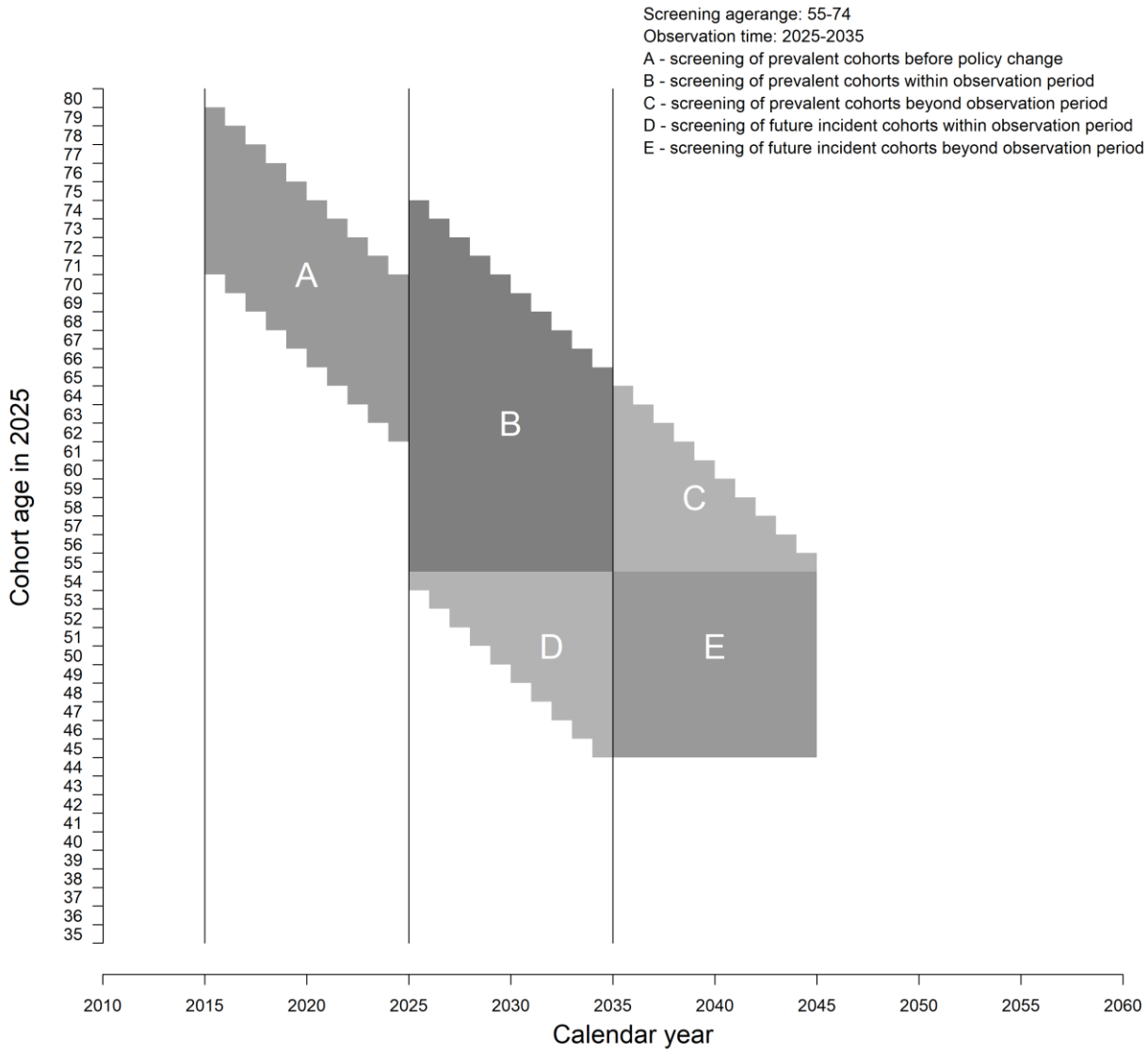


Figure 4- 4. Details of birth cohorts for screening strategy covering age group of 55-74 years

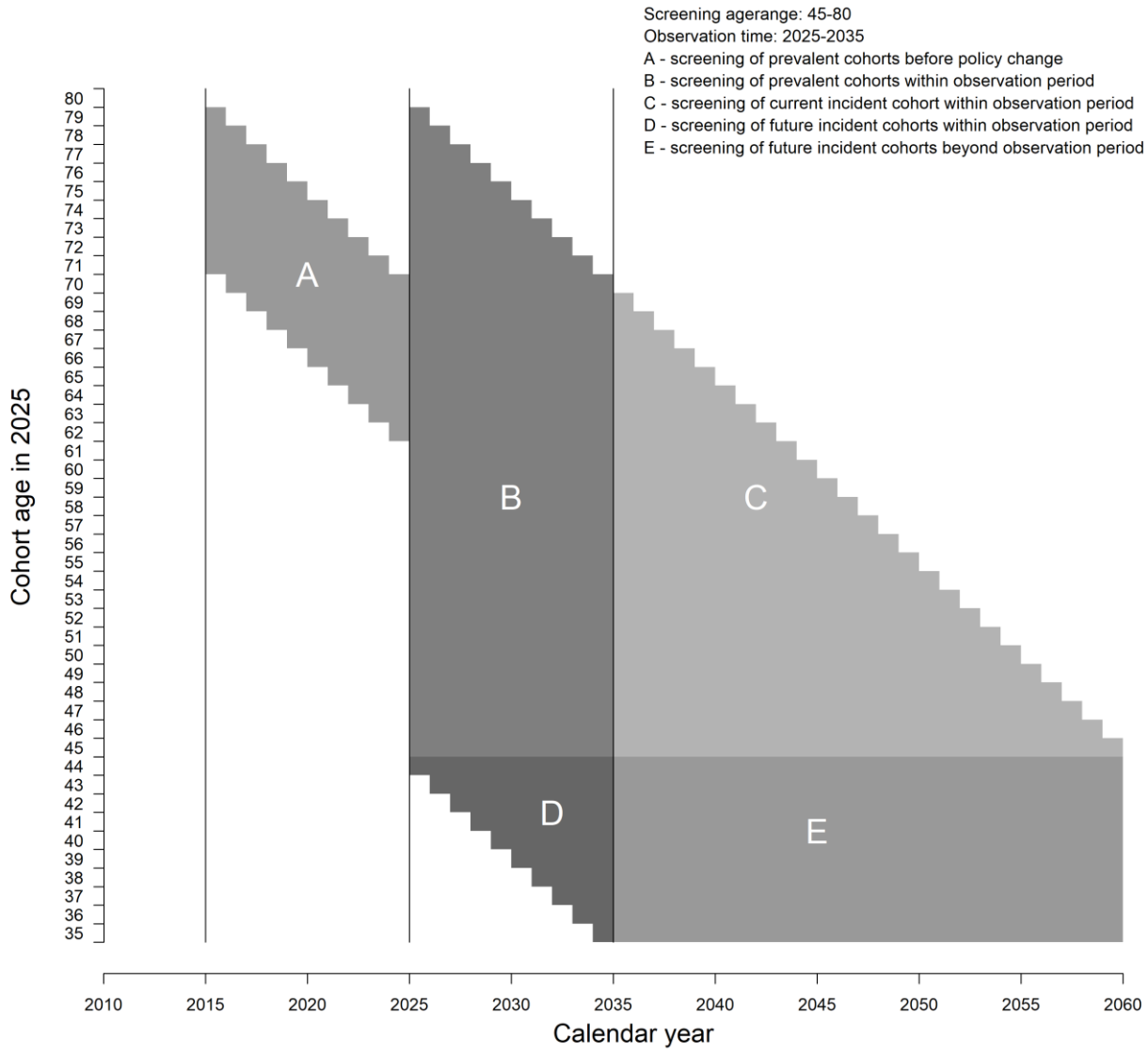


Figure 4-5. Details of birth cohorts for screening strategy covering age group of 45-80 years

4.2.6 Time horizon

All cohorts are simulated from birth until death in the model. Screening begins for eligible cohorts in 2013, and we record the colonoscopy volume from this point onward. For the prospective period over which we compare alternative policies, we used a time horizon of 10 years from 2025 to 2034. The period of simulation before 2025 is required to ensure individuals have representative screening histories, as their past screening will influence the outcomes in the period 2025-2034.

4.2.7 Key assumptions

The following provides a non-exhaustive list of assumptions important to the model.

1. Our model assumed a uniform risk of CRC over the simulation period. That is, while incidence increases with age within each cohort, the age-specific incidence does not vary between cohorts. Though there is emerging evidence on rise of some risk factors and decline of others, the net effect of these trends is not clear. So, the assumption of constant incidence was used.
2. We assumed all the individuals who participated in the programme would send a satisfactory FIT test. The NBSP contacts participants to resubmit if they don't send a satisfactory submission. So, it seems justified to make the simplifying assumption that there's 100% successful initial submission, especially given that this model is not a CEA.
3. We assumed that if individuals invited for index colonoscopy do not attend, they are not sent reminders to attend. They are invited to primary screening only.
4. We assumed the lesions detected at index or surveillance colonoscopy are removed with 100% success. This is in alignment with a base case assumption within the MISCAN-Colon model.
5. We did not intensify the surveillance colonoscopy interval based on the surveillance colonoscopy findings. The screening interval for the population identified to be at

intermediate risk were extended as per the surveillance guidelines however it remained unchanged if the risk level persisted or increased.

6. In order to streamline the handling of different protocols in the model, we assumed that the population can only attend screens at intervals in accordance with the policy and do so with respect to the first screening age. For example, if the screening policy is biennial screening between 59 and 69 years, individuals can only attend at 59 years, 61 years, 63 years to and so on, not at 60 years, 62 years, and 64 years and so on. This assumption does not change the number of lifetime screens for the population hence is unlikely to make substantial difference in the estimates.

4.2.8 Participation

The NBSP, Ireland has published four reports on programme performance for four rounds of screening. The first round covered the period from late 2012 to 31 December 2015 [50], the second round covered the period from 01 January 2016 to 31 December 2017 [97], the third round covered the period from 01 January 2018 to 31 December 2019 [98] and the fourth round covered the period from 01 January 2020 to 31 December 2021 [96]. The aggregate participation rates for FIT primary screening reported for these periods are 40.17%, 41.41%, 41.92% and 46.56% for the first, the second, the third and the fourth round respectively. Further the reports also provide uptake rates disaggregated for initial and subsequent participants from the second round. Initial participants are those never invited in the screening programme and those who were invited in the previous but did not participate. Subsequent participants are those who were screened in the previous round. However, the eligible population defined on each round change substantially between years. Moreover, what determines an eligible individual is determined is not stated explicitly within the NBSP reports and it is not possible to replicate the reported participation rates from published data.

We generated screen participation schedules for the male and female cohorts separately. We assumed that 40% of the eligible population would never attend screening, and 20% would attend

with low, moderate and perfect adherence respectively. We chose attendance rates for the low and moderate groups that resulted in an aggregate adherence rate that approximates what is observed from comparison of the size of the potentially eligible population and those attending screening.

We calculated a FIT primary screening participation rate for use in our model from the absolute number of FITs reported by the NBSP divided by our model estimate of the gross number of individuals in the population aged within the eligible screening age. Accordingly, this can be considered a crude participation rate which does not adjust eligibility for relevant pre-existing health conditions, a decision not to consent to screening or anything else that would make an individual ineligible for screening. While the NBSP reports the numbers of FITs conducted for four periods, which determined our participation rates with respect to the second and third round of 01 January 2016 to 31 December 2017 inclusive and 01 January 2018 to 31 December 2019 inclusive as the observed crude participation in the other periods appeared low, likely relating to changes during the programme's initial adoption between 2012 and 2015 and then disruption due to the COVID 19 pandemic. For the combined periods of 2016/2017 and 2018/19 we estimated a crude participation rate of approximately 38% and 33% for females and males respectively (Table 4-2).

Table 4-2 Adherence rate based on population simulated in the model and screened population in the NBSP [97,98]

Sex	**Population aged 60-68 years in the model**	**Population screened in the NBSP**	**Uptake rate (%)**	**Average uptake rate (%)**
Male				
2016-17	305,120	101,470 [97]	33.26	33%
2018-19	320,640	107,020 [98]	33.38	
Female				
2016-17	315,420	117,200 [97]	37.16	38%
2018-19	333,280	123,700 [98]	37.12	

4.2.9 Parameter estimates

We conducted a comprehensive literature review for parameter estimation. Table 4-3 presents the parameter values, and their sources used in the base case scenario. Expert opinion was used to elicit information where required data was otherwise unavailable. Irish data was used where available. We modelled three FIT cut-offs of 50, 100 and 225 ng Hb/mL (equivalent to 10, 20, 40 µg Hb/g). Although 40 µg Hb/g is typically equivalent to 200 ng Hb/mL, for the purposes of this model, we assumed it to be equivalent to 225 ng Hb/mL.

Table 4-3 Parameter estimates used in the base case analysis

Parameter	**Value**	**Source**
FIT at 50 ng Hb/mL		McFerran et al [189] Whyte et al [132] Goede et al [140]
Specificity, %	95.79	
Sensitivity, %		
Adenoma 1-5mm	0.00	
Adenoma 6-9mm	9.60	
Adenoma larger than10 mm	16.10	
Preclinical cancer stage I and II	65.00	
Preclinical cancer stage III and IV	90.00	
FIT at 100 ng Hb/mL		
Specificity, %	97.76	
Sensitivity, %		
Adenoma 1-5mm	0.00	
Adenoma 6-9mm	4.40	
Adenoma larger than 10 mm	13.10	
Preclinical cancer stage I and II	52.00	
Preclinical cancer stage III and IV	83.50	
FIT at 200 ng Hb/mL		
Specificity, %	98.70	
Sensitivity, %		
Adenoma 1-5mm	0.00	
Adenoma 6-9mm	2.50	
Adenoma 10 mm and larger	10.30	
Preclinical cancer stage I and II	50.00	
Preclinical cancer stage III and IV	82.50	

Colonoscopy		
Specificity, %	100.00	
Sensitivity, %		
Adenoma 1-5mm	75.00	
Adenoma 6-9mm	85.00	
Adenoma larger than 10 mm	95.00	
Preclinical cancer stage I and II	95.00	
Preclinical cancer stage III and IV	95.00	
Uptake of primary test	33% for males, 38% for females	National Bowel Screening Programme Annual Reports [97, 98]
Uptake of triage colonoscopy	80%	National Bowel Screening Programme Annual Reports [50, 96-98]
Uptake of surveillance colonoscopy	45%	Expert opinion

FIT- Faecal Immunochemical Test

Model operation

The model operates on an annual basis. It considers the number of clinically presenting cases of CRC would occur and assumes one colonoscopy is conducted for each. If a given cohort receives screening in a given model year, then screening is simulated by identifying which individuals within the simulated cohorts participate in screening, retrieving their true disease state and the application of lesion-specific FIT test sensitivities is used to determine if a true test positive occurs. FIT test false positives are calculated on the basis of the test specificity in application to the screened population without disease. All test positives, true and false, are referred for colonoscopy. The number of colonoscopies that occur is determined by applying the colonoscopy participation rate.

Those identified with disease at colonoscopy are referred to surveillance according to the grade of disease uncovered. Individuals remain in surveillance colonoscopy according to the surveillance algorithm and do not return to primary FIT testing until they have been released. The model records all the surveillance colonoscopies conducted.

As a pragmatic approach we assume that all screens and intervention occur at the point of eligibility by age. For instance, an individual eligible for screening at age 59 years will be

screened on their 59th birthday. Primary test positive indicated colonoscopy is assumed to be performed immediately (there is no delay in which the disease state can change). Furthermore, in the example given, an individual scheduled for surveillance colonoscopy with an interval of one year would then undergo colonoscopy on their 60th birthday. All screening ceases at the individual screen scenario end age. All surveillance ceases at age 80 years. The model runs in annual loops until age 100 years for each cohort. The model continues to run until age 100 years to capture additional clinical presentations that may occur. The model counts the annual total number of colonoscopies by indication across all of the simulated cohorts. The model is repeated across the alternative screening scenarios considered.

4.2.10 Recalibration of MISCAN-Colon model

Our research collaborators at the Erasmus Medical Centre, Rotterdam, supported us in recalibrating the MISCAN-Colon model to and Irish setting. The MISCAN-Colon model has been previously calibrated to CRC incidence in a Dutch population [248, 250] and was recalibrated to match the age-specific CRC incidence by location and stage distribution observed before the implementation of the population-based CRC screening in Ireland. We adjusted demographic assumptions such as population size, demographic structure over time, all-cause mortality by age, and observed natural history information such as localization of CRC and CRC relative survival by stage in the Dutch model to Irish data. The demographic data was collected from the CSO [267]. CRC localisation and survival data was obtained from NCRI (NCRI personal data request, 10th February 2023). We assumed the other unobservable parameters to be the same as in the Dutch calibration and others were allowed were varied in the recalibration.

The recalibration used a genetic algorithm to search for the set of parameter values that best predicted the observed outputs. Key steps involved in iterating genetic algorithm are described in detail by van Duuren 2022 [249]. In simple terms, it starts with forming an initial population using ranges of the parameters, then selecting a subset of parents according to a selection method. Then it forms offsprings by applying cross over operation and applies random mutation to the

offsprings. Acceptable offsprings are added to the population. The model calibration was run until the model predicted outcomes were within the 95% confidence interval of the observed outcome.

4.2.11 Calibration targets used in recalibration and their source

We used four calibration targets. These data were from period 2007 to 2011. They were chosen as recent data prior to the implementation of population-based CRC screening in Ireland. Details of these data are presented in Appendix 6.

A formal data request was sent to NCRI to assess data that were not publicly available. The following data was provided by NCRI [12]:

1. Annual number of CRC cases by 5-year age group and sex for period 2007 and 2011

2.Annual number of CRC cases by stage, age and sex for period 2007 and 2011

3. Annual Number of CRC cases by stage, location and sex for period 2007 and 2011.

Age and sex specific incidence rates calculated by dividing the total number of CRC cases by the total person-years at risk of CRC.

NCRI provided the localization data based on the following locations of CRC:

i. C18.0 Caecum
ii. C18.1 Appendix
iii. C18.2 Ascending colon
iv. C18.3 Hepatic flexure of colon
v. C18.4 Transverse colon
vi. C18.5 Splenic flexure of colon
vii. C18.6 Descending colon
viii. C18.7 Sigmoid colon
ix. C18.8 Overlapping lesion of colon
x. C18.9 Colon, NOS
xi. C19.9 Rectosigmoid junction
xii. C20.9 Rectum, NOS

Based on the above details, the total number of right-sided CRC was calculated by adding CRC cases located at caecum, ascending colon, hepatic flexure and transverse colon. Similarly, left-sided CRC was calculated by adding CRC cases on splenic flexure, descending colon, and

sigmoid colon. CRC cases located at overlapping lesion of colon and appendix were grouped as others.

[12].

The population size and the number of deaths due to CRC by 5-year age group and sex was extracted from the CSO website CSO [222].

4.2.12 Analysis

For each screening scenario, our decision analysis model estimated the following outcomes:

i. Year-specific estimates of colonoscopy for symptomatic patients between 2025 and 2034
ii. Year-specific estimates of colonoscopy for screening activities between 2025 and 2034
iii. Year-specific estimates of colonoscopy for surveillance activities between 2025 and 2034

One-way sensitivity analysis was performed to assess the influence of parameter uncertainty. We assessed the impact of varying adherence assumptions. For high density adherence assumption, the total adherence was concentrated in one section of the population whereas for low density adherence the total adherence was distributed among the population. Further, we assessed the impact of sex-specific FIT test sensitivity and specificity (Table 4-4) on the total volume generated based on the values reported by van der Meulen et al [164]. Additionally, we assessed the impact of variation in the incidence of CRC in the population on the model estimates. We assumed 10% higher in the incidence as high incidence and 10% lower as the low incidence.

Table 4- 4. Specificity and Sensitivity data of the various FIT cut-off values [164] and colonoscopy

Parameter	**Value**	
FIT at various cut-off levels	**Males**	**Females**
FIT at 50 ng Hb/mL		
Specificity, %	95.0	95.9
Sensitivity, %		
Adenoma 6-9 mm	19.1	1

Adenoma larger 10mm	46.7	26.5
Preclinical CRC (shortly before clinical diagnosis)	78.4	77.8
Preclinical CRC (long before clinical diagnosis)	46.7	42.9
FIT at 100 ng Hb/mL		
Specificity, %	97.7	97.8
Sensitivity, %		
Adenoma 6-9 mm	11.3	1
Adenoma 10mm and larger	38.1	18.1
Preclinical CRC (shortly before clinical diagnosis)	78.0	73.8
Preclinical CRC (long before clinical diagnosis)	43.2	37.8
FIT at 225 ng Hb/mL		
Specificity, %	98.7	98.7
Sensitivity, %		
Adenoma 6-9 mm	7.8	1.0
Adenoma larger than 10mm	30	15.6
Preclinical CRC (shortly before clinical diagnosis)	63.8	63.2
Preclinical CRC (long before clinical diagnosis)	30.0	27.0
Colonoscopy		
Specificity, %	100.00	
Sensitivity, %		
Adenoma 1-5mm	75.00	
Adenoma more 6-9mm	85.00	
Adenoma more than 10 mm	95.00	
Carcinoma	95.00	

FIT- Faecal Immunochemical Test

4.2.13 Colonoscopy cost analysis

We calculated the total cost of screening and surveillance colonoscopy under different screening scenarios. These costs are calculated as simply the product of our colonoscopy cost estimates from Study 2 by the respective colonoscopy volumes generated in the model and the HSE's activity-based funding pricelist of 2023 (day case colonoscopy item code G48B) [232]. We assumed all the false positive cases generated from our model do not require additional intervention and used the colonoscopy cost without intervention. Similarly, we used the cost of colonoscopy with polypectomy and biopsy for true positive cases generated from our model. In case of activity-based funding the cost of colonoscopy is not disaggregated by intervention hence we used the flat rate for both true positive and false positive cases. The analysis is considered in constant pricing, and no adjustment is made for inflation. Future costs are not discounted. We provided the total and annual cost related to colonoscopy for each scenario. Our analysis does not include the resources saved as a consequence of a particular strategy. We also do not consider the cost implications of the additional primary screening testing or the avoided treatment costs.

4.3 RESULTS

4.3.1 Recalibration results

We used four calibration targets in the recalibration i) CRC incidence by sex ii) CRC mortality by sex iii) CRC cases by stage of diagnosis, age, and sex and iv) CRC incidence by stage, location, and sex. The simulated outcomes do not fall within confidence intervals for all outcomes across all age groups for both sexes in the following sections, but the calibration was broadly consistent with what had been achieved in prior calibrations of the model to Dutch data and was considered reasonable fit [247, 248].

4.3.1.1 Colorectal cancer incidence by sex

Among males, the observed average CRC incidence rate prior to the CRC screening implementation from 2007 to 2011 was lower among individuals aged 50 years compared to older individuals above 50 years old. It ranged from 1 per 100,000 person-years (PYs) to 32 per 100,000 PYs among individuals younger than age 50 years. Whereas it ranged from 55 per 100,000 PYs to 595 per 100,000 PYs among individuals older than 50 years. The highest rate among the older population was in the age group 80 to 84 years old with 595 per 100,000 PYs. The model predictions of CRC incidence in the 5-year age group were within 95% CI for all age groups except among the population aged 85 years and above among both males and females. The observed incidence rate in this age group 85 years and above was 527 per 100,000 PYs. The model predicted somewhat lower incidence in this age group.

Among females, the model predicted a higher incidence rate among age group 75-79 years and lower in the age group 85 years and above compared to the observed incidence. The observed incidence rates were 287 per 100,000PYs and 342 per 100,000PYs among age group 75-79 years and 85 years and above respectively (Figure 4-6).

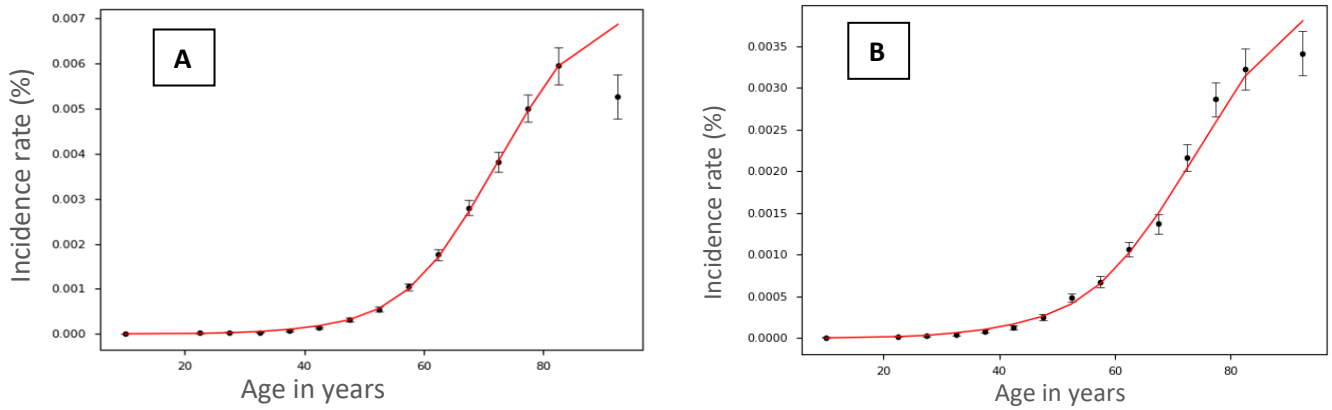


Figure 4-6. Calibrated model predictions of CRC incidence vs observed incidence in 2007-2011 by 5 years age group among male (A) and among female (B). The dots and whiskers denotes mean values and 95% CI of the incidence rate of CRC in the Irish population from period 2007 to 2011. The red lines connect the calibrated incidence rates figures obtained by the model for each of the age categories. Note: The scales of Y-axis are different in figure A and B.

4.3.1.2 CRC mortality by sex

The model predicted CRC mortality rates for the year 2007-2011 were within the 95% CI of the observed mortality rates for all age groups except 85+ years among males and 80-84 years among females. The observed mortality rate was 412 per 100,000 Person Years in the 85+ years age group among males but the model predicted less. The observed mortality rate among females in the age group 80-84 years was 362 per 100,000 Person Years but the model

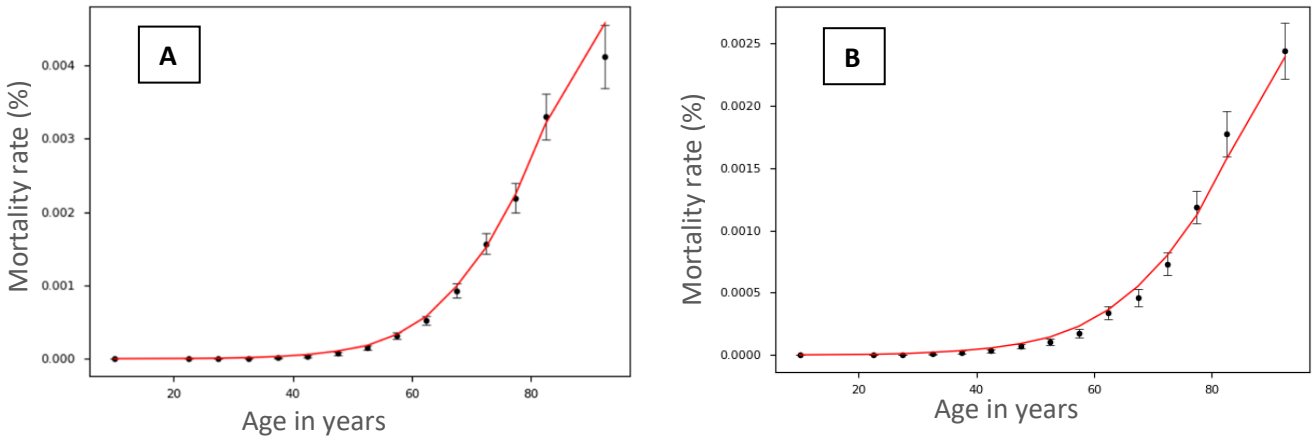


Figure 4-7. Calibrated model predictions of CRC mortality (red line) vs observed incidence in 2007-2011(dot and whiskers represent mean and 95% CI) by 5 years age group category among males (A) and females (B). Note: The scales of Y-axis are different in figure A and B.

predicted slightly higher (Figure4-7).

4.3.1.3 Colorectal cancer cases by Stage of diagnosis, age and sex

The model predicted CRC cases by stage of diagnosis i.e., stage I, stage II, stage III, and stage IV were within 95% CI of observed values for all age group among males. For females, the predicted

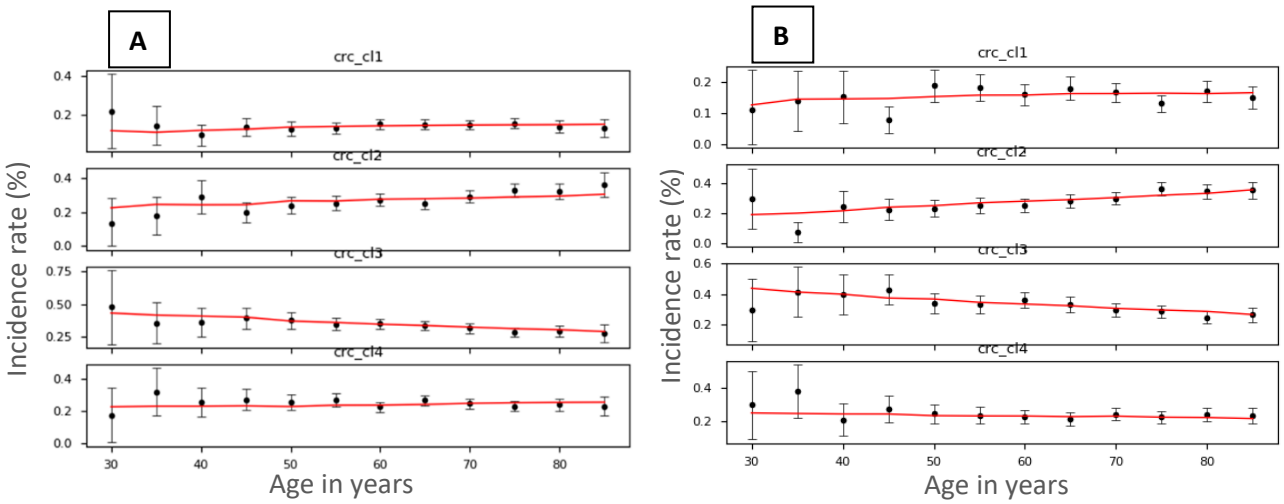


Figure 4-8. Calibrated model predictions of CRC incidence by stage and age (red line) vs observed incidence by stage and age in 2007-2011(dot and whiskers – dot denote mean, and whiskers denote 95% CI.) by 5 years age group intervals among males (A) and females (B). Crc_cl1, crc_cl2, crc_cl3 and crc_cl4 indicate the 4 stages of CRC. Note: The scales of Y-axis are different in figure A and B.

data was within 95% CI across all age groups for stage III and stage IV cancer. For stage III, the predicted cases were lower than observed cases among the 35-39 years age group, and for stage IV the predicted cases were lower than observed cases among females aged 45-49 years (Figure 4-8).

4.3.1.4 Colorectal cancer incidence by stage, location and sex

The model predicted CRC cases by stage and location were within 95% observed cases in both males and females (Figures 4-9, 4-10).

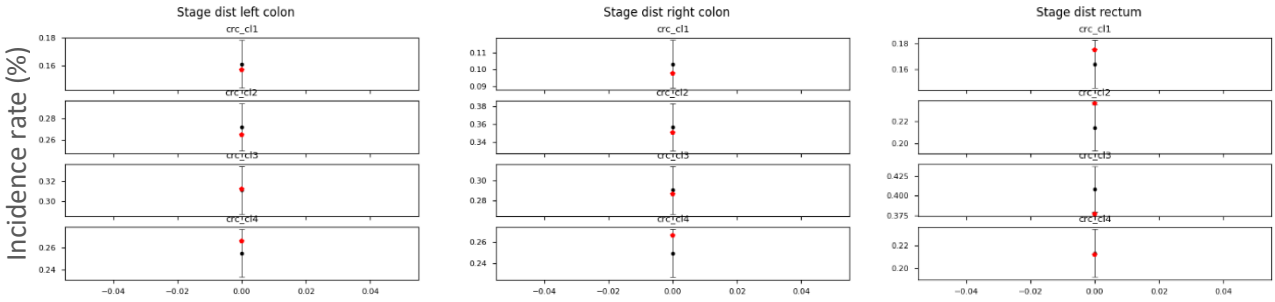


Figure 4-9. Calibrated model predictions of CRC incidence by stage and location vs observed incidence by stage and location in 2007-2011 for left colon, right colon and rectum in males. Red dots represent predicted rate by the model whereas the black dot and the whiskers represent mean and 95% CI of the observed values. Crc_cl1, crc_cl2, crc_cl3 and crc_cl4 indicate the 4 stages of CRC. Note: The scales of Y-axis are different across the figures.

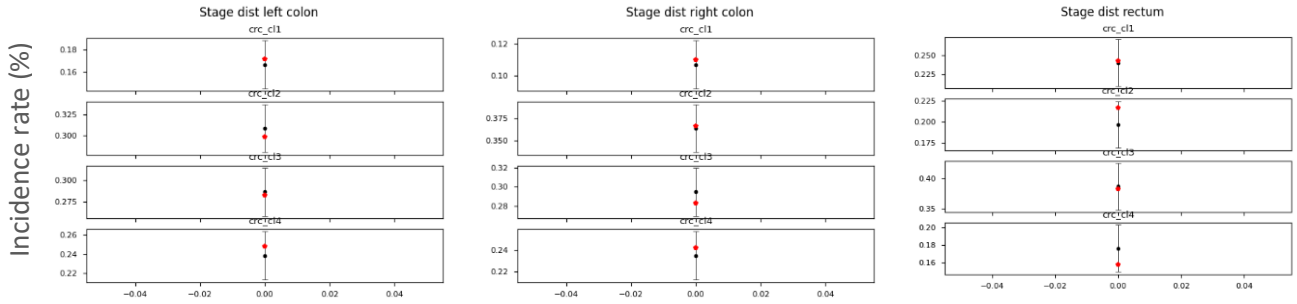


Figure 4-10. Calibrated model predictions of CRC incidence by stage and location vs observed incidence by stage and location vs observed incidence by stage and location in 2007-2011 for left colon, right colon and rectum in females. Red dots represent predicted rate by the model whereas the black dot and the whiskers represent mean and 95% CI of the observed values. Crc_cl1, crc_cl2, crc_cl3 and crc_cl4 indicate the 4 stages of CRC. Note: The scales of Y-axis are different across the figures.

4.3.2 Screening simulation results

4.3.2.1 Comparison to observed data

We compared our model estimates of colonoscopy capacity requirements with the reported colonoscopy volume in the four rounds of the NBSP [50, 96-98] (Table 4-5). The values are jointly reported for the years 2016 and 2017, 2018 and 2019, and 2020 and 2021 in the NBSP reports. It is important to note the reporting period of 2020 to 2021 was affected by the COVID-19 pandemic and screening invitations were suspended for a few months [96].

The eligible population between our models and those reported by the NBSP are not expected to match as our definition of eligible population is based on a crude age-based definition while the definition of the NBSP is not clear. The total population eligible for screening in our model exceeds the number defined as eligible by the NBSP. We simulated the population projection of the Central Statistics Office (CSO) and considered those in the age group 60-68 years alive at the time of screening implementation as the eligible population. Similarly, the population screened is lower in our models except for the NSBP reports of the years 2013 and 2021. The FIT positivity rates generated in our model were lower in the first and the second years of implementation compared to the NBSP's FIT positivity rate. However, the FIT positivity rate was comparable in the following years.

The primary outcome of note from Table 4-5 is the comparison of the observed number of triage and surveillance colonoscopies. Our model estimates comparable volumes from 2015 onwards until the period disrupted by COVID-19.

Table 4-5. Comparison of model estimates with observed data

	2013		**2014**		**2015**		**1st Jan 2016, to 31st Dec 2017**		**1st Jan 2018 to 31st Dec 2019**		**1st Jan 2020 to 31st Dec 2021**	
	Reported data	**Model estimates**	**Reported data**	**Model estimates**	**Reported data**	**Model estimates**	**Reported data**	**Model estimates**	**Reported data**	**Model estimates**	**Reported data**	**Model estimates**
Total eligible	59,694	223,570	205,899	227,060	223,045	231,880	546,767	468,740	534,926	480,450	299,898	494,040
Population screened	27,164	77,650	87,595	79,230	92,494	80,680	239,682	162,500	249,112	166,530	154,472	170,420
FIT positivity rate	8.00%	2.67%	5.00%	2.01%	4.10%	3.24%	3.60%	3.50%	3.30%	4.03%	3.40%	4.27%
Triage colonoscopy	**1,703**	**2,070**	**3,438**	**1,590**	**2,921**	**2,610**	**6,523**	**5,680**	**5,826**	**6,710**	**3,878**	**7,270**
Surveillance colonoscopy				270	1353*	360	1,702	1,870	2,817	1,900	3,233	2,320

*For the period of 2012-2015

4.3.2.2 Colonoscopy requirement for base-case

Our model predicted that for the base case on average 315,612 individuals will be invited for a FIT test from 2025 to 2034. Of the total invited, on average 108,960 individuals will participate annually in the screening programme. On average 32 colonoscopies per 1000 will be required for screening and surveillance activities for the coming decade. The total volume ranged from 8,690 to 11,780 colonoscopies in the projected period. Further, additional colonoscopies ranging from 3,280 to 4,440 colonoscopies will be required for clinical cases (Table 4-6). The number of clinical cases rises primarily because the simulated population is not a complete population of overlapping annual birth cohorts from birth to death, but is the population aged 36 to 80 in the year 2025 followed for ten years.

Table 4-6. Total colonoscopy required for symptomatic, screening and surveillance activities for base case estimated by the model

Year	Clinical cases	Triage	Surveillance	Total for triage and surveillance	Total including clinical cases
2025	3,280	3,610	1,800	5,410	8,690
2026	3,640	4,220	1,320	5,540	9,180
2027	3,650	3,720	1,450	5,170	8,820
2028	3,940	4,430	1,490	5,920	9,860
2029	4,150	3,950	1,570	5,520	9,670
2030	4,070	4,630	1,870	6,500	10,570
2031	4,440	3,990	1,540	5,530	9,970
2032	4,170	5,460	1,580	7,040	11,210
2033	4,330	4,170	1,890	6,060	10,390
2034	4,170	5,810	1,800	7,610	11,780

4.3.2.3 Colonoscopy requirement for various screening scenarios

Figure 4-11 shows the estimated colonoscopy requirement under various screening scenarios from 2013 to 2034. Detailed numerical estimates are provided in Appendix 9. In our model, we introduced a policy change from 2025. As evident from the figure, the demand for colonoscopies increases with the intensification of the screening strategy. The colonoscopy volume considerably increases when the screening interval is reduced from biennial to annual. There is roughly a doubling of the requirement between Scenario 1 compared to Scenario 3 and Scenario 2 compared to Scenario 8. Similarly, the colonoscopy volume requirement increases with the use of more sensitive FIT cut-offs (Scenario 4, 8 and 6). The highest number of colonoscopies required was for the strategy covering the age group 45-80 years with an annual screening interval using a FIT cut-off threshold of 50 Hb/ml (Scenario 5).

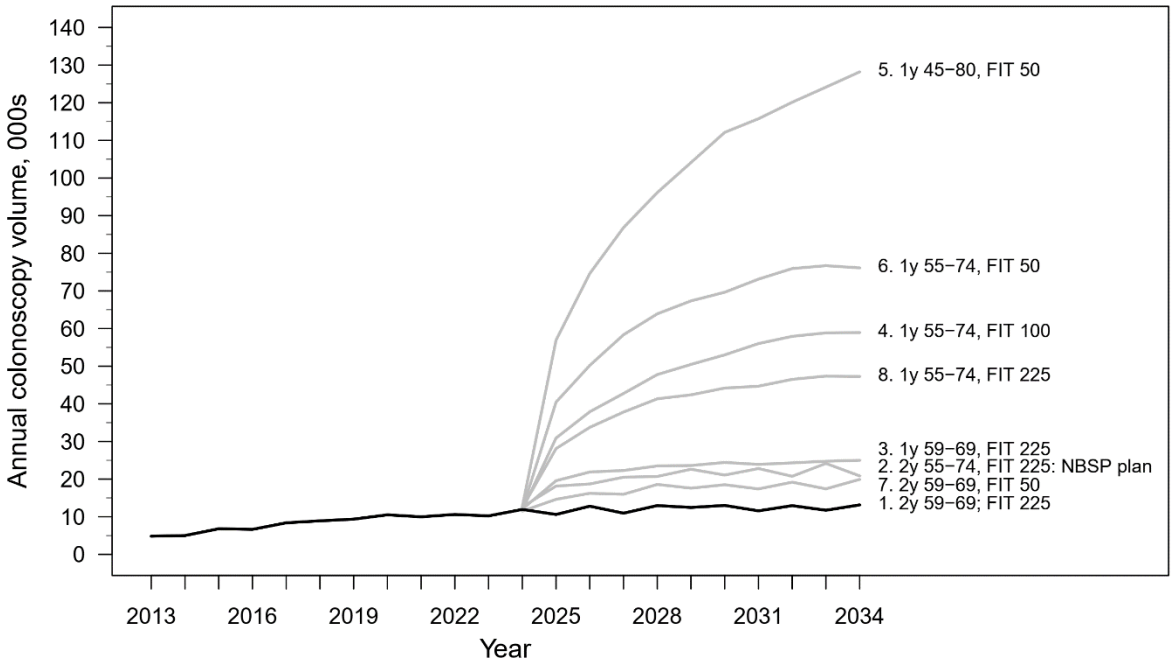


Figure 4-11. Total colonoscopy estimated from the model for symptomatic, screening and surveillance activities for various screening scenarios.

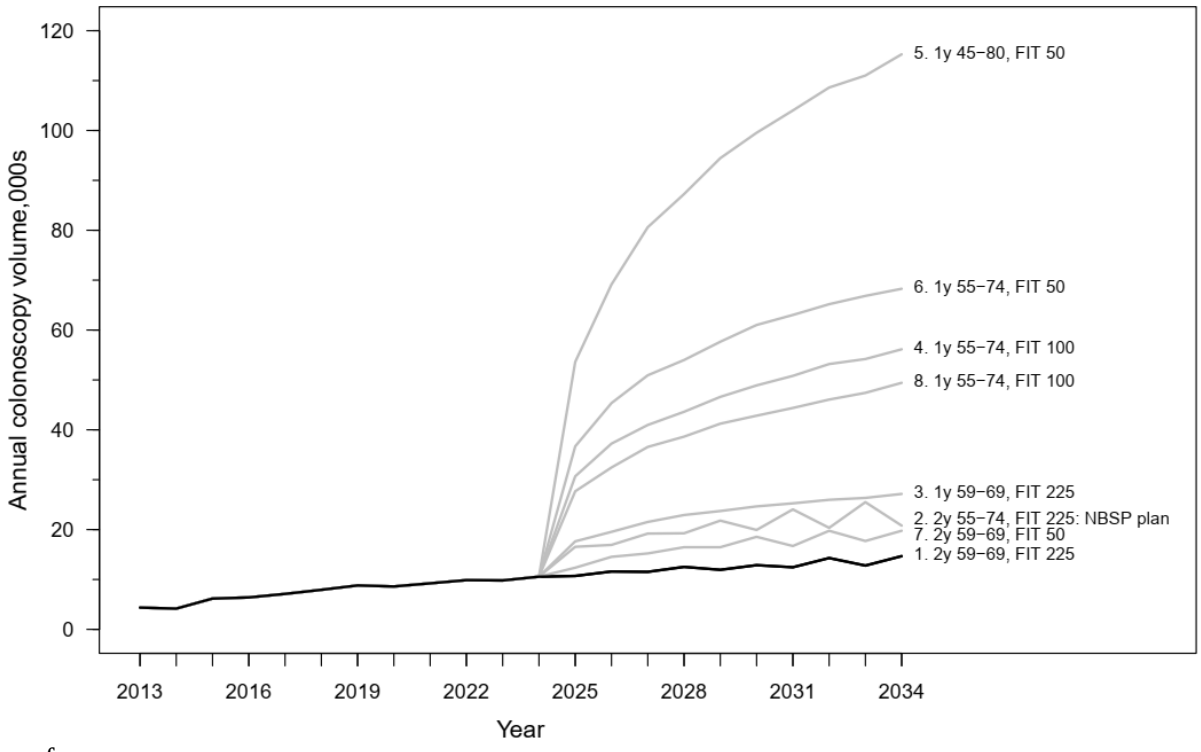
Screening scenarios: 1. Biennial screening of population aged 59 to 69 years using a FIT cut-off threshold of 225 ng Hb/mL, 2. Biennial screening of population aged 55 to 74 years using a FIT cut-off threshold of 225 ng Hb/mL (which id the NBSP extension plan), 3. Annual screening of population aged 59 to 69 years using a FIT cut-off threshold of 225 ng Hb/mL, 4. Annual screening of population aged 55 to 74 years using a FIT cut-off threshold of 100 ng Hb/mL,5. Annual screening of population aged 45 to 80 years using a FIT cut-off threshold of 50 ng Hb/mL,6. Annual screening of population aged 55 to 74 years using a FIT cut-off threshold of 50 ng Hb/mL,7. Biennial screening of population aged 59 to 69 years using a FIT cut-off threshold of 50 ng Hb/mL, 8. Annual screening of population aged 55 to74 years using a FIT cut-off threshold of 225 ng Hb/mL

For scenarios with biennial screening intervals (1, 2, and 7), the fluctuations in annual volume requirements are artifacts of the model due to the policy change of dropping the screening start age from 60 to 59 years. This occurs as there are then two consecutive cohorts receiving screening in the same years rather than one following the other. In actual implementation, this will likely not be observed or be very much attenuated by actual variation in screening participation.

4.3.2.4 Sensitivity analyses

In the sensitivity analysis, we varied the test performances based on sex, incidence rate and the adherence density assumptions.

Figure 4-12 presents the total colonoscopy estimates of various screening scenarios under the sex specific FIT test and colonoscopy sensitivity and specificity for the period of 2025 to 2034. The estimates are comparable with the base case analysis scenarios using aggregated tests



performance.

Figure 4-12. Total colonoscopy estimates for various scenarios with sex-specific test performances. Screening scenarios: 1. Biennial screening of population aged 59 to 69 years using a FIT cut-off threshold of 225 ng Hb/mL, 2. Biennial screening of population aged 55 to 74 years using a FIT cut-off threshold of 225 ng Hb/ml (which id the NBSP extension plan), 3. Annual screening of population aged 59 to 69 years using a FIT cut-off threshold of 225 ng Hb/mL, 4. Annual screening of population aged 55 to 74 years using a FIT cut-off threshold of 100 ng Hb/mL 5. Annual screening of population aged 45 to 80 years using a FIT cut-off threshold of 50 ng Hb/ml,6.

Annual screening of population aged 55 to 74 years using a FIT cut-off threshold of 50 ng Hb/mL,7. Biennial screening of population aged 59 to 69 years using a FIT cut-off threshold of 50 ng Hb/mL, 8. Annual screening of population aged 55 to74 years using a FIT cut-off threshold of 225 ng Hb/mL

Figure 4-13 presents the total colonoscopy estimates of various screening scenarios using low incidence and high incidence assumption for the period of 2025-2034. The low incidence was assumed to be 10% lower than as estimated by the model and the high incidence was assumed to be 10% higher than as estimated by the model. As expected, the estimates are higher for the high incidence assumption compared to the lower incidence assumptions. For example, the current screening strategy yields 9,140 to 12,450 annual colonoscopies from 2025- 2034 under low incidence assumption compared to 7520 to 10,340 annual colonoscopies under high incidence assumption.

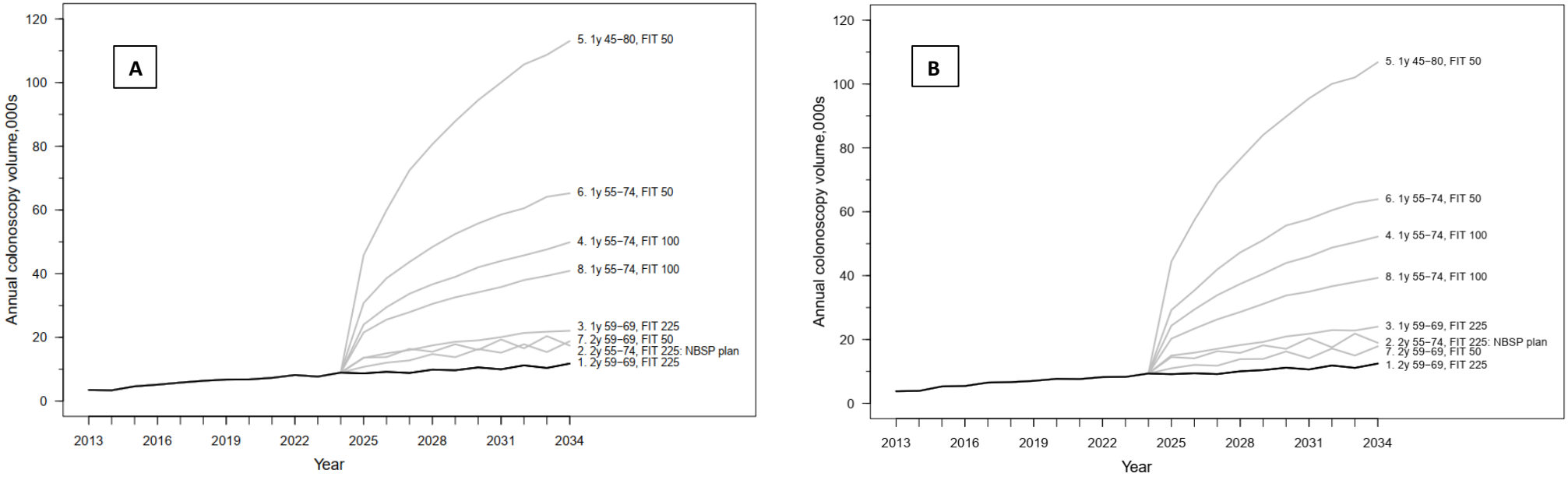


Figure 4-13. Total colonoscopy estimates for various scenarios with low incidence (A) and high incidence (B).

Screening scenarios: 1. Biennial screening of population aged 59 to 69 years using a FIT cut-off threshold of 225 Hb/ml, 2. Biennial screening of population aged 55 to 74 years using a FIT cut-off threshold of 225 ng Hb/mL (which is the NBSP extension plan), 3. Annual screening of population aged 59 to 69 years using a FIT cut-off threshold of 225 Hb/ml, 4. Annual screening of population aged 55 to 74 years using a FIT cut-off threshold of 100 ng Hb/mL,5. Annual screening of population aged 45 to 80 years using a FIT cut-off threshold of 50 ng

Hb/mL,6. Annual screening of population aged 55 to 74 years using a FIT cut-off threshold of 50 ng Hb/mL,7. Biennial screening of population aged 59 to 69 years using a FIT cut-off threshold of 50 ng Hb/mL, 8. Annual screening of population aged 55 to74 years using a FIT cut-off threshold of 225 ng Hb/mL.

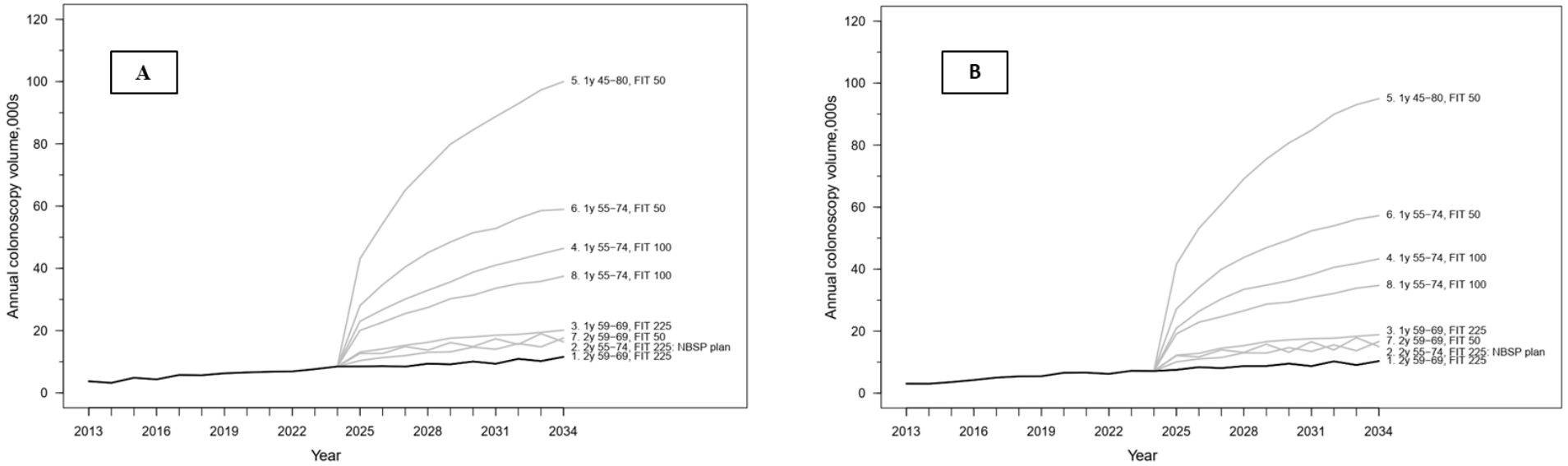


Figure 4- 14 Total colonoscopy estimates for various scenarios with high density (A) and low density (B) adherence assumptions.

Screening scenarios: 1. Biennial screening of population aged 59 to 69 years using a FIT cut-off threshold of 225 Hb/ml, 2. Biennial screening of population aged 55 to 74 years using a FIT cut-off threshold of 225 ng Hb/mL (which id the NBSP extension plan), 3. Annual screening of population aged 59 to 69 years using a FIT cut-off threshold of 225 ng Hb/mL, 4. Annual screening of population aged 55 to 74 years using a FIT cut-off threshold of 100 ng Hb/mL,5. Annual screening of population aged 45 to 80 years using a FIT cut-off threshold of 50 ng Hb/mL,6. Annual screening of population aged 55 to 74 years using a FIT cut-off threshold of 50 ng Hb/mL,7. Biennial screening of population aged 59 to 69 years using a FIT cut-off threshold of 50 ng Hb/mL, 8. Annual screening of population aged 55 to74 years using a FIT cut-off threshold of 225 ng Hb/mL.

Figure 4-14 presents the total colonoscopy estimates of various screening scenarios using low density and high-density assumption for the period of 2025-2034. Under the low-density assumption, the total adherence was distributed across the population and under the high-density assumption the total adherence was concentrated in one section of the population. The estimates are higher for the high-density assumption compared to the low-density

assumptions. For example, the current screening scenario yields 7,520 to 10,340 annual colonoscopies from 2025- 2034 under low density assumption compared to annual 8,430 to 11,560 colonoscopies under high density assumption.

4.3.2.5 Colonoscopy cost implications

We calculated the cost implications of current screening policy over the coming decade using the cost estimated from our micro-costing study and the current ABF rate in Ireland. As presented in the results section of the micro-costing study, we disaggregated the colonoscopy cost based on the intervention. The cost for colonoscopy was €277 without any additional intervention and €825 with polypectomy and biopsy. In 2023, the HSE's activity-based funding price for colonoscopy was €994. Table 4-7 presents the annual cost of colonoscopy for various scenarios using the cost from our micro-costing study and table 4-8 presents the annual cost of colonoscopy for various scenarios using the HSE's activity-based funding price. The comparison of the annual total colonoscopy costs between the HSE's activity-based funding and the micro-costing study reveals a consistent pattern of higher costs associated with the HSE's funding approach across all screening strategies. The percentage differences vary across different scenarios and years. The cost difference between micro costing-based estimates and ABF-based estimates for the current screening scenario (biennial screening for individuals aged 59-69 with a threshold of 225 ng Hb/mL) was approximately 30% across all years from 2025 to 2034. Since the HSE's unit price for colonoscopy is higher than our estimates and does not account for whether additional interventions are required, the total annual cost implications are greater when using the HSE's pricing.

Table 4-7 Annual cost of total colonoscopy for screening and surveillance activities based on micro-costing study

Strategy (Age group in years, interval, FIT cut-off ng Hb/mL)	**Annual total cost of colonoscopy (Euro)**									
	2025	**2026**	**2027**	**2028**	**2029**	**2030**	**2031**	**2032**	**2033**	**2034**
Biennial 59-69 at 225	4,160,829	4,207,785	4,006,708	4,477,377	4,213,204	5,037,945	4,248,847	5,357,322	4,669,554	5,871,289
Biennial 55-74 at 225	7,931,825	8,032,799	10,018,153	9,082,946	10,790,934	9,533,817	11,778,162	9,786,676	12,737,580	10,394,496
Annual 59-69 at 225	7,955,917	8,912,625	9,624,960	10,565,232	11,294,121	11,813,271	12,393,637	13,622,648	13,782,367	14,147,811
Annual 55-74 at 100	15,512,585	19,881,256	22,939,622	25,262,492	27,129,013	29,398,221	30,877,204	32,641,683	33,759,237	35,705,290
Annual 45-80 at 50	28,658,896	40,318,503	50,162,678	56,763,491	62,806,209	67,953,910	72,410,540	76,753,358	79,531,985	82,921,676
Annual 55-74 at 50	19,414,815	25,469,380	29,785,557	33,261,090	36,332,827	39,224,512	41,053,926	43,279,226	45,810,253	46,900,631
Biennial 59-69 at 50	5,186,012	5,994,553	6,643,079	7,702,541	7,094,010	8,912,169	7,889,061	9,982,114	8,133,673	10,826,001
Annual 55-74 at 100	14,157,660	17,291,840	19,215,978	20,987,241	22,636,426	23,876,810	25,017,744	26,852,221	27,962,458	29,021,682

Table 4- 8 Annual cost of total colonoscopy for screening and surveillance activities based on the HSE's activity-based funding

Strategy (Age group in years, interval, FIT cut-off ng Hb/mL)	**Annual total cost of colonoscopy (Euro)**									
	2025	**2026**	**2027**	**2028**	**2029**	**2030**	**2031**	**2032**	**2033**	**2034**
Biennial 59-69 at 225	5,377,540	5,506,760	5,138,980	5,884,480	5,486,880	6,461,000	5,496,820	6,997,760	6,023,640	7,564,340
Biennial 55-74 at 225	10,476,760	10,347,540	12,852,420	11,580,100	13,85,6360	12,116,860	15,118,740	12,395,180	16,241,960	13,200,320
Annual 59-69 at 225	10,287,900	11,421,060	12,365,360	13,498,520	14,482,580	14,949,760	15,735,020	17,235,960	17,514,280	17,882,060
Annual 55-74 at 100	20,814,360	26,072,620	30,128,140	32,821,880	34,978,860	38,050,320	39,779,880	41,708,240	43,497,440	45,684,240
Annual 45-80 at 50	42,751,940	56,697,760	69,083,000	76,925,660	84,102,340	90,622,980	95,980,640	101,755,780	104,787,480	108,793,300
Annual 55-74 at 50	27,663,020	35,137,900	40,247,060	44,561,020	48,507,200	51,787,400	54,361,860	56,489,020	60,087,300	61,031,600
Biennial 59-69 at 50	7,425,180	8,478,820	9,154,740	10,755,080	9,711,380	12,186,440	10,834,600	13,627,740	11,102,980	14,591,920
Annual 55-74 at 100	18,428,760	22,186,080	24,372,880	26,738,600	28,587,440	30,227,540	31,589,320	34,0246,20	35,197,540	36,718,360

4.4 DISCUSSION

We estimated the required colonoscopy capacity for Ireland's current CRC screening programme and a series of 7 policy alternatives. The estimates are from model constructed for the Irish situation and uses natural history estimates of CRC from a previous model that was recalibrated to age and sex specific incidence in Ireland.

Recalibration results and comparison recalibration with other studies

The recalibrated model predicted the calibration targets within the 95% CI of the observed values in most cases, with exceptions for certain age groups. Those were older age groups, in which there are smaller numbers of both individuals alive and disease cases. Our screening and surveillance estimates were not affected by this deviance as we only modelled individuals up until the age of 80 years, as this corresponds to the current end age of surveillance colonoscopy.

Gini et al, 2021 [248] developed and validated country-specific MISCAN-Colon model versions for Italy, Slovenia and Finland using the best available evidence for screening effectiveness for the respective countries. The models predicted CRC mortality within 95% CI of the trial results. Similarly, Buskermolen 2018 [247] validated MISCAN-Colon model using the Norwegian Colorectal Cancer Prevention (NORCCAP) trial, a randomized controlled trial that examined the effectiveness of once-only flexible sigmoidoscopy (FS) screening and found that the model predicted the hazard ratio (HR) of overall CRC incidence within the limits of the 95% confidence intervals of the trial results. Accordingly, this provides confidence that the natural history model we have used is appropriate and that our recalibration is consistent with other recalibrations of MISCAN-Colon model for other specific-country settings.

Colonoscopy demand

Our model estimates do not match the first implementation period (1st January 2012-31st December 2015) and the latest reporting period (1st January 2020 to 31st December 2021 inclusive) well. However, our estimates are fairly close to the reported screening and surveillance

colonoscopy volume for the 1st of January 2016 - 1st of December 2019 period. Compared to the reported data from the early period of screening implementation and the period affected by COVID-19, our estimates are higher for screening colonoscopies and lower for surveillance colonoscopies. The direct comparison with the NBSP's data is challenging due to several factors. First, the initial years of programme implementation could not be expected to be smooth. Additionally, the period affected by COVID-19 resulted in the suspension of routine screening for months. So, the discrepancy between the reported data and model estimates during these periods is understandable. Furthermore, interpreting the reported NBSP eligibility and participation numbers is difficult due to the variability in data. The reported participation numbers fluctuate substantially from year to year.

In our model we assumed no association between individuals' risk and screening behaviour. Studies have suggested individuals with modifiable risk factors participate less in the screening programme [268]. It is likely that participants in the bowel screen programme are at lower risk of CRC than those who do not participate. As a result, the resulting colonoscopy volume from the BowelScreen programme might be lower compared to our model estimates. Our parameter for the participation rate in surveillance colonoscopy is based on expert clinical opinion as it is not reported by the National Bowel Screening Programme. It is possible that our parameter is somewhat low, leading to an underestimation of surveillance volumes. Additionally, the last reporting period with National Bowel Screening Programme's latest reports for 1st January 2020 to 31st December 2021 inclusive was affected by COVID 19 and the invitation was suspended for a few months resulting in lower participation and colonoscopy volume [96].

Regarding the alternative policy scenarios, our model estimated a substantial increase in colonoscopy demand. The FIT cut-off level appears to have the major impact on this demand. For the same age group with the same screening interval, lowering of the FIT cut-off led to a significant increase in demand. For the NBSP's expansion plan to cover individuals aged 55–74-years, the required colonoscopy was almost two times higher compared to the current policy. Moreover, the strategy identified as optimally cost-effective in the Irish context i.e., screening the

45-80 years age group annually at a FIT cut-off level of 50ng Hb/mL resulted in the highest colonoscopy demand. Implementing this strategy would necessitate almost an 8.5-fold increase in the colonoscopy volume compared to the current screening strategy. If policy makers plan to gradually transition to this optimal policy, they could start by lowering the FIT cut-off. Unlike changes in screening intervals and age ranges, FIT cut-off is a less visible policy change to the public. This may offer an advantage of being able to adjust the programme without potentially confusing the eligible screening population regarding programme changes. This is likely to be of practical appeal, as any potential confusion of the screening population could bring understandable fears to programme managers of reduced screening participation.

Comparison of findings on colonoscopy volume with other studies

Our model predicted comparable colonoscopy volume requirements to a resource modelling study conducted in an Irish setting conducted by Sharp et al [92]. The comparisons are hampered by the fact that they simulated the initially planned a screening age range 55-74 years as initially planned by the NBSP, but our model results are for a base case of 60-69 years. That study predicted 11,095 diagnostic colonoscopies for screening 55-74 years old individuals biennially in the first year of programme implementation. While our model predicted 5,740 diagnostic colonoscopies in 2013 screening in 60–69-year-olds. Further, Sharp et al predicted demand would rise to 12,414 in the tenth year of programme implementation which compares to 8,060 in our model. Our model prediction is lower because we simulated smaller age range identical to the actual programme implementation, used lower adherence rate and higher FIT cut off. In case of surveillance colonoscopy, Sharp et al predicted 2,406 surveillance colonoscopies in the tenth year of programme implementation. Our model predicted 1,590 surveillance colonoscopies in 2022. The surveillance assumptions used was similar to ours i.e., one yearly surveillance of high-risk group and three yearly surveillances for intermediate risk group stopping at age 80 years. Further, comparing our results with another study that predicted colonoscopy volume for Ireland was challenging [189]. They only reported the overall lifetime colonoscopies required for a single cohort without indicating when they would need them. The study predicted 464 colonoscopies per

1000 for screening 60 to 70 years old biennially with FIT at the positivity threshold of 200 ng Hb/mL. Our study predicted on average 256 colonoscopy per 1000. An important difference between the two studies is that McFerran et al [189] assume 100% participation, we assume much lower rates in accordance with what is observed. This likely explains our lower estimate, at least in part.

Sufficient volume of colonoscopy

Many countries face challenges meeting the high demand for colonoscopy procedures arising from the screening and surveillance activities in national population-based screening programmes [125, 140, 159, 195]. In Ireland, the HTA of the population-based CRC screening programme recommended the biennial screening among the age group 55-74 years as optimal. However, due to colonoscopy capacity, the screening programme began with 60-69 years age group. The government aims to expand the age group to the recommended age group of 55-74 years, recently reducing the start age to 59 years. Despite the government's plan to expand the capacity as needed, the colonoscopy waiting list remains high [260].

A 2008 report on the planning and implementation of colonoscopy services recommended the establishment of four dedicated screening centres each equipped with two endoscopy suites without impacting symptomatic services. The same report also proposed an alternative of eight-colonoscopy centre model based on 50% utilisation by the screening service and a 50% utilisation for symptomatic purposes [90]. However, neither proposal materialised. Ireland's current screening colonoscopy service operate within the symptomatic services. Advocacy group have suggested that the funding has not been adequate to implement the strategy. The National Cancer Control Strategy published in 2017 [269] has only been able to receive proper funding in less than one third of the time in the seven budgets announced since then. Consequently, the National Cancer Control Programme has not been able to meet its full objectives [270].

Long waiting time for colonoscopy can have significant implications in the clinical and emotional wellbeing of patients. Several studies have reported the implications of waiting time and clinical

outcomes in patients screened and tested positive for FIT. Forbes et al [271] conducted a systematic review in 2020 to elucidate the association between time to colonoscopy after positive FIT test and CRC outcomes. They included eight studies with five studies reporting CRC based outcomes. All five studies [272-276] demonstrated that the delays to colonoscopy led to significantly higher incidence of CRC and more advanced stage at diagnosis.

Initiatives to meet the colonoscopy demand

Expanding colonoscopy capacity in a health system is a time intensive process. It involves advanced post graduate medical training of up to 3 years [277]. Further accreditation of the colonoscopy site is needed for quality assurance and safety which requires a minimum number of procedures to be conducted at the site [50]. These facts also highlight the importance of resource modelling for long term planning.

The availability of a qualified workforce is a critical consideration for the expansion of the service. The current physician workforce is insufficient to meet screening needs [189]. Expanding colonoscopy service especially for the screening services through advanced nurse practitioner is considered as the alternative model of care and is being implemented in the UK, US and Australia [278-280]. In Ireland, this model of care has been implemented at St James Hospital, Dublin. However, current literature on the performance of nurse endoscopist is limited and existing studies suffer from methodological design flaws [281, 282]. High quality studies are needed to determine if this approach yields comparable positive outcomes in terms of medical results, patient contentment, and expenses when compared to gastroenterologists. A systematic review published in 2015 found that endoscopic services provided by nurse endoscopists are not more cost effective than the standard service models due to increased need for subsequent endoscopies, specialist follow-ups and primary care consultations [283].

Discrepancies in surveillance guidelines

Studies have reported discrepancies in the surveillance guidelines modelled. One major issue is whether patients with normal colonoscopies should be returned to screening programme or

discharged from the programme. Dutch guideline recommends returning to the screening programme in 10 years only [265]. Current NBSP practice is to return individuals who are negative on colonoscopy to the national FIT based screening immediately. It seems that both FIT and triage colonoscopy services could be used more efficiently if individuals with negative colonoscopies did not return to screening immediately.

Optimising available colonoscopy resource

With the existing constraint, the programme is unlikely to expand coverage without a substantial colonoscopy capacity development. Thus, the potential for improved effectiveness and cost-effectiveness within available constraint needs to be explored. Studies have suggested the optimal strategies such as expanding the screening age interval and reducing FIT cut off [162, 189], lowering the start age among me [162] and increasing the FIT cut off [160]. At the same time, it is also important to make the efficient use of available capacity. The acceptance rate for index colonoscopy following a FIT positive result was low in the NBSP. Further, the number of additional planned colonoscopy procedures reported in the NBSP reports was high. One important reason for additional planned colonoscopy procedure, is due to inadequate bowel preparation [97, 98]. These repeat colonoscopies are a burden to both patients and healthcare services. A systematic review reported in 2019 that included studies from Italy, Spain and the UK suggested that reducing the risk of inadequate bowel cleansing can provide financial benefits to healthcare systems [284].

Additional demand from high-risk group surveillance

Study 3 only considers colonoscopy demand within an average risk population. Colonoscopy service expansion plan should also consider the volume arising high-risk group surveillance. Ireland has recently launched the Hereditary Cancer Model of Care (HCMC) for the surveillance of high-risk groups [285]. Studies have suggested for more intensive screening programmes for high-risk populations, such as people with family history of CRC or people with gene mutation associated with HNPCC and FAP [286, 287]. It is likely that such surveillance measures will put

further pressure on the services in terms of colonoscopy demand. Quantification of such demand is also essential for service planning.

Strengths and limitations

There are a very few resource modelling studies that estimated the colonoscopy demand for CRC screening and surveillance in population-based screening programme. Our study addresses this gap in the programme planning literature on colonoscopy capacity. Given that model structures, assumptions, parameters and the policy context vary by setting, country-specific resource modelling is most useful for service planning. We used a validated MISCAN-Colon model to estimate the colonoscopy demand in Ireland, adapting it to the Irish population structure and incidence. We estimated the required volume for the current screening strategy, planned screening strategy and the optimal cost-effective strategy in Irish context and a few other policy alternatives. Further, we used realistic adherence rates providing close approximations of actual demand. Additionally, we employed a multi-cohort approach which is closer to the actual implementation. The previous resource modelling study in an Irish setting was conducted a decade ago and did not utilize various FIT cut-off levels. Our sensitivity analysis indicates a significant impact of the FIT cut-off on colonoscopy demand. Another Irish study [189], a CEA, provided lifetime colonoscopy demand without indicating when they would be required under a perfect adherence assumption. Our study is more comprehensive that this prior work in the Irish context and offers clearer guidance to policy makers in understanding colonoscopy demand for alternative policy scenarios.

Regarding our study limitations, the model structure of MISCAN-Colon model does not incorporate serrated neoplasia pathways for CRC [250]. Thus, the model estimates might have underestimated the prevalence of CRC in the population. Our estimates might be different if we have used different underlying natural history model. Validation of our model is limited. Out of four reporting periods from the NBSP that are available for comparison, one is affected by COVID 19 pandemic, and another was the initial years of programme implementation. This time

period might not truly reflect the screening behaviours of population. The latest publication from the NBSP covers up to the end of 2021 only. It would be useful to repeat the analysis once additional post-COVID data becomes available as the NBSP publishes data. However, the lag in publishing means that this will not be possible for a few years. Further, the NBSP is not very clear in its description of eligible population, or the absolute numbers of individuals screened, therefore it might be a mistake to place too much emphasis on the comparisons of absolute numbers of screens, or colonoscopies. The relative number of FIT positives might be more relevant to compare. Our model employs a closed population with no international migration. meaning the demographic structure may be less representative of reality in the medium to long term and may overestimate the eligible population.

In our sensitivity analysis we did not vary the all the parameters that could potentially impact the colonoscopy estimates. We only varied the adherence pattern not the overall adherence rate. Additionally, we did not assess the impact of varying the uptake of diagnostic and surveillance colonoscopy and uptake and the surveillance guidelines. Additionally, we used a proxy of 40 µg Hb/g for 200 ng Hb/mL for the comparison of 225 ng Hb/mL for the test performances which likely slightly overestimate the test sensitivity and underestimate the test specificity.

CHAPTER 5 GENERAL DISCUSSION

The aim of this thesis was to answer various policy related questions on CRC screening. This was achieved by conducting three distinct studies. In this section we discuss how these studies complemented each other and the general observations from these studies. The last paragraph of this section also discusses general findings from another systematic review that I contributed to as a co-author during my doctoral research.

Population-based CRC screening programmes contribute to reducing the burden of CRC [14]. Policy makers need various information for the successful implementation of such programmes such as the optimal policy to implement, knowing what resource requirements this will impose and understanding the cost implications of optimal care. Evidence on the optimality of the screening policy is generated from CEAs; cost estimates to be used within CEAs are generated through costing studies; and resource requirements can be obtained from resource modelling.

The cost-effectiveness of CRC screening has been extensively researched especially in Europe, the US and Australia. However, CEAs do not typically include detailed results relevant to the implementation in their analysis. Comparatively few CEAs report the colonoscopy volume generated from screening and surveillance activities. Typically, CEAs simulate a single cohort of population eligible for screening and provide aggregated lifetime outputs. Further these CEAs often do not consider the actual demographic structure of the population and behaviour of screenees. Such results are less helpful for policy makers in planning and implementing screening programmes. Practically, these decision makers need to know when these colonoscopy volumes are generated year wise. Additionally, changes in demand in relation to attendance behaviours and demographic changes are also needed. This information will help them to assess the additional colonoscopy demand under various implementation scenarios and plan for the capacity to meet those. The resource modelling study included in this thesis provides the information tailored to policy makers' need for actual implementation. While we have modelled the Irish case, the study also highlights the need to complement CEAs with resource modelling elsewhere.

One prerequisite for conducting a CEA of CRC screening is the cost of colonoscopy service. Colonoscopy is one of the largest cost contributors of CRC screening programmes. Given the extent of the CEAs of CRC screening the number of studies on cost of colonoscopy are surprisingly low based on our targeted review of the literature. The paucity of micro-costing studies could be attributed to the lack of standardised guidelines on micro-costing methodology with sufficient details. In general, cost measurement appears to have received little attention compared to effect measurements in economic evaluations. In the absence of standardised guidelines, it is important for the costing studies to be as transparent as possible. The micro-costing study included in this thesis addresses this gap in the literature.

The implementation of the optimal cost-effective strategy depends on the colonoscopy capacity in the health system. System planners need to think carefully about colonoscopy capacity, especially if they want to expand to optimal screening. Resource modelling is important even in the case of capacity constraints because such constraints can be addressed by quantifying the need and the gap. However, it may be difficult to rapidly expand the colonoscopy capacity mainly because of time involved in training skilled human resources. In the future, risk-stratified screening could be a way to solve the colonoscopy capacity problem. There is emerging evidence regarding risk-stratified screening based on age, sex, prior screening history, lifestyle and/or genetic information could improve diagnostic performance, clinical outcomes and cost-effectiveness of CRC screening without using significant additional screening resources [288-290]. Thus, the policies that provide optimally cost-effective CRC prevention might not necessarily require universal screening policy and the large associated colonoscopy capacity needs. Instead of universal policy, the screening could be tailored based on individuals' risk to improve selection to colonoscopy to those at higher risk of developing adenomas and cancer [291]. [290]. Irrespective of the potential for risk-stratified screening to moderate colonoscopy capacity requirements, resource modelling will still be beneficial to estimate the key practical benefit of risk- stratified screening compared to universal screening programmes in terms of potential lower volume of colonoscopy demand.

The finding of the systematic review included in this thesis that policy makers might choose a sub-optimal policy for implementation if a broad range of screening strategies are not included in a CEA is a methodological issue. Another systematic review that I contributed to as a co-author during my doctoral research also highlighted this issue. The detail of this systematic review is provided in the appendix 10. That systematic review also highlighted misinterpretation of ICERs in CEAs of CRC screening. These methodological issues might be a result of absence of screening-specific CEA guidelines. While there are many guidelines and checklists for economic evaluation, they are primarily drafted for therapeutic interventions. Thus, it is understandable that the screening-specific issue such as the inclusion of sufficient variation of screening intervals, age ranges and FIT cut-offs are inadequately addressed in those guidelines and checklists. In the absence of guidelines to support the judgement of appropriateness of the strategy choice, analysts and policy makers may not comprehend the shortcomings of choosing limited strategy in a CEA. So, it is important for policy makers to consider the strategies analysed in a CEA while interpreting the recommendation of a CEA on the optimal strategy. As mentioned above, it is important to assess the feasibility of implementing the optimal strategy through resource modelling and its affordability through cost estimation and calculating the cost implications.

Policy implications

There are following policy implications based on the results of this thesis.

Our systematic review found that annual screening interval to be optimally cost-effective strategy among model-based CEAs that have included the annual strategy in their analysis. The implication of this finding is that the policy makers need to consider what has been analysed in a CEA while interpreting its results and recommendations. This also implies that policy makers need to consider intensifying the current biennial interval screening strategy to annual interval in order to optimise the gain from the CRC screening.

Our micro-costing study estimated the cost of colonoscopy using bottom-up micro-costing methodology which is considered the most precise cost estimate methodology. Policy makers

need to consider this cost in the future CEA of CRC in Ireland. We also observed substantial differences in the cost of colonoscopy based on indication and referral route of colonoscopy. Though this finding needs to be further tested with larger sample sizes, especially for screen-indicated colonoscopies. Currently the HSE reimburses a flat rate for day colonoscopy. It is worthwhile to carefully investigate this policy.

Our resource modelling study estimated substantially higher volumes of colonoscopy required to meet the demand of screening and surveillance activities in Ireland. Policy makers need to strategically plan to meet this demand. Sufficient budget allocation for infrastructure and training endoscopists is needed. The colonoscopy volume varies based on the positivity threshold of the primary test (FIT cut-off), screening interval and the age range covered. As Ireland is planning to expand the age coverage, careful consideration of the result volume of colonoscopy and plan to meet the demand is needed.

Thesis contribution

This thesis has a methodological and practical contribution in the field of CRC screening. Systematic review included in this thesis emphasized the importance of including relevant screening strategies in a CEA of a CRC screening. We found the CEAs which included annual screening strategy in the analysis found them to be optimally cost-effective. Had these studies not included the annual interval in their analysis, their recommendations on the optimal CEA policy would have been sub-optimal. This methodological issue of including sufficient screening strategy in a CEA has not been adequately addressed by previous systematic reviews of CEAs. Our systematic review is a unique contribution to the literature, highlighting the need of including all relevant strategies, particularly the annual interval, in a CEA of CRC screening. This study also contributes to identifying the optimal cost-effective strategy by making the policy makers aware about the need to carefully interpret the CEA results based on the analysis.

Our micro-costing study contributes to the limited literature in the field of colonoscopy cost derived from micro-costing approach. In the Irish context, our study was the first to investigate the cost of colonoscopy applying this methodology. So, the study findings contribute to the

costing of various policy plans including the expansion of the population-based screening in Ireland. The cost estimates also contribute to the future cost -effectiveness analysis in Ireland and in similar settings. The disaggregated results of our study based on the intervention and referral route could be utilised in investigating the current higher HSE's reimbursement rates.
Our resource modelling study contributes to the service planning of colonoscopy in Ireland especially for the screening and surveillance activities for the coming decade based on the yearly colonoscopy estimates. The yearly budget implications for the current and various policy scenarios contributes to the resource allocation. Further, the study also makes the policy makers aware of the large colonoscopy capacity required to implement the planned age expansion of the NBSP as well as the optimal cost-effectiveness policy. The study adheres to the best methodological recommendation for resource modelling including adapting the model to the population specific structure and incidence, using the multi-cohort approach, assessing the uncertainty related to participation density assumptions. Thus, the study could also serve as example for methodological guide in resource modelling for high- risk group.

Recommendations for future research

We recommend the following research:

Our micro-costing study was conducted in one clinical site. We recommend micro-costing studies in other hospitals with various capacity with similar methodology for generalizable results with more certainty. In addition, the number of screen-indicated colonoscopies included in our study was low. This was because screening colonoscopies are conducted within the symptomatic centres and only 3 screening colonoscopes are invited per day. A study with more screen-indicated cases would provide more accurate estimate of the screening colonoscopy cost. Study with large sample size is also needed to understand the estimated cost discrepancies between the colonoscopy based on referral route and intervention.

Study 3 estimated the colonoscopy capacity requirements for Ireland. We recommend a number of possible extensions of this study and other studies required to generate a reliable sets of input

parameters for resource modelling and to understand a colonoscopy capacity need in a system for screening and surveillance activities. A study to understand the association between the individuals' risk and screening behaviour is needed. This will help analysts to use more accurate adherence assumptions in the model. Additionally, a study to measure the service providers' actual compliance with the surveillance guidelines is also needed. Such a study will help estimating volume required for various surveillance uptake scenarios. Further, there has been no study to investigate the test sensitivity and specificity using observed data from the NBSP. Such a study would be highly useful in obtaining the accurate estimates of colonoscopy volume in future.

In terms of further extensions of this work, we suggest cost-effectiveness evaluation of various scenarios modelled in the study. Further, similar resource modelling study to estimate the volume required for surveillance of high-risk population would be required to support the implementation of hereditary model of cancer care envisioned by the National Cancer Control Strategy. Study to optimise the strategies based on the available colonoscopy capacity using a multicohort approach is also needed. We did not vary the surveillance guidelines in our study. The cost-effectiveness of different surveillance guidelines and ensuing colonoscopy volume would be useful.

Further, in terms of capacity planning, a comprehensive survey of the current and potential capacity in the system would be useful. There is no published data on current colonoscopy capacity available in Ireland, either in terms of endoscopy suites or trained staff.

Challenges and points of learning from the thesis

A planned placement at the national bowel screening service in the first year of my doctoral research could not be executed due to the COVID-19 pandemic and associated restrictions. Consequently, we had to rely on the data publicly available from the NBSP's reports only. This posed significant challenges, particularly in understanding how the NBSP defined their data, including the criteria for determining the eligible population for screening in each round.

The infrastructure constraints of our research institute and the size of our research group was another challenge during the PhD. We do not possess a sophisticated disease model required for

the resource simulation and we did not have capacity to conduct the recalibration of a model ourselves. However, I had the benefit of working in collaboration with an expert modelling group from the Erasmus Medical Center who provided access to the MISCAN-Colon model and supported us in recalibrating it to Irish data. That collaboration and the natural history estimates it offered provided the basis for the colonoscopy demand model I constructed.

CHAPTER 6 CONCLUSION

This thesis aimed to answer various policy related questions on CRC screening such as the identification of the optimal CRC screening strategy, the cost of colonoscopy and the number of colonoscopies for symptomatic, screening and surveillance activities.

The thesis concluded that the widely adopted biennial stool-based testing in Europe is likely sub-optimal based on the CEA evidence. Every CEA that examined annual screening found it to be optimally cost-effective. It is the responsibility of modellers to include a wide range of strategies beyond those examined in trials or recommended within guidelines to correctly identify optimal strategies and best inform decision-makers. CRC screening strategies, especially the intervals in FIT based testing should be reconsidered. More CRC-related deaths might be prevented, throughout Europe, if programmes could offer more intensive annual screening. The feasibility of offering such frequent screening depends however on the colonoscopy capacity within each health system.

Further, this thesis provides detailed estimates of the direct costs of conducting a colonoscopy in routine clinical settings from an Irish healthcare perspective with disaggregated costs based on intervention and referral routes using bottom-up micro-costing approach. There are significant differences in the time and cost of colonoscopy procedures-based on whether the intervention was performed. Similarly, the difference in the procedure time and the cost for the screen indicated cases were significantly lower than the other routes. We recommend future studies to examine the factors associated with these cost discrepancies with a larger number of screening colonoscopies in the sample

Additionally, the thesis provides the estimate of colonoscopy volume required in Ireland using a decision analytical model for the ten-year period from 2025 to 2034 inclusive for various screening implementation scenarios. The natural history is drawn from an existing validated model of CRC (MISCAN-Colon model) that was recalibrated for Irish CRC incidence. The estimated volume is higher than the current capacity in the system and could exacerbate the

waiting times for colonoscopy. Further, the planned age expansion needs due consideration for developing additional colonoscopy capacity in the system.

In conclusion, this thesis highlighted the need to consider strategies analysed within a CEA while interpreting its results and concluded annual screening interval to be optimally cost effective based on evidence from CEAs that have compared it with biennial interval. Further the thesis provided an updated precise estimate of colonoscopy cost that could inform future economic evaluations of CRC screening in Ireland and in similar settings and offers insights for private sector reimbursements comparison. Finally, the thesis estimated colonoscopy volume for symptomatic, screening and surveillance cases in Ireland for the next decade utilising a decision analytical model calibrated with Irish incidence data. These estimates are useful in assessing the feasibility of service expansion and resource allocation.

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APPENDICES

Appendix 1 ICD codes for colorectal cancer

ICD-10-CM	Description
C18.0	Malignant neoplasm of cecum
C18.2	Malignant neoplasm of ascending colon
C18.3	Malignant neoplasm of hepatic flexure
C18.4	Malignant neoplasm of transverse colon
C18.5	Malignant neoplasm of splenic flexure
C18.6	Malignant neoplasm of descending colon
C18.7	Malignant neoplasm of sigmoid colon
C18.8	Malignant neoplasm of overlapping sites of colon
C18.9	Malignant neoplasm of colon, unspecified
C19	Malignant neoplasm of rectosigmoid junction
C20	Malignant neoplasm of rectum
C21.8	Malignant neoplasm of overlapping sites of rectum, anus and anal canal
C78.5	Secondary malignant neoplasm of large intestine and rectum
C78.6	Secondary malignant neoplasm of retroperitoneum and peritoneum
D37.4	Neoplasm of uncertain behaviour of colon
D37.5	Neoplasm of uncertain behaviour of rectum

Appendix 2 List of hospitals participating in National Bowel Screening Programme

Fifteen hospitals across Ireland are vital screening service for the national bowel screening programme.

1. Mater Misericordiae University Hospital, University College Dublin, Dublin
2. St. Vincent's University Hospital, University College Dublin, Dublin
3. Connolly University Hospital, Royal College of Surgeons in Ireland University of Medical and Health Science, Dublin
4. St. James University Hospital, Trinity College Dublin, University of Dublin, Dublin
5. Beaumont Hospital, Royal College of Surgeons in Ireland University of Medical and Health Sciences, Dublin
6. Louth County Hospital, Royal College of Surgeons in Ireland University of Medical and Health Science, Louth
7. Ennis Hospital, University of Limerick, Clare
8. Letterkenny University Hospital, Royal College of Surgeons in Ireland University of Medical and Health Science, Donegal
9. Mercy University Hospital, University College Cork, Cork
10. University Hospital Kerry, University College Cork, Kerry
11. Galway University Hospital, National University of Galway, Galway
12. Sligo University Hospital, National University of Galway, Sligo
13. University Hospital Waterford, University College Cork, Waterford
14. Wexford General Hospital, University College Dublin, Wexford
15. Roscommon University Hospital, National University of Galway, Roscommon

Appendix 3 Micro-costing study ethics approval

Dr Jan Leyden

Mater Misericordiae University Hospital
Sisters of Mercy
Eccles Street, Dublin D07 R2WY, Ireland
Ospidéal Ollscoile Mater Misericordiae
Siúracha na Trócaire
Sráid Eccles, Baile Átha Cliath D07 R2WY, Éire
Tel: +353 1 8032000 Web: www.mater.ie

Not for prescription purposes

Dr. Jan Leyden
Consultant Gastroenterologist
Mater Misericordiae University Hospital
Eccles Street Dublin 7

9th March 2023 Institutional Review Board Reference: 1/378/2339

RE: Micro-costing of colonoscopy in Ireland

MMUH DPO email regarding DPIA (11th January 2023)
Standard Application Form (13th January 2023)
Narrative Summary
Research Protocol
Participant Information Leaflet (Version 2, February 2023)
Participant Consent Form (Version 2, Feb 2023)
Insurance Certificate (4th October 2022)
Structured interview questionnaire
Interview Topic Guide

Dear Dr. Leyden,

I acknowledge receipt of your correspondence received 09th March 2023 enclosing points of clarification, Participant Information Leaflet (Version 2, February 2023), Participant Consent Form (Version 2, Feb 2023), Interview Topic Guide and email correspondence with the Finance Department (24th — 27th February 2023) for the above research study to be carried out at the Mater Misericordiae University Hospital (MMUH).

This correspondence has been noted and approval for this research study to proceed at the MMUH is granted.

It is your responsibility to adhere to the approved research protocol and ensure the following:

1. Only Investigators named on the approved IRB application form are involved in the research; 2 All investigators involved with the research only use the approved documents without deviation (unless they have been approved by the IRB).

3. To submit annual reports setting out the progress of the research;
4. To notify the IRB when the research is concluded.

It is your responsibility to comply with your legal obligations under Data Protection Law and the Health Research Regulations. You should consult with the research study site Data Protection Officer on any deta protection issues in particular in relation to the sharing of any personal data outside of the MMUH. Detailed GDPR Guidance for research is available on the HRB website: https://www.hrb.ie/funding/gdpr-guidance-for-researchers/

Yours sincerely

G. Flood

Dr. Georgina Flood

Chairperson
Institutional Review Board

Cc: Ms. Rajani Pokharel, PhD student, Trinity College Dublin

[C0Tfilihnant to Exce;tence'

Chairman: Mr David Begg Vice Chair: Mr
O'Kelty CEO: Mr Aian Sharp
Direct05s: Rod Enscr. Prof CeciEy Kelieher, Dr
May McMenamin.
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Appendix 4 Micro-costing study tools

Appendix 4.1 Structured interview questionnaire for clinical/administrative staff pf gastroenterology department

Micro-costing of Colonoscopy in Ireland
Structured interview questionnaire

The aim of this study is to estimate the cost of colonoscopy for the Health Service Executive. An accurate estimate of the cost for an individual colonoscopy will aid the HSE in resource allocation and service planning of screening programmes. Cost data is also important for economic evaluation studies.

Respondent- Clinical/administrative staff of gastroenterology department

SECTION A COLONOSCOPY PROPORTION

Q.N.	Questions	Response	Notes
1	Total working days per week in the department		
2	Total working hours per day in the department		
3	Average total number of procedures conducted per week in the department		
4	Average total number of colonoscopies conducted per week in the department		
5	Average total polypectomy per week in the department		
6	Percentage of complicated colonoscopy cases per week (on average or approx.) in the department		
7	Total number of polypectomies with biopsy forceps 583		
8	Total number of polypectomies with snare 583		
9	Total number of polypectomies with diathermy		

SECTION B PATIENT PATHWAY

Q.N. 6 Please describe the patient pathway during the colonoscopy procedure. (Example of patient pathway is in the appendix)

Q.N. 7 Are there any cost that the patient pays at the point of service? (If Yes, go to Q.N.8, if No go to section C)

Q.N. 8 What are those cost?

Q.N. 9 Are these reimbursed by the HSE? If so, all or what proportion?

SECTION C STAFF

Q.N. 10 Please provide the following information about staff involved in the colonoscopy procedure.

Staff category	**Number**	**Grade**	**Department**	**Dedicated to the department or shared across departments**	**Working time proportion to the department (if shared across department)**
Admin staff					
Clinical staff					

SECTION D EQUIPMENT

Q.N. 11 Please provide the following information about endoscopic equipment and accessories.

Endoscopic equipment	**Quantity**
Colonoscope	
Video processor and light source	
Monitor	
Dual-scope reprocessing	
Electrosurgical generator	

Endoscopic accessories	
Biopsy forceps	
Biopsy snare	
Cleaning brush long	
Cleaning brush short	
Biopsy valve	
Water bottle	
Electric plate	
Silicon	

(Items are listed as prompts only)

SECTION E CONSUMABLES & MEDICATIONS

Q.N. 12 Please provide the following information about consumables and medications per patient.

Consumables	**Quantity**
Anallergic gloves	
Polhyethilene gloves	
Latex gloves	
Syringe (list according to size)	
Lubricant	
Gauze	
Disposable bed linen	
Medications and pharmacy supply	
Buscopan	
Midazolam	
Pethidine	

(Items are listed as prompts only)

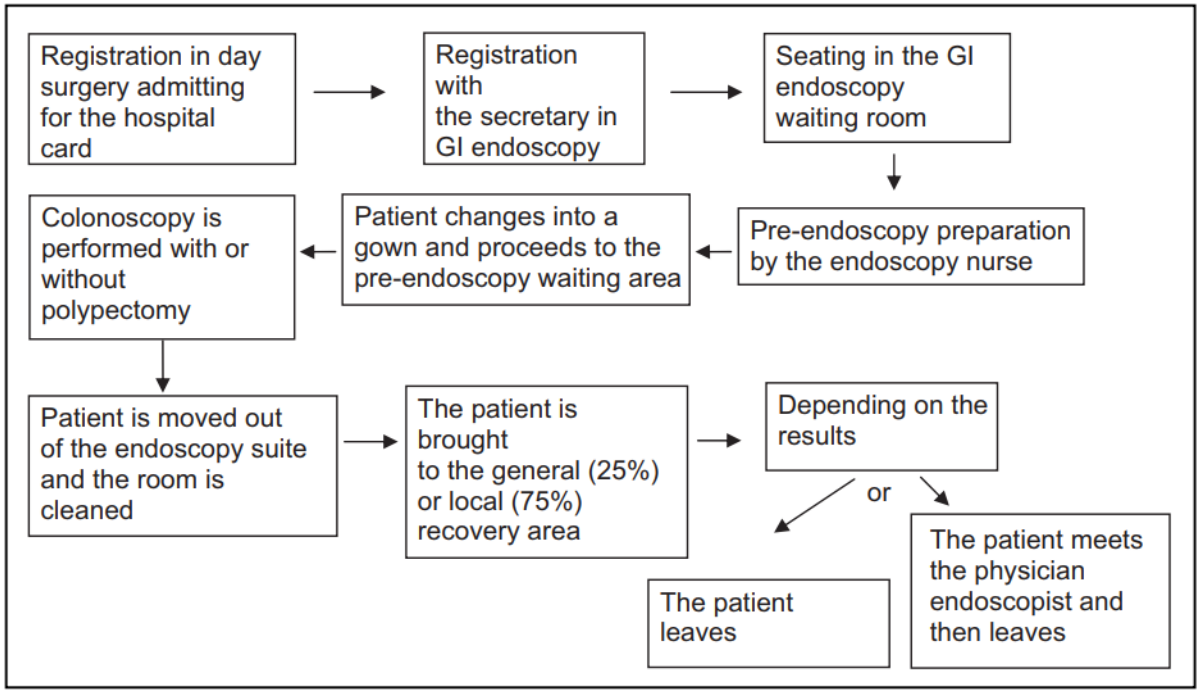
Q.N. 13 On average, what proportion of consumables are wasted?

Q.N. 14 On average, what proportion of medicines are wasted?

Thank you!

Appendix 1

Example of patient pathway



Source: 5. Sharara, N., Adam, V., Crott, R., & Barkun, A. N. (2008). The costs of colonoscopy in a Canadian hospital using a micro-costing approach. Canadian Journal of Gastroenterology, 22(6), 565-570.

Appendix 4.2 Structured Interview Questionnaire (Finance Department)

Micro costing of Colonoscopy in Ireland

Structured interview questionnaire

The aim of this study is to estimate the cost of colonoscopy for the Health Service Executive. An accurate estimate of the cost for an individual colonoscopy will aid the HSE in resource allocation and service planning of screening programmes. Cost data is also important for economic evaluation studies.

Respondent- Finance department
(to be conducted after completion of interviews with clinical and administrative staff of gastroenterology department)

SECTION A COST DURING PATIENT PATHWAY

Q.N.1 Are there any cost incurred by the hospital transferring specific cases? (If yes, go to Q.N.2, if no go to section Q.N.4)

Q.N.2 What is the number of such cases per week/month?

Q.N.3 Do you have an idea of average cost per case?

Q.N. 4 Are there any cost that the patient pays at the point of service? (If yes, go to Q.N.5, if no go to section B)

Q.N. 5 What are those cost?

Q.N. 6 Are these reimbursed by the HSE? If so, all or what proportion?

SECTION B STAFF COST

Q.N. 7 Please provide the following information about staff involved in the colonoscopy procedure pathway.

Staff category	**Number (Obtained from gastroenterology dept.)**	**Grade**	**Category**	**Department**	**Dedicated to the department or shared across departments**	**Working time proportion to the department (if shared across department)**
Admin staff						
Clinical staff						

SECTION C EQUIPMENT COST

Q.N. 8 Please provide the following information about endoscopic equipment and accessories.

Endoscopic equipment	**Quantity (Obtained from gastroenterology dept.)**	**Life year**	**Purchase price**	**Maintenance cost**
Colonoscope				
Video processor and light source				
Monitor				
Dual-scope reprocessing				
Electrosurgical generator				
Endoscopic accessories				
Biopsy forceps				
Biopsy snare				
Cleaning brush long				
Cleaning brush short				
Biopsy valve				

Water bottle				
Electric plate				
Silicon				

(Items are listed as prompts only)

SECTION D CONSUMABLES & MEDICATIONS COST

Q.N. 9 Please provide the cost about consumables and medications per patient.

Consumables	**Quantity (obtained from gastroenterology dept.)**	**Unit cost**
Anallergic gloves		
Polhyethilene gloves		
Latex gloves		
Syringe (list according to size)		
Lubricant		
Gauze		
Disposable bed linen		
Medications and pharmacy supply		
Buscopan		
Midazolam		
Pethidine		

(Items are listed as prompts only)

Q.N. 10 On average, what proportion of consumables are wasted?

Q.N. 11 On average, what proportion of medicines are wasted?

SECTION E FACILITY COST

Facility	**Area (m^2)**	**Proportion used for colonoscopy patient**	**Rent cost**
Waiting room			
Recovery room			

Appendix 4.3 Participant consent form

Trinity College Dublin
Coláiste na Tríonóide, Baile Átha Cliath
The University of Dublin

PARTICIPANT CONSENT FORM

Study title: Micro-costing of colonoscopy in Ireland

Centre ID:

Identification Number for study:

There are 2 sections in this form. Each section has a statement and asks you to tick the box if you agree. The end of this form is for the researchers to complete.

Please ask any questions you may have when reading each of the statements.
Thank you for participating.

Please Initial the box if you agree with the statement. Please feel free to ask questions if there is something you do not understand.

General	**Tick box**
I confirm I have read and understood the **Information Leaflet** for the above study. The information has been fully explained to me and I have been able to ask questions, all of which have been answered to my satisfaction.	
I understand that this study **is entirely voluntary, and if I decide that I do not want to take part, I can stop taking part in this study at any time without giving a reason**.	
I understand that I **will not be paid for taking part in this study.**	
I know how to contact the research team if I need to.	
I agree to take part in this research study having been fully informed of the **risks, benefits and alternatives** which are set out in full in the information leaflet which I have been provided with.	
I agree to being contacted by researchers as part of this research study.	
I have been given a copy of the Information Leaflet and this completed consent form for my records.	
Data	
I give informed **explicit consent** to have the data I provide to be processed as part of this research study and retained for 5 years.	

I understand that anonymous information from this study will be used for research purpose such as publication in a scientific journal.	

Participant Name (Block Capitals) Participant Signature Date

Witness Name (Block Capitals) Witness Signature Date

To be completed by the Principal Investigator or nominee.

I, the undersigned, have taken the time to fully explain to the above patient the nature and purpose of this study in a way that they could understand. I have explained the risks and possible benefits involved. I have invited them to ask questions on any aspect of the study that concerned them.
I have given a copy of the information leaflet and consent form to the participant with contacts of the study team.

Researcher name: Rajani Pokharel

Title and qualifications: PhD student, MPH

Signature

Date

| | |

Principal investigator: Dr Jan Leyden

Title and qualifications: Consultant Gastroenterologist, MD FRCPI

Signature

Date

| | |

3 copies to be made: 1 for research participant, 1 for PI and 1 for hospital records.

Appendix 4.4 Participant information leaflet

Trinity College Dublin
Coláiste na Tríonóide, Baile Átha Cliath
The University of Dublin

Participant Information Leaflet

Micro-costing of colonoscopy in Ireland

Site	Mater Misericordiae University Hospital, Dublin
Principal Investigator(s) and Co-Investigator(s)	Dr Jan Leyden (Principal Investigator) Mater Misericordiae University Hospital Email: giunit@mater.ie Phone: 01 803 2366 Dr James O'Mahony (Academic supervisor) Trinity College Dublin Email: jfomahon@tcd.ie Phone: 01 896 4612 Ms Rajani Pokharel (PhD student) Trinity College Dublin Email: pokharer@tcd.ie Phone: 01 896 4612
Study organiser	Trinity College Dublin (for PhD research project)
Data Controller	Mater Misericordiae University Hospital, Dublin
Data Protection Officer	Ronan O'Halloran Mater Misericordiae University Hospital Email: ronanohalloran@mater.ie Phone: 01 803 4035, Mobile: +353 83 017 0743

You are being invited to take part in a research study that is being done by Jan Leyden at Mater Misericordiae University Hospital. Before you decide whether or not you wish to take part, please read this information sheet carefully. Ask questions if anything you read is not clear or if you would like more information. Take time to decide whether or not you wish to take part. Thank you for reading this.

This leaflet has four main parts:

Part 1 – Information about the Study

Part 2 – Information on how your data will be used and stored

Part 3 – Information about Costs, Funding and Approval

Part 4 – Further Information

Part 1 – Information about the Study

Why is this study being done?
The aim of the study is to estimate the colonoscopy cost from the health care payer perspective. The findings from the study will aid the HSE in decision making regarding colorectal cancer screening especially resource allocation and service planning. This is not a performance assessment or audit.
Who is organising and funding this study?
This study is a part of a PhD project being conducted by Ms Rajani Pokharel funded by the Health Research Board (HRB) SPHERE programme. https://www.sphereprogramme.ie/
Why am I being asked to take part?
This information needed for the study is being collected from clinicians and finance department personnel of the Mater Hospital. So, you are asked to participate.
Do I have to take part? Can I withdraw?
You do not have to take part in this study. It is entirely voluntary. If you decide not to take part, it will not affect you in anyway. You can change your mind about taking part in the study and opt out at any time even if the study has started. You do not have to give a reason for not taking part or for opting out. If you wish to opt out, please contact Ms Rajani Pokharel at 0894633307 or pokharer@tcd.ie who will be able to organise this for you.
How will the study be carried out?
The study will take place in March 2023 at the MMUH. The study utilises different methods for data collection. Three interviews will be conducted with clinicians and a finance department

representative. Ms Rajani Pokharel will seek the consent from the prospective interviewee. Dr Jan Leyden will not be involved in the consent taking process. The colonoscopy procedure will be observed for a week to record the time dedicated by each staff in the process.

What will happen to me if I decide to take part? What will I need to do?

If you decide to take part in the study, you will be asked to participate in an interview which will take approximately one hour. The interview will be conducted at the Mater hospital by Ms Rajani Pokharel and could be scheduled at your convenient time. Topic guide for the interview is also attached.

We will observe the patient pathway in the colonoscopy procedure i.e. from admission to the hospital to the discharge and record time dedicated by each staff in the process. If you decide to take part in the study, you will be observed on your duty to record required for each patient.

Are there any benefits to taking part in this research?

Taking part in this study will not directly benefit you. However, research using the data and information you provide may help us to estimate the cost of colonoscopy in a tertiary hospital in Ireland. This result is important for service planning and resource allocation to the decision makers.

Are there any risks to me or others if I take part?

There is a risk that a connection to your identity could be made. Great care will be taken to ensure the confidentiality of all data and the risk to participants of a breach of confidentiality is considered very low.

Is the study confidential?

Yes, we will not obtain any personal information from you. We will not disclose any information capable of identifying you in any publications or presentations from the study.

Part 2 – Information on how the data will be used and stored

How will the data be used?

Data from this research project may be published in future in scientific journals. The aggregated data will also be presented in the Ph.D. dissertation. You will not be able to be identified in any reports or publications.

Who will have the access to and use the data as part of the study? How will the data be stored?

Rajani Pokharel, PhD student at TCD, will collect and enter the data. The data collected in paper records via interview and observation will be entered into password-protected Microsoft Excel spreadsheets on the same day and the paper records will be destroyed immediately using a safe paper shredding facility provided by TCD. The electronic data (Excel sheets) will be stored in TCD networked computer based on Centre for Health and Policy Management,

School of Medicine, Trinity College Dublin. Only Rajani Pokharel has access to the computer via their TCD login credentials. If needed, internal data sharing will be facilitated among the research team using files encrypted with password sent via TCD email. The data will not be shared outside of Ireland. Data will be stored for 5 years and subsequently destroyed. Electronic files will be erased permanently. Hard drive will be cleaned by an appropriate IT staff member if upgrading or changing of PC is required during the data retention period.

What are my rights?

You are entitled to:

- The right to access to the data you provided and receive a copy of it
- The right to restrict or object to processing of the data you provided
- The right to object to any further processing of the information we hold about you (except where it is de-identified)
- The right to have inaccurate information about you corrected or deleted
- The right to receive the data you provided in a portable format and to have it transferred to another data controller
- The right to request deletion of the data you provided

You can exercise these rights by contacting Dr Jan Leyden (Mater Misericordiae University Hospital,Email: giunit@mater.ie,Phone: 01 803 2366) or the Data Protection Officer of the MMUH, Ronan O'Halloran (Email: ronanohalloran@mater.ie , Phone: 01 803 4035, Mobile: +353 83 017 0743), https://www.mater.ie/data-protection/)

Part 3 – Information about Costs, Funding and Approval

Has this study been approved by a research ethics committee?

Yes, this study has been approved by the Research Ethics Committee of the Mater Hospital on 9th March 2023 and the Research Ethics Committee of Trinity College Dublin on 31st March, 2023.

Is there any payment for taking part?

No, we are not paying participants to take part in the study.

Part 4 – Further Information

If you have any concerns or questions, you can contact:
Principal Investigator: Dr Jan Leyden (Principal Investigator)
Mater Misericordiae University Hospital
Email: giunit@mater.ie
Phone: 01 803 2366

Will I be contacted again?
If you would like to take part in this study, you will be asked to sign the Consent Form on the next page. You will be given a copy of this information leaflet and the signed Consent Form to keep. We will not contact you after the interviews/observation.

Appendix 4.5 Topic guide

Micro-costing of colonoscopy in Ireland

Topic guide for interviews with clinician

1. Colonoscopy proportion – total number of colonoscopies conducted per week at the department
2. Patient pathway during the colonoscopy procedure i.e., stages involved from a patient's admission at the hospital, discharge from the hospital and follow up appointment, if any
3. List of staff category and number involved in the procedure
4. Quantity of endoscopic equipment and accessories used in the procedure per patient
5. Quantity of consumables and medications used per patient for the procedure per patient

Topic guide for interview with finance department representative

1. Cost during the patient pathway such as cost incurred by the hospital transferring specific cases or any cost borne by patient and later reimbursed by the HSE
2. A list of staff category, number, grade, department of affiliation, cost of each staff borne by gastroenterology department or shared across departments
3. Unit cost of endoscopic equipment and accessories used during the colonoscopy procedure
4. Unit cost of consumables and medications used during the colonoscopy procedure
5. Facility cost such as the waiting and recovery rooms

Appendix 4.6 Direct observation checklist

Micro costing of Colonoscopy in Ireland

Observation checklist

Steps in colonoscopy procedure *	Staff Category	Number involved	Grade	Start time	End time	Equipment	Equipment quantity	Consumables	Consumable quantity	Medications	Medication quantity
Registration in day surgery admitting for the hospital card											
Registration with the secretary in GI endoscopy											
Seating in the GI endoscopy waiting room											
Pre-endoscopy preparation by the endoscopy nurse											
Patient changes into gown and proceeds to the pre-endoscopy waiting area											
Colonoscopy is performed with or											

Steps in colonoscopy procedure *	**Staff Category**	**Number involved**	**Grade**	**Start time**	**End time**	**Equipment**	**Equipment quantity**	**Consumables**	**Consumable quantity**	**Medications**	**Medication quantity**
without polypectomy											
Patient is moved out of the endoscopy suite and the room is cleaned											
The patient is brought to the general recovery area											
The patient leaves											

Note: Steps in the colonoscopy procedure subject to change based on interviews with clinicians

Appendix 5 Details of code

We obtained a natural history simulation file from Erasmus Medical Centre. The file contained the details of individuals, the age of different events such as lesions development and their progression, death due to cancer and other cause death. We estimated the counterfactual death age for people who died with colorectal cancer based on gender specific survival probability that was used in the natural history simulation. Based on this information we developed code in R programming language to implement screening and surveillance activities for male and female separately. We developed a main simulation file and separate files for codes related to population size, participation arrays, screening policies, sensitivity, specificity, surveillance and post processing. We used source function to read and execute these files in the main simulation file. The details of the codes are explained below:

SECTION 1 SCREENING POLICIES

The purpose of this file is to generate strategies for simulation. We simulated 8 screening strategies in the base case.

```
#1. 2y 59-69, FIT 225
#2. 2y 55(50)-74, FIT 225
#3. 1y 59-69, FIT 225
#4. 1y 55(50)-74, FIT 100
#5. 1y 45-80, FIT 50
#6. 1y 55(50)-74, FIT 50
#7. 2y 59-69, FIT 50
#8. 1y 55(50)-74 FIT 100


#Set working directory
try(setwd("Directory location"))


#Load readxl package
library(readxl)

#BASECASE POLICY1
#Biennial FIT screening among age group 59-69 years and diagnosti
c colonoscopy after a positive FIT result at a cut-off of 225ng/m
l
#2y 59-69, FIT 225

#Read Policies file from InputFiles folder.
Policies1Age <- read_excel("InputFiles/Policies.xlsx", sheet=1)

Policies1Fit <- read_excel("InputFiles/Policies.xlsx", sheet=2)
```

```
TargetCohorts=seq(1:31)
for(i in TargetCohorts){
assign(paste("Age1Schedule",i,sep=""),Policies1Age[Policies1Age$C
ohort==i,-1][!(is.na(Policies1Age[Policies1Age$Cohort==i,-1]))])

assign(paste("Fit1Schedule",i,sep=""),Policies1Fit[Policies1Fit$C
ohort==i,-1][!(is.na(Policies1Fit[Policies1Fit$Cohort==i,-1]))])}


Schedules1=list(
  Age1Schedule1=Age1Schedule1,
  Age1Schedule2=Age1Schedule2,
  Age1Schedule3=Age1Schedule3,
  Age1Schedule4=Age1Schedule4,
  Age1Schedule5=Age1Schedule5,
  Age1Schedule6=Age1Schedule6,
  Age1Schedule7=Age1Schedule7,
  Age1Schedule8=Age1Schedule8,
  Age1Schedule9=Age1Schedule9,
  Age1Schedule10=Age1Schedule10,
  Age1Schedule11=Age1Schedule11,
  Age1Schedule12=Age1Schedule12,
  Age1Schedule13=Age1Schedule13,
  Age1Schedule14=Age1Schedule14,
  Age1Schedule15=Age1Schedule15,
  Age1Schedule16=Age1Schedule16,
  Age1Schedule17=Age1Schedule17,
  Age1Schedule18=Age1Schedule18,
  Age1Schedule19=Age1Schedule19,
  Age1Schedule20=Age1Schedule20,
  Age1Schedule21=Age1Schedule21,
  Age1Schedule22=Age1Schedule22,
  Age1Schedule23=Age1Schedule23,
  Age1Schedule24=Age1Schedule24,
  Age1Schedule25=Age1Schedule25,
  Age1Schedule26=Age1Schedule26,
  Age1Schedule27=Age1Schedule27,
  Age1Schedule28=Age1Schedule28,
  Age1Schedule29=Age1Schedule29,
  Age1Schedule30=Age1Schedule30,
  Age1Schedule31=Age1Schedule31,
  Fit1Schedule1=Fit1Schedule1,
  Fit1Schedule2=Fit1Schedule2,
  Fit1Schedule3=Fit1Schedule3,
  Fit1Schedule4=Fit1Schedule4,
  Fit1Schedule5=Fit1Schedule5,
  Fit1Schedule6=Fit1Schedule6,
```

```
  Fit1Schedule7=Fit1Schedule7,
  Fit1Schedule8=Fit1Schedule8,
  Fit1Schedule9=Fit1Schedule9,
  Fit1Schedule10=Fit1Schedule10,
  Fit1Schedule11=Fit1Schedule11,
  Fit1Schedule12=Fit1Schedule12,
  Fit1Schedule13=Fit1Schedule13,
  Fit1Schedule14=Fit1Schedule14,
  Fit1Schedule15=Fit1Schedule15,
  Fit1Schedule16=Fit1Schedule16,
  Fit1Schedule17=Fit1Schedule17,
  Fit1Schedule18=Fit1Schedule18,
  Fit1Schedule19=Fit1Schedule19,
  Fit1Schedule20=Fit1Schedule20,
  Fit1Schedule21=Fit1Schedule21,
  Fit1Schedule22=Fit1Schedule22,
  Fit1Schedule23=Fit1Schedule23,
  Fit1Schedule24=Fit1Schedule24,
  Fit1Schedule25=Fit1Schedule25,
  Fit1Schedule26=Fit1Schedule26,
  Fit1Schedule27=Fit1Schedule27,
  Fit1Schedule28=Fit1Schedule28,
  Fit1Schedule29=Fit1Schedule29,
  Fit1Schedule30=Fit1Schedule30,
  Fit1Schedule31=Fit1Schedule31)



#Save the
saveRDS(Schedules1, file="InputFiles/ScreenSchedules/Schedules1.R
Data")



#=================ALATERNATIVE SCENARIOS=========================
===
#POLICY 2
#Biennial FIT screening among age group 55(50)-74 years and diagn
ostic colonoscopy after a positive FIT result at a cut-off of 225
ng/ml (planned NGSP strategy)
#2y 55(50)-74, FIT 225 NGSP plan
Policies2Age <- read_excel("InputFiles/Policies4.xlsx", sheet=3)

Policies2Fit <- read_excel("InputFiles/Policies4.xlsx", sheet=4)

TargetCohorts=seq(1:35)
for(i in TargetCohorts){
  assign(paste("Age2Schedule",i,sep=""),Policies2Age[Policies2Age
$Cohort==i,-1][!(is.na(Policies2Age[Policies2Age$Cohort==i,-1]))]
```

```
)

  assign(paste("Fit2Schedule",i,sep=""),Policies2Fit[Policies2Fit
$Cohort==i,-1][!(is.na(Policies2Fit[Policies2Fit$Cohort==i,-1]))]
)}

Schedules2=list(

  Age2Schedule1=Age2Schedule1,
  Age2Schedule2=Age2Schedule2,
  Age2Schedule3=Age2Schedule3,
  Age2Schedule4=Age2Schedule4,
  Age2Schedule5=Age2Schedule5,
  Age2Schedule6=Age2Schedule6,
  Age2Schedule7=Age2Schedule7,
  Age2Schedule8=Age2Schedule8,
  Age2Schedule9=Age2Schedule9,
  Age2Schedule10=Age2Schedule10,
  Age2Schedule11=Age2Schedule11,
  Age2Schedule12=Age2Schedule12,
  Age2Schedule13=Age2Schedule13,
  Age2Schedule14=Age2Schedule14,
  Age2Schedule15=Age2Schedule15,
  Age2Schedule16=Age2Schedule16,
  Age2Schedule17=Age2Schedule17,
  Age2Schedule18=Age2Schedule18,
  Age2Schedule19=Age2Schedule19,
  Age2Schedule20=Age2Schedule20,
  Age2Schedule21=Age2Schedule21,
  Age2Schedule22=Age2Schedule22,
  Age2Schedule23=Age2Schedule23,
  Age2Schedule24=Age2Schedule24,
  Age2Schedule25=Age2Schedule25,
  Age2Schedule26=Age2Schedule26,
  Age2Schedule27=Age2Schedule27,
  Age2Schedule28=Age2Schedule28,
  Age2Schedule29=Age2Schedule29,
  Age2Schedule30=Age2Schedule30,
  Age2Schedule31=Age2Schedule31,
  Age2Schedule32=Age2Schedule32,
  Age2Schedule33=Age2Schedule33,
  Age2Schedule34=Age2Schedule34,
  Age2Schedule35=Age2Schedule35,
  Fit2Schedule1=Fit2Schedule1,
  Fit2Schedule2=Fit2Schedule2,
  Fit2Schedule3=Fit2Schedule3,
  Fit2Schedule4=Fit2Schedule4,
  Fit2Schedule5=Fit2Schedule5,
  Fit2Schedule6=Fit2Schedule6,
```

```
  Fit2Schedule7=Fit2Schedule7,
  Fit2Schedule8=Fit2Schedule8,
  Fit2Schedule9=Fit2Schedule9,
  Fit2Schedule10=Fit2Schedule10,
  Fit2Schedule11=Fit2Schedule11,
  Fit2Schedule12=Fit2Schedule12,
  Fit2Schedule13=Fit2Schedule13,
  Fit2Schedule14=Fit2Schedule14,
  Fit2Schedule15=Fit2Schedule15,
  Fit2Schedule16=Fit2Schedule16,
  Fit2Schedule17=Fit2Schedule17,
  Fit2Schedule18=Fit2Schedule18,
  Fit2Schedule19=Fit2Schedule19,
  Fit2Schedule20=Fit2Schedule20,
  Fit2Schedule21=Fit2Schedule21,
  Fit2Schedule22=Fit2Schedule22,
  Fit2Schedule23=Fit2Schedule23,
  Fit2Schedule24=Fit2Schedule24,
  Fit2Schedule25=Fit2Schedule25,
  Fit2Schedule26=Fit2Schedule26,
  Fit2Schedule27=Fit2Schedule27,
  Fit2Schedule28=Fit2Schedule28,
  Fit2Schedule29=Fit2Schedule29,
  Fit2Schedule30=Fit2Schedule30,
  Fit2Schedule31=Fit2Schedule31,
  Fit2Schedule32=Fit2Schedule32,
  Fit2Schedule33=Fit2Schedule33,
  Fit2Schedule34=Fit2Schedule34,
  Fit2Schedule35=Fit2Schedule35
  )


#Check for equal lengths of age and FIT strategies


if(length(Age2Schedule1) ==length(Fit2Schedule1) ){}else{print("E
rror Cohort 1)")}
if(length(Age2Schedule2) ==length(Fit2Schedule2) ){}else{print("E
rror Cohort 2)")}
if(length(Age2Schedule3) ==length(Fit2Schedule3) ){}else{print("E
rror Cohort 3)")}
if(length(Age2Schedule4) ==length(Fit2Schedule4) ){}else{print("E
rror Cohort 4)")}
if(length(Age2Schedule5) ==length(Fit2Schedule5) ){}else{print("E
rror Cohort 5)")}
if(length(Age2Schedule6) ==length(Fit2Schedule6) ){}else{print("E
rror Cohort 6)")}
if(length(Age2Schedule7) ==length(Fit2Schedule7) ){}else{print("E
rror Cohort 7)")}
```

```
if(length(Age2Schedule8) ==length(Fit2Schedule8) ){}else{print("E
rror Cohort 8)")}
if(length(Age2Schedule9) ==length(Fit2Schedule9) ){}else{print("E
rror Cohort 9)")}
if(length(Age2Schedule10)==length(Fit2Schedule10)){}else{print("E
rror Cohort 10")}
if(length(Age2Schedule11)==length(Fit2Schedule11)){}else{print("E
rror Cohort 11")}
if(length(Age2Schedule12)==length(Fit2Schedule12)){}else{print("E
rror Cohort 12")}
if(length(Age2Schedule13)==length(Fit2Schedule13)){}else{print("E
rror Cohort 13")}
if(length(Age2Schedule14)==length(Fit2Schedule14)){}else{print("E
rror Cohort 14")}
if(length(Age2Schedule15)==length(Fit2Schedule15)){}else{print("E
rror Cohort 15")}
if(length(Age2Schedule16)==length(Fit2Schedule16)){}else{print("E
rror Cohort 16")}
if(length(Age2Schedule17)==length(Fit2Schedule17)){}else{print("E
rror Cohort 17")}
if(length(Age2Schedule18)==length(Fit2Schedule18)){}else{print("E
rror Cohort 18")}
if(length(Age2Schedule19)==length(Fit2Schedule19)){}else{print("E
rror Cohort 19")}
if(length(Age2Schedule20)==length(Fit2Schedule20)){}else{print("E
rror Cohort 20")}
if(length(Age2Schedule21)==length(Fit2Schedule21)){}else{print("E
rror Cohort 21")}
if(length(Age2Schedule22)==length(Fit2Schedule22)){}else{print("E
rror Cohort 22")}
if(length(Age2Schedule23)==length(Fit2Schedule23)){}else{print("E
rror Cohort 23")}
if(length(Age2Schedule24)==length(Fit2Schedule24)){}else{print("E
rror Cohort 24")}
if(length(Age2Schedule25)==length(Fit2Schedule25)){}else{print("E
rror Cohort 25")}
if(length(Age2Schedule26)==length(Fit2Schedule26)){}else{print("E
rror Cohort 26")}
if(length(Age2Schedule27)==length(Fit2Schedule27)){}else{print("E
rror Cohort 27")}
if(length(Age2Schedule28)==length(Fit2Schedule28)){}else{print("E
rror Cohort 28")}
if(length(Age2Schedule29)==length(Fit2Schedule29)){}else{print("E
rror Cohort 29")}
if(length(Age2Schedule30)==length(Fit2Schedule30)){}else{print("E
rror Cohort 30")}
if(length(Age2Schedule31)==length(Fit2Schedule31)){}else{print("E
rror Cohort 31")}
if(length(Age2Schedule32)==length(Fit2Schedule32)){}else{print("E
```

```
rror Cohort 32")}
if(length(Age2Schedule33)==length(Fit2Schedule33)){}else{print("E
rror Cohort 33")}
if(length(Age2Schedule34)==length(Fit2Schedule34)){}else{print("E
rror Cohort 34")}
if(length(Age2Schedule35)==length(Fit2Schedule35)){}else{print("E
rror Cohort 35")}



#Save the
saveRDS(Schedules2, file="InputFiles/ScreenSchedules/Schedules2.R
Data")

#Retrieve the schedules
#readRDS("Schedules2.RData")


#================================================================
=
#POLICY 3 Annual FIT screening among age group 60-69 years and di
agnostic colonoscopy after a positive FIT result at a cut-off of
100ng/ml
#3. 1y 59-69, FIT 225
Policies3Age <- read_excel("InputFiles/Policies3.xlsx", sheet=5)

Policies3Fit <- read_excel("InputFiles/Policies3.xlsx", sheet=6)

TargetCohorts=seq(1:31)
for(i in TargetCohorts){
  assign(paste("Age3Schedule",i,sep=""),Policies3Age[Policies3Age
$Cohort==i,-1][!(is.na(Policies3Age[Policies3Age$Cohort==i,-1]))]
)

  assign(paste("Fit3Schedule",i,sep=""),Policies3Fit[Policies3Fit
$Cohort==i,-1][!(is.na(Policies3Fit[Policies3Fit$Cohort==i,-1]))]
)}
Schedules3=list(


  Age3Schedule1=Age3Schedule1,
  Age3Schedule2=Age3Schedule2,
  Age3Schedule3=Age3Schedule3,
  Age3Schedule4=Age3Schedule4,
  Age3Schedule5=Age3Schedule5,
  Age3Schedule6=Age3Schedule6,
  Age3Schedule7=Age3Schedule7,
  Age3Schedule8=Age3Schedule8,
  Age3Schedule9=Age3Schedule9,
```

```
Age3Schedule10=Age3Schedule10,
Age3Schedule11=Age3Schedule11,
Age3Schedule12=Age3Schedule12,
Age3Schedule13=Age3Schedule13,
Age3Schedule14=Age3Schedule14,
Age3Schedule15=Age3Schedule15,
Age3Schedule16=Age3Schedule16,
Age3Schedule17=Age3Schedule17,
Age3Schedule18=Age3Schedule18,
Age3Schedule19=Age3Schedule19,
Age3Schedule20=Age3Schedule20,
Age3Schedule21=Age3Schedule21,
Age3Schedule22=Age3Schedule22,
Age3Schedule23=Age3Schedule23,
Age3Schedule24=Age3Schedule24,
Age3Schedule25=Age3Schedule25,
Age3Schedule26=Age3Schedule26,
Age3Schedule27=Age3Schedule27,
Age3Schedule28=Age3Schedule28,
Age3Schedule29=Age3Schedule29,
Age3Schedule30=Age3Schedule30,
Age3Schedule31=Age3Schedule31,
Fit3Schedule1=Fit3Schedule1,
Fit3Schedule2=Fit3Schedule2,
Fit3Schedule3=Fit3Schedule3,
Fit3Schedule4=Fit3Schedule4,
Fit3Schedule5=Fit3Schedule5,
Fit3Schedule6=Fit3Schedule6,
Fit3Schedule7=Fit3Schedule7,
Fit3Schedule8=Fit3Schedule8,
Fit3Schedule9=Fit3Schedule9,
Fit3Schedule10=Fit3Schedule10,
Fit3Schedule11=Fit3Schedule11,
Fit3Schedule12=Fit3Schedule12,
Fit3Schedule13=Fit3Schedule13,
Fit3Schedule14=Fit3Schedule14,
Fit3Schedule15=Fit3Schedule15,
Fit3Schedule16=Fit3Schedule16,
Fit3Schedule17=Fit3Schedule17,
Fit3Schedule18=Fit3Schedule18,
Fit3Schedule19=Fit3Schedule19,
Fit3Schedule20=Fit3Schedule20,
Fit3Schedule21=Fit3Schedule21,
Fit3Schedule22=Fit3Schedule22,
Fit3Schedule23=Fit3Schedule23,
Fit3Schedule24=Fit3Schedule24,
Fit3Schedule25=Fit3Schedule25,
Fit3Schedule26=Fit3Schedule26,
Fit3Schedule27=Fit3Schedule27,
```

```
  Fit3Schedule28=Fit3Schedule28,
  Fit3Schedule29=Fit3Schedule29,
  Fit3Schedule30=Fit3Schedule30,
  Fit3Schedule31=Fit3Schedule31)

#Save the
saveRDS(Schedules3, file="InputFiles/ScreenSchedules/Schedules3.R
Data")


#Check for equal lengths of age and FIT strategies


if(length(Age3Schedule1) ==length(Fit3Schedule1) ){}else{print("E
rror Cohort 1)")}
if(length(Age3Schedule2) ==length(Fit3Schedule2) ){}else{print("E
rror Cohort 2)")}
if(length(Age3Schedule3) ==length(Fit3Schedule3) ){}else{print("E
rror Cohort 3)")}
if(length(Age3Schedule4) ==length(Fit3Schedule4) ){}else{print("E
rror Cohort 4)")}
if(length(Age3Schedule5) ==length(Fit3Schedule5) ){}else{print("E
rror Cohort 5)")}
if(length(Age3Schedule6) ==length(Fit3Schedule6) ){}else{print("E
rror Cohort 6)")}
if(length(Age3Schedule7) ==length(Fit3Schedule7) ){}else{print("E
rror Cohort 7)")}
if(length(Age3Schedule8) ==length(Fit3Schedule8) ){}else{print("E
rror Cohort 8)")}
if(length(Age3Schedule9) ==length(Fit3Schedule9) ){}else{print("E
rror Cohort 9)")}
if(length(Age3Schedule10)==length(Fit3Schedule10)){}else{print("E
rror Cohort 10")}
if(length(Age3Schedule11)==length(Fit3Schedule11)){}else{print("E
rror Cohort 11")}
if(length(Age3Schedule12)==length(Fit3Schedule12)){}else{print("E
rror Cohort 12")}
if(length(Age3Schedule13)==length(Fit3Schedule13)){}else{print("E
rror Cohort 13")}
if(length(Age3Schedule14)==length(Fit3Schedule14)){}else{print("E
rror Cohort 14")}
if(length(Age3Schedule15)==length(Fit3Schedule15)){}else{print("E
rror Cohort 15")}
if(length(Age3Schedule16)==length(Fit3Schedule16)){}else{print("E
rror Cohort 16")}
if(length(Age3Schedule17)==length(Fit3Schedule17)){}else{print("E
rror Cohort 17")}
if(length(Age3Schedule18)==length(Fit3Schedule18)){}else{print("E
rror Cohort 18")}
```

```
if(length(Age3Schedule19)==length(Fit3Schedule19)){}else{print("E
rror Cohort 19")}
if(length(Age3Schedule20)==length(Fit3Schedule20)){}else{print("E
rror Cohort 20")}
if(length(Age3Schedule21)==length(Fit3Schedule21)){}else{print("E
rror Cohort 21")}
if(length(Age3Schedule22)==length(Fit3Schedule22)){}else{print("E
rror Cohort 22")}
if(length(Age3Schedule23)==length(Fit3Schedule23)){}else{print("E
rror Cohort 23")}
if(length(Age3Schedule24)==length(Fit3Schedule24)){}else{print("E
rror Cohort 24")}
if(length(Age3Schedule25)==length(Fit3Schedule25)){}else{print("E
rror Cohort 25")}
if(length(Age3Schedule26)==length(Fit3Schedule26)){}else{print("E
rror Cohort 26")}
if(length(Age3Schedule27)==length(Fit3Schedule27)){}else{print("E
rror Cohort 27")}
if(length(Age3Schedule28)==length(Fit3Schedule28)){}else{print("E
rror Cohort 28")}
if(length(Age3Schedule29)==length(Fit3Schedule29)){}else{print("E
rror Cohort 29")}
if(length(Age3Schedule30)==length(Fit3Schedule30)){}else{print("E
rror Cohort 30")}
if(length(Age3Schedule31)==length(Fit3Schedule31)){}else{print("E
rror Cohort 31")}



#=================================================================
===

#POLICY 4 Annual FIT screening among age group 55(50)-74 years an
d diagnostic colonoscopy after a positive FIT result at a cut-off
of 100ng/ml
#4. 1y 55(50)-74, FIT 100
Policies4Age <- read_excel("InputFiles/Policies4.xlsx", sheet=7)

Policies4Fit <- read_excel("InputFiles/Policies4.xlsx", sheet=8)

TargetCohorts=seq(1:35)
for(i in TargetCohorts){
  assign(paste("Age4Schedule",i,sep=""),Policies4Age[Policies4Age
$Cohort==i,-1][!(is.na(Policies4Age[Policies4Age$Cohort==i,-1]))]
)

  assign(paste("Fit4Schedule",i,sep=""),Policies4Fit[Policies4Fit
$Cohort==i,-1][!(is.na(Policies4Fit[Policies4Fit$Cohort==i,-1]))]
)}
```

```
Schedules4=list(
Age4Schedule1=Age4Schedule1,
Age4Schedule2=Age4Schedule2,
Age4Schedule3=Age4Schedule3,
Age4Schedule4=Age4Schedule4,
Age4Schedule5=Age4Schedule5,
Age4Schedule6=Age4Schedule6,
Age4Schedule7=Age4Schedule7,
Age4Schedule8=Age4Schedule8,
Age4Schedule9=Age4Schedule9,
Age4Schedule10=Age4Schedule10,
Age4Schedule11=Age4Schedule11,
Age4Schedule12=Age4Schedule12,
Age4Schedule13=Age4Schedule13,
Age4Schedule14=Age4Schedule14,
Age4Schedule15=Age4Schedule15,
Age4Schedule16=Age4Schedule16,
Age4Schedule17=Age4Schedule17,
Age4Schedule18=Age4Schedule18,
Age4Schedule19=Age4Schedule19,
Age4Schedule20=Age4Schedule20,
Age4Schedule21=Age4Schedule21,
Age4Schedule22=Age4Schedule22,
Age4Schedule23=Age4Schedule23,
Age4Schedule24=Age4Schedule24,
Age4Schedule25=Age4Schedule25,
Age4Schedule26=Age4Schedule26,
Age4Schedule27=Age4Schedule27,
Age4Schedule28=Age4Schedule28,
Age4Schedule29=Age4Schedule29,
Age4Schedule30=Age4Schedule30,
Age4Schedule31=Age4Schedule31,
Age4Schedule32=Age4Schedule32,
Age4Schedule33=Age4Schedule33,
Age4Schedule34=Age4Schedule34,
Age4Schedule35=Age4Schedule35,
Fit4Schedule1=Fit4Schedule1,
Fit4Schedule2=Fit4Schedule2,
Fit4Schedule3=Fit4Schedule3,
Fit4Schedule4=Fit4Schedule4,
Fit4Schedule5=Fit4Schedule5,
Fit4Schedule6=Fit4Schedule6,
Fit4Schedule7=Fit4Schedule7,
Fit4Schedule8=Fit4Schedule8,
Fit4Schedule9=Fit4Schedule9,
Fit4Schedule10=Fit4Schedule10,
Fit4Schedule11=Fit4Schedule11,
Fit4Schedule12=Fit4Schedule12,
```

```
Fit4Schedule13=Fit4Schedule13,
Fit4Schedule14=Fit4Schedule14,
Fit4Schedule15=Fit4Schedule15,
Fit4Schedule16=Fit4Schedule16,
Fit4Schedule17=Fit4Schedule17,
Fit4Schedule18=Fit4Schedule18,
Fit4Schedule19=Fit4Schedule19,
Fit4Schedule20=Fit4Schedule20,
Fit4Schedule21=Fit4Schedule21,
Fit4Schedule22=Fit4Schedule22,
Fit4Schedule23=Fit4Schedule23,
Fit4Schedule24=Fit4Schedule24,
Fit4Schedule25=Fit4Schedule25,
Fit4Schedule26=Fit4Schedule26,
Fit4Schedule27=Fit4Schedule27,
Fit4Schedule28=Fit4Schedule28,
Fit4Schedule29=Fit4Schedule29,
Fit4Schedule30=Fit4Schedule30,
Fit4Schedule31=Fit4Schedule31,
Fit4Schedule32=Fit4Schedule32,
Fit4Schedule33=Fit4Schedule33,
Fit4Schedule34=Fit4Schedule34,
Fit4Schedule35=Fit4Schedule35
)

#Save the
saveRDS(Schedules4, file="InputFiles/ScreenSchedules/Schedules4.R
Data")

#Check for equal lengths of age and FIT strategies
if(length(Age4Schedule1) ==length(Fit4Schedule1) ){}else{print("E
rror Cohort 1)")}
if(length(Age4Schedule2) ==length(Fit4Schedule2) ){}else{print("E
rror Cohort 2)")}
if(length(Age4Schedule3) ==length(Fit4Schedule3) ){}else{print("E
rror Cohort 3)")}
if(length(Age4Schedule4) ==length(Fit4Schedule4) ){}else{print("E
rror Cohort 4)")}
if(length(Age4Schedule5) ==length(Fit4Schedule5) ){}else{print("E
rror Cohort 5)")}
if(length(Age4Schedule6) ==length(Fit4Schedule6) ){}else{print("E
rror Cohort 6)")}
if(length(Age4Schedule7) ==length(Fit4Schedule7) ){}else{print("E
rror Cohort 7)")}
if(length(Age4Schedule8) ==length(Fit4Schedule8) ){}else{print("E
rror Cohort 8)")}
if(length(Age4Schedule9) ==length(Fit4Schedule9) ){}else{print("E
rror Cohort 9)")}
if(length(Age4Schedule10)==length(Fit4Schedule10)){}else{print("E
```

```
rror Cohort 10")}
if(length(Age4Schedule11)==length(Fit4Schedule11)){}else{print("E
rror Cohort 11")}
if(length(Age4Schedule12)==length(Fit4Schedule12)){}else{print("E
rror Cohort 12")}
if(length(Age4Schedule13)==length(Fit4Schedule13)){}else{print("E
rror Cohort 13")}
if(length(Age4Schedule14)==length(Fit4Schedule14)){}else{print("E
rror Cohort 14")}
if(length(Age4Schedule15)==length(Fit4Schedule15)){}else{print("E
rror Cohort 15")}
if(length(Age4Schedule16)==length(Fit4Schedule16)){}else{print("E
rror Cohort 16")}
if(length(Age4Schedule17)==length(Fit4Schedule17)){}else{print("E
rror Cohort 17")}
if(length(Age4Schedule18)==length(Fit4Schedule18)){}else{print("E
rror Cohort 18")}
if(length(Age4Schedule19)==length(Fit4Schedule19)){}else{print("E
rror Cohort 19")}
if(length(Age4Schedule20)==length(Fit4Schedule20)){}else{print("E
rror Cohort 20")}
if(length(Age4Schedule21)==length(Fit4Schedule21)){}else{print("E
rror Cohort 21")}
if(length(Age4Schedule22)==length(Fit4Schedule22)){}else{print("E
rror Cohort 22")}
if(length(Age4Schedule23)==length(Fit4Schedule23)){}else{print("E
rror Cohort 23")}
if(length(Age4Schedule24)==length(Fit4Schedule24)){}else{print("E
rror Cohort 24")}
if(length(Age4Schedule25)==length(Fit4Schedule25)){}else{print("E
rror Cohort 25")}
if(length(Age4Schedule26)==length(Fit4Schedule26)){}else{print("E
rror Cohort 26")}
if(length(Age4Schedule27)==length(Fit4Schedule27)){}else{print("E
rror Cohort 27")}
if(length(Age4Schedule28)==length(Fit4Schedule28)){}else{print("E
rror Cohort 28")}
if(length(Age4Schedule29)==length(Fit4Schedule29)){}else{print("E
rror Cohort 29")}
if(length(Age4Schedule30)==length(Fit4Schedule30)){}else{print("E
rror Cohort 30")}
if(length(Age4Schedule31)==length(Fit4Schedule31)){}else{print("E
rror Cohort 31")}
if(length(Age4Schedule32)==length(Fit4Schedule32)){}else{print("E
rror Cohort 32")}
if(length(Age4Schedule33)==length(Fit4Schedule33)){}else{print("E
rror Cohort 33")}
if(length(Age4Schedule34)==length(Fit4Schedule34)){}else{print("E
rror Cohort 34")}
```

```r
if(length(Age4Schedule35)==length(Fit4Schedule35)){}else{print("E
rror Cohort 35")}


#=================================================================
===
#POLICY 5 Annual FIT screening among age group 45-80 years and di
agnostic colonoscopy after a positive FIT result at a cut-off of
50ng/ml (optimal strategy recommended by research in Irish contex
t)
#5. 1y 45-80, FIT 50
Policies5Age <- read_excel("InputFiles/Policies3.xlsx", sheet=9)

Policies5Fit <- read_excel("InputFiles/Policies3.xlsx", sheet=10)

TargetCohorts=seq(1:45)
for(i in TargetCohorts){
  assign(paste("Age5Schedule",i,sep=""),Policies5Age[Policies5Age
$Cohort==i,-1][!(is.na(Policies5Age[Policies5Age$Cohort==i,-1]))]
)
  assign(paste("Fit5Schedule",i,sep=""),Policies5Fit[Policies5Fit
$Cohort==i,-1][!(is.na(Policies5Fit[Policies5Fit$Cohort==i,-1]))]
)}

Schedules5=list(
  Age5Schedule1=Age5Schedule1,
  Age5Schedule2=Age5Schedule2,
  Age5Schedule3=Age5Schedule3,
  Age5Schedule4=Age5Schedule4,
  Age5Schedule5=Age5Schedule5,
  Age5Schedule6=Age5Schedule6,
  Age5Schedule7=Age5Schedule7,
  Age5Schedule8=Age5Schedule8,
  Age5Schedule9=Age5Schedule9,
  Age5Schedule10=Age5Schedule10,
  Age5Schedule11=Age5Schedule11,
  Age5Schedule12=Age5Schedule12,
  Age5Schedule13=Age5Schedule13,
  Age5Schedule14=Age5Schedule14,
  Age5Schedule15=Age5Schedule15,
  Age5Schedule16=Age5Schedule16,
  Age5Schedule17=Age5Schedule17,
  Age5Schedule18=Age5Schedule18,
  Age5Schedule19=Age5Schedule19,
  Age5Schedule20=Age5Schedule20,
  Age5Schedule21=Age5Schedule21,
  Age5Schedule22=Age5Schedule22,
  Age5Schedule23=Age5Schedule23,
  Age5Schedule24=Age5Schedule24,
```

```
Age5Schedule25=Age5Schedule25,
Age5Schedule26=Age5Schedule26,
Age5Schedule27=Age5Schedule27,
Age5Schedule28=Age5Schedule28,
Age5Schedule29=Age5Schedule29,
Age5Schedule30=Age5Schedule30,
Age5Schedule31=Age5Schedule31,
Age5Schedule32=Age5Schedule32,
Age5Schedule33=Age5Schedule33,
Age5Schedule34=Age5Schedule34,
Age5Schedule35=Age5Schedule35,
Age5Schedule36=Age5Schedule36,
Age5Schedule37=Age5Schedule37,
Age5Schedule38=Age5Schedule38,
Age5Schedule39=Age5Schedule39,
Age5Schedule40=Age5Schedule40,
Age5Schedule41=Age5Schedule41,
Age5Schedule42=Age5Schedule42,
Age5Schedule43=Age5Schedule43,
Age5Schedule44=Age5Schedule44,
Age5Schedule45=Age5Schedule45,
Fit5Schedule1=Fit5Schedule1,
Fit5Schedule2=Fit5Schedule2,
Fit5Schedule3=Fit5Schedule3,
Fit5Schedule4=Fit5Schedule4,
Fit5Schedule5=Fit5Schedule5,
Fit5Schedule6=Fit5Schedule6,
Fit5Schedule7=Fit5Schedule7,
Fit5Schedule8=Fit5Schedule8,
Fit5Schedule9=Fit5Schedule9,
Fit5Schedule10=Fit5Schedule10,
Fit5Schedule11=Fit5Schedule11,
Fit5Schedule12=Fit5Schedule12,
Fit5Schedule13=Fit5Schedule13,
Fit5Schedule14=Fit5Schedule14,
Fit5Schedule15=Fit5Schedule15,
Fit5Schedule16=Fit5Schedule16,
Fit5Schedule17=Fit5Schedule17,
Fit5Schedule18=Fit5Schedule18,
Fit5Schedule19=Fit5Schedule19,
Fit5Schedule20=Fit5Schedule20,
Fit5Schedule21=Fit5Schedule21,
Fit5Schedule22=Fit5Schedule22,
Fit5Schedule23=Fit5Schedule23,
Fit5Schedule24=Fit5Schedule24,
Fit5Schedule25=Fit5Schedule25,
Fit5Schedule26=Fit5Schedule26,
Fit5Schedule27=Fit5Schedule27,
Fit5Schedule28=Fit5Schedule28,
```

```
  Fit5Schedule29=Fit5Schedule29,
  Fit5Schedule30=Fit5Schedule30,
  Fit5Schedule31=Fit5Schedule31,
  Fit5Schedule32=Fit5Schedule32,
  Fit5Schedule33=Fit5Schedule33,
Fit5Schedule34=Fit5Schedule34,
Fit5Schedule35=Fit5Schedule35,
Fit5Schedule36=Fit5Schedule36,
Fit5Schedule37=Fit5Schedule37,
Fit5Schedule38=Fit5Schedule38,
Fit5Schedule39=Fit5Schedule39,
Fit5Schedule40=Fit5Schedule40,
Fit5Schedule41=Fit5Schedule41,
Fit5Schedule42=Fit5Schedule42,
Fit5Schedule43=Fit5Schedule43,
Fit5Schedule44=Fit5Schedule44,
Fit5Schedule45=Fit5Schedule45)



#Check for equal lengths of age and FIT strategies
if(length(Age5Schedule1) ==length(Fit5Schedule1) ){}else{print("E
rror Cohort 1)")}
if(length(Age5Schedule2) ==length(Fit5Schedule2) ){}else{print("E
rror Cohort 2)")}
if(length(Age5Schedule3) ==length(Fit5Schedule3) ){}else{print("E
rror Cohort 3)")}
if(length(Age5Schedule4) ==length(Fit5Schedule4) ){}else{print("E
rror Cohort 4)")}
if(length(Age5Schedule5) ==length(Fit5Schedule5) ){}else{print("E
rror Cohort 5)")}
if(length(Age5Schedule6) ==length(Fit5Schedule6) ){}else{print("E
rror Cohort 6)")}
if(length(Age5Schedule7) ==length(Fit5Schedule7) ){}else{print("E
rror Cohort 7)")}
if(length(Age5Schedule8) ==length(Fit5Schedule8) ){}else{print("E
rror Cohort 8)")}
if(length(Age5Schedule9) ==length(Fit5Schedule9) ){}else{print("E
rror Cohort 9)")}
if(length(Age5Schedule10)==length(Fit5Schedule10)){}else{print("E
rror Cohort 10")}
if(length(Age5Schedule11)==length(Fit5Schedule11)){}else{print("E
rror Cohort 11")}
if(length(Age5Schedule12)==length(Fit5Schedule12)){}else{print("E
rror Cohort 12")}
if(length(Age5Schedule13)==length(Fit5Schedule13)){}else{print("E
rror Cohort 13")}
if(length(Age5Schedule14)==length(Fit5Schedule14)){}else{print("E
rror Cohort 14")}
```

```
if(length(Age5Schedule15)==length(Fit5Schedule15)){}else{print("E
rror Cohort 15")}
if(length(Age5Schedule16)==length(Fit5Schedule16)){}else{print("E
rror Cohort 16")}
if(length(Age5Schedule17)==length(Fit5Schedule17)){}else{print("E
rror Cohort 17")}
if(length(Age5Schedule18)==length(Fit5Schedule18)){}else{print("E
rror Cohort 18")}
if(length(Age5Schedule19)==length(Fit5Schedule19)){}else{print("E
rror Cohort 19")}
if(length(Age5Schedule20)==length(Fit5Schedule20)){}else{print("E
rror Cohort 20")}
if(length(Age5Schedule21)==length(Fit5Schedule21)){}else{print("E
rror Cohort 21")}
if(length(Age5Schedule22)==length(Fit5Schedule22)){}else{print("E
rror Cohort 22")}
if(length(Age5Schedule23)==length(Fit5Schedule23)){}else{print("E
rror Cohort 23")}
if(length(Age5Schedule24)==length(Fit5Schedule24)){}else{print("E
rror Cohort 24")}
if(length(Age5Schedule25)==length(Fit5Schedule25)){}else{print("E
rror Cohort 25")}
if(length(Age5Schedule26)==length(Fit5Schedule26)){}else{print("E
rror Cohort 26")}
if(length(Age5Schedule27)==length(Fit5Schedule27)){}else{print("E
rror Cohort 27")}
if(length(Age5Schedule28)==length(Fit5Schedule28)){}else{print("E
rror Cohort 28")}
if(length(Age5Schedule29)==length(Fit5Schedule29)){}else{print("E
rror Cohort 29")}
if(length(Age5Schedule30)==length(Fit5Schedule30)){}else{print("E
rror Cohort 30")}
if(length(Age5Schedule31)==length(Fit5Schedule31)){}else{print("E
rror Cohort 31")}
if(length(Age5Schedule32)==length(Fit5Schedule32)){}else{print("E
rror Cohort 32")}
if(length(Age5Schedule33)==length(Fit5Schedule33)){}else{print("E
rror Cohort 33")}
if(length(Age5Schedule34)==length(Fit5Schedule34)){}else{print("E
rror Cohort 34")}
if(length(Age5Schedule35)==length(Fit5Schedule35)){}else{print("E
rror Cohort 35")}
if(length(Age5Schedule36)==length(Fit5Schedule36)){}else{print("E
rror Cohort 36")}
if(length(Age5Schedule37)==length(Fit5Schedule37)){}else{print("E
rror Cohort 37")}
if(length(Age5Schedule38)==length(Fit5Schedule38)){}else{print("E
rror Cohort 38")}
if(length(Age5Schedule39)==length(Fit5Schedule39)){}else{print("E
```

```
rror Cohort 39")}
if(length(Age5Schedule40)==length(Fit5Schedule40)){}else{print("E
rror Cohort 40")}
if(length(Age5Schedule41)==length(Fit5Schedule41)){}else{print("E
rror Cohort 41")}
if(length(Age5Schedule42)==length(Fit5Schedule42)){}else{print("E
rror Cohort 42")}
if(length(Age5Schedule43)==length(Fit5Schedule43)){}else{print("E
rror Cohort 43")}
if(length(Age5Schedule44)==length(Fit5Schedule44)){}else{print("E
rror Cohort 44")}
if(length(Age5Schedule45)==length(Fit5Schedule45)){}else{print("E
rror Cohort 45")}

#=================================================================
===
#POLICY 6 Annual FIT screening among age group 55(50)-74 years an
d diagnostic colonoscopy after a positive FIT result at a cut-off
of 50ng/ml
#6. 1y 55(50)-74, FIT 50
Policies6Age <- read_excel("InputFiles/Policies4.xlsx", sheet=7)

Policies6Fit <- read_excel("InputFiles/Policies4.xlsx", sheet=11)

TargetCohorts=seq(1:35)
for(i in TargetCohorts){
  assign(paste("Age6Schedule",i,sep=""),Policies6Age[Policies6Age
$Cohort==i,-1][!(is.na(Policies6Age[Policies6Age$Cohort==i,-1]))]
)

  assign(paste("Fit6Schedule",i,sep=""),Policies6Fit[Policies6Fit
$Cohort==i,-1][!(is.na(Policies6Fit[Policies6Fit$Cohort==i,-1]))]
)}


Schedules6=list(
  Age6Schedule1=Age6Schedule1,
  Age6Schedule2=Age6Schedule2,
  Age6Schedule3=Age6Schedule3,
  Age6Schedule4=Age6Schedule4,
  Age6Schedule5=Age6Schedule5,
  Age6Schedule6=Age6Schedule6,
  Age6Schedule7=Age6Schedule7,
  Age6Schedule8=Age6Schedule8,
  Age6Schedule9=Age6Schedule9,
  Age6Schedule10=Age6Schedule10,
  Age6Schedule11=Age6Schedule11,
  Age6Schedule12=Age6Schedule12,
  Age6Schedule13=Age6Schedule13,
```

```
  Age6Schedule14=Age6Schedule14,
  Age6Schedule15=Age6Schedule15,
  Age6Schedule16=Age6Schedule16,
  Age6Schedule17=Age6Schedule17,
  Age6Schedule18=Age6Schedule18,
  Age6Schedule19=Age6Schedule19,
  Age6Schedule20=Age6Schedule20,
  Age6Schedule21=Age6Schedule21,
  Age6Schedule22=Age6Schedule22,
  Age6Schedule23=Age6Schedule23,
  Age6Schedule24=Age6Schedule24,
  Age6Schedule25=Age6Schedule25,
  Age6Schedule26=Age6Schedule26,
  Age6Schedule27=Age6Schedule27,
  Age6Schedule28=Age6Schedule28,
  Age6Schedule29=Age6Schedule29,
  Age6Schedule30=Age6Schedule30,
  Age6Schedule31=Age6Schedule31,
  Age6Schedule32=Age6Schedule32,
  Age6Schedule33=Age6Schedule33,
  Age6Schedule34=Age6Schedule34,
  Age6Schedule35=Age6Schedule35,
  Fit6Schedule1=Fit6Schedule1,
  Fit6Schedule2=Fit6Schedule2,
  Fit6Schedule3=Fit6Schedule3,
  Fit6Schedule4=Fit6Schedule4,
  Fit6Schedule5=Fit6Schedule5,
  Fit6Schedule6=Fit6Schedule6,
  Fit6Schedule7=Fit6Schedule7,
  Fit6Schedule8=Fit6Schedule8,
  Fit6Schedule9=Fit6Schedule9,
  Fit6Schedule10=Fit6Schedule10,
  Fit6Schedule11=Fit6Schedule11,
  Fit6Schedule12=Fit6Schedule12,
  Fit6Schedule13=Fit6Schedule13,
  Fit6Schedule14=Fit6Schedule14,
  Fit6Schedule15=Fit6Schedule15,
  Fit6Schedule16=Fit6Schedule16,
  Fit6Schedule17=Fit6Schedule17,
  Fit6Schedule18=Fit6Schedule18,
  Fit6Schedule19=Fit6Schedule19,
  Fit6Schedule20=Fit6Schedule20,
  Fit6Schedule21=Fit6Schedule21,
  Fit6Schedule22=Fit6Schedule22,
  Fit6Schedule23=Fit6Schedule23,
  Fit6Schedule24=Fit6Schedule24,
  Fit6Schedule25=Fit6Schedule25,
  Fit6Schedule26=Fit6Schedule26,
  Fit6Schedule27=Fit6Schedule27,
```

```
  Fit6Schedule28=Fit6Schedule28,
  Fit6Schedule29=Fit6Schedule29,
  Fit6Schedule30=Fit6Schedule30,
  Fit6Schedule31=Fit6Schedule31,
  Fit6Schedule32=Fit6Schedule32,
  Fit6Schedule33=Fit6Schedule33,
  Fit6Schedule34=Fit6Schedule34,
  Fit6Schedule35=Fit6Schedule35
  )

#Save the
saveRDS(Schedules6, file="InputFiles/ScreenSchedules/Schedules6.R
Data")

#Check for equal lengths of age and FIT strategies
if(length(Age6Schedule1) ==length(Fit6Schedule1) ){}else{print("E
rror Cohort 1)")}
if(length(Age6Schedule2) ==length(Fit6Schedule2) ){}else{print("E
rror Cohort 2)")}
if(length(Age6Schedule3) ==length(Fit6Schedule3) ){}else{print("E
rror Cohort 3)")}
if(length(Age6Schedule4) ==length(Fit6Schedule4) ){}else{print("E
rror Cohort 4)")}
if(length(Age6Schedule5) ==length(Fit6Schedule5) ){}else{print("E
rror Cohort 5)")}
if(length(Age6Schedule6) ==length(Fit6Schedule6) ){}else{print("E
rror Cohort 6)")}
if(length(Age6Schedule7) ==length(Fit6Schedule7) ){}else{print("E
rror Cohort 7)")}
if(length(Age6Schedule8) ==length(Fit6Schedule8) ){}else{print("E
rror Cohort 8)")}
if(length(Age6Schedule9) ==length(Fit6Schedule9) ){}else{print("E
rror Cohort 9)")}
if(length(Age6Schedule10)==length(Fit6Schedule10)){}else{print("E
rror Cohort 10")}
if(length(Age6Schedule11)==length(Fit6Schedule11)){}else{print("E
rror Cohort 11")}
if(length(Age6Schedule12)==length(Fit6Schedule12)){}else{print("E
rror Cohort 12")}
if(length(Age6Schedule13)==length(Fit6Schedule13)){}else{print("E
rror Cohort 13")}
if(length(Age6Schedule14)==length(Fit6Schedule14)){}else{print("E
rror Cohort 14")}
if(length(Age6Schedule15)==length(Fit6Schedule15)){}else{print("E
rror Cohort 15")}
if(length(Age6Schedule16)==length(Fit6Schedule16)){}else{print("E
rror Cohort 16")}
if(length(Age6Schedule17)==length(Fit6Schedule17)){}else{print("E
rror Cohort 17")}
```

```
if(length(Age6Schedule18)==length(Fit6Schedule18)){}else{print("E
rror Cohort 18")}
if(length(Age6Schedule19)==length(Fit6Schedule19)){}else{print("E
rror Cohort 19")}
if(length(Age6Schedule20)==length(Fit6Schedule20)){}else{print("E
rror Cohort 20")}
if(length(Age6Schedule21)==length(Fit6Schedule21)){}else{print("E
rror Cohort 21")}
if(length(Age6Schedule22)==length(Fit6Schedule22)){}else{print("E
rror Cohort 22")}
if(length(Age6Schedule23)==length(Fit6Schedule23)){}else{print("E
rror Cohort 23")}
if(length(Age6Schedule24)==length(Fit6Schedule24)){}else{print("E
rror Cohort 24")}
if(length(Age6Schedule25)==length(Fit6Schedule25)){}else{print("E
rror Cohort 25")}
if(length(Age6Schedule26)==length(Fit6Schedule26)){}else{print("E
rror Cohort 26")}
if(length(Age6Schedule27)==length(Fit6Schedule27)){}else{print("E
rror Cohort 27")}
if(length(Age6Schedule28)==length(Fit6Schedule28)){}else{print("E
rror Cohort 28")}
if(length(Age6Schedule29)==length(Fit6Schedule29)){}else{print("E
rror Cohort 29")}
if(length(Age6Schedule30)==length(Fit6Schedule30)){}else{print("E
rror Cohort 30")}
if(length(Age6Schedule31)==length(Fit6Schedule31)){}else{print("E
rror Cohort 31")}
if(length(Age6Schedule32)==length(Fit6Schedule32)){}else{print("E
rror Cohort 32")}
if(length(Age6Schedule33)==length(Fit6Schedule33)){}else{print("E
rror Cohort 33")}
if(length(Age6Schedule34)==length(Fit6Schedule34)){}else{print("E
rror Cohort 34")}
if(length(Age6Schedule35)==length(Fit6Schedule35)){}else{print("E
rror Cohort 35")}



#================================================================
==
#Policy 7 Biennial FIT screening among age group 59-69 years and
diagnostic colonoscopy after a positive FIT result at a cut-off o
f 50ng/ml
#7. 2y 59-69 FIT 50
Policies7Age <- read_excel("InputFiles/Policies3.xlsx", sheet=1)

Policies7Fit <- read_excel("InputFiles/Policies3.xlsx", sheet=13)
```

```
TargetCohorts=seq(1:31)
for(i in TargetCohorts){
assign(paste("Age7Schedule",i,sep=""),Policies7Age[Policies7Age$C
ohort==i,-1][!(is.na(Policies7Age[Policies7Age$Cohort==i,-1]))])
assign(paste("Fit7Schedule",i,sep=""),Policies7Fit[Policies7Fit$C
ohort==i,-1][!(is.na(Policies7Fit[Policies7Fit$Cohort==i,-1]))])}


  Schedules7=list(
    Age7Schedule1=Age7Schedule1,
    Age7Schedule2=Age7Schedule2,
    Age7Schedule3=Age7Schedule3,
    Age7Schedule4=Age7Schedule4,
    Age7Schedule5=Age7Schedule5,
    Age7Schedule6=Age7Schedule6,
    Age7Schedule7=Age7Schedule7,
    Age7Schedule8=Age7Schedule8,
    Age7Schedule9=Age7Schedule9,
    Age7Schedule10=Age7Schedule10,
    Age7Schedule11=Age7Schedule11,
    Age7Schedule12=Age7Schedule12,
    Age7Schedule13=Age7Schedule13,
    Age7Schedule14=Age7Schedule14,
    Age7Schedule15=Age7Schedule15,
    Age7Schedule16=Age7Schedule16,
    Age7Schedule17=Age7Schedule17,
    Age7Schedule18=Age7Schedule18,
    Age7Schedule19=Age7Schedule19,
    Age7Schedule20=Age7Schedule20,
    Age7Schedule21=Age7Schedule21,
    Age7Schedule22=Age7Schedule22,
    Age7Schedule23=Age7Schedule23,
    Age7Schedule24=Age7Schedule24,
    Age7Schedule25=Age7Schedule25,
    Age7Schedule26=Age7Schedule26,
    Age7Schedule27=Age7Schedule27,
    Age7Schedule28=Age7Schedule28,
    Age7Schedule29=Age7Schedule29,
    Age7Schedule30=Age7Schedule30,
    Age7Schedule31=Age7Schedule31,
    Fit7Schedule1=Fit7Schedule1,
    Fit7Schedule2=Fit7Schedule2,
    Fit7Schedule3=Fit7Schedule3,
    Fit7Schedule4=Fit7Schedule4,
    Fit7Schedule5=Fit7Schedule5,
    Fit7Schedule6=Fit7Schedule6,
    Fit7Schedule7=Fit7Schedule7,
    Fit7Schedule8=Fit7Schedule8,
```

```
    Fit7Schedule9=Fit7Schedule9,
    Fit7Schedule10=Fit7Schedule10,
    Fit7Schedule11=Fit7Schedule11,
    Fit7Schedule12=Fit7Schedule12,
    Fit7Schedule13=Fit7Schedule13,
    Fit7Schedule14=Fit7Schedule14,
    Fit7Schedule15=Fit7Schedule15,
    Fit7Schedule16=Fit7Schedule16,
    Fit7Schedule17=Fit7Schedule17,
    Fit7Schedule18=Fit7Schedule18,
    Fit7Schedule19=Fit7Schedule19,
    Fit7Schedule20=Fit7Schedule20,
    Fit7Schedule21=Fit7Schedule21,
    Fit7Schedule22=Fit7Schedule22,
    Fit7Schedule23=Fit7Schedule23,
    Fit7Schedule24=Fit7Schedule24,
    Fit7Schedule25=Fit7Schedule25,
    Fit7Schedule26=Fit7Schedule26,
    Fit7Schedule27=Fit7Schedule27,
    Fit7Schedule28=Fit7Schedule28,
    Fit7Schedule29=Fit7Schedule29,
    Fit7Schedule30=Fit7Schedule30,
    Fit7Schedule31=Fit7Schedule31)

  #Save the
  saveRDS(Schedules7, file="InputFiles/ScreenSchedules/Schedules7
.RData")

#Check for equal lengths of age and FIT strategies
if(length(Age7Schedule1) ==length(Fit7Schedule1) ){}else{print("E
rror Cohort 1)")}
if(length(Age7Schedule2) ==length(Fit7Schedule2) ){}else{print("E
rror Cohort 2)")}
if(length(Age7Schedule3) ==length(Fit7Schedule3) ){}else{print("E
rror Cohort 3)")}
if(length(Age7Schedule4) ==length(Fit7Schedule4) ){}else{print("E
rror Cohort 4)")}
if(length(Age7Schedule5) ==length(Fit7Schedule5) ){}else{print("E
rror Cohort 5)")}
if(length(Age7Schedule6) ==length(Fit7Schedule6) ){}else{print("E
rror Cohort 6)")}
if(length(Age7Schedule7) ==length(Fit7Schedule7) ){}else{print("E
rror Cohort 7)")}
if(length(Age7Schedule8) ==length(Fit7Schedule8) ){}else{print("E
rror Cohort 8)")}
if(length(Age7Schedule9) ==length(Fit7Schedule9) ){}else{print("E
rror Cohort 9)")}
if(length(Age7Schedule10)==length(Fit7Schedule10)){}else{print("E
rror Cohort 10")}
```

```
if(length(Age7Schedule11)==length(Fit7Schedule11)){}else{print("E
rror Cohort 11")}
if(length(Age7Schedule12)==length(Fit7Schedule12)){}else{print("E
rror Cohort 12")}
if(length(Age7Schedule13)==length(Fit7Schedule13)){}else{print("E
rror Cohort 13")}
if(length(Age7Schedule14)==length(Fit7Schedule14)){}else{print("E
rror Cohort 14")}
if(length(Age7Schedule15)==length(Fit7Schedule15)){}else{print("E
rror Cohort 15")}
if(length(Age7Schedule16)==length(Fit7Schedule16)){}else{print("E
rror Cohort 16")}
if(length(Age7Schedule17)==length(Fit7Schedule17)){}else{print("E
rror Cohort 17")}
if(length(Age7Schedule18)==length(Fit7Schedule18)){}else{print("E
rror Cohort 18")}
if(length(Age7Schedule19)==length(Fit7Schedule19)){}else{print("E
rror Cohort 19")}
if(length(Age7Schedule20)==length(Fit7Schedule20)){}else{print("E
rror Cohort 20")}
if(length(Age7Schedule21)==length(Fit7Schedule21)){}else{print("E
rror Cohort 21")}
if(length(Age7Schedule22)==length(Fit7Schedule22)){}else{print("E
rror Cohort 22")}
if(length(Age7Schedule23)==length(Fit7Schedule23)){}else{print("E
rror Cohort 23")}
if(length(Age7Schedule24)==length(Fit7Schedule24)){}else{print("E
rror Cohort 24")}
if(length(Age7Schedule25)==length(Fit7Schedule25)){}else{print("E
rror Cohort 25")}
if(length(Age7Schedule26)==length(Fit7Schedule26)){}else{print("E
rror Cohort 26")}
if(length(Age7Schedule27)==length(Fit7Schedule27)){}else{print("E
rror Cohort 27")}
if(length(Age7Schedule28)==length(Fit7Schedule28)){}else{print("E
rror Cohort 28")}
if(length(Age7Schedule29)==length(Fit7Schedule29)){}else{print("E
rror Cohort 29")}
if(length(Age7Schedule30)==length(Fit7Schedule30)){}else{print("E
rror Cohort 30")}
if(length(Age7Schedule31)==length(Fit7Schedule31)){}else{print("E
rror Cohort 31")}


#=============================================================
===
  #Policy 8 Annual FIT screening among age group 55(50)-74 years
and diagnostic colonoscopy after a positive FIT result at a cut-o
ff of 225ng/ml
```

```
#8. 1y 55(50)-74 FIT 225

  Policies8Age <- read_excel("InputFiles/Policies4.xlsx", sheet=7
)

  Policies8Fit <- read_excel("InputFiles/Policies4.xlsx", sheet=1
2)

  TargetCohorts=seq(1:35)
  for(i in TargetCohorts){
    assign(paste("Age8Schedule",i,sep=""),Policies8Age[Policies8A
ge$Cohort==i,-1][!(is.na(Policies8Age[Policies8Age$Cohort==i,-1])
)])
    assign(paste("Fit8Schedule",i,sep=""),Policies8Fit[Policies8F
it$Cohort==i,-1][!(is.na(Policies8Fit[Policies8Fit$Cohort==i,-1])
)])}


    Schedules8=list(
      Age8Schedule1=Age8Schedule1,
      Age8Schedule2=Age8Schedule2,
      Age8Schedule3=Age8Schedule3,
      Age8Schedule4=Age8Schedule4,
      Age8Schedule5=Age8Schedule5,
      Age8Schedule6=Age8Schedule6,
      Age8Schedule7=Age8Schedule7,
      Age8Schedule8=Age8Schedule8,
      Age8Schedule9=Age8Schedule9,
      Age8Schedule10=Age8Schedule10,
      Age8Schedule11=Age8Schedule11,
      Age8Schedule12=Age8Schedule12,
      Age8Schedule13=Age8Schedule13,
      Age8Schedule14=Age8Schedule14,
      Age8Schedule15=Age8Schedule15,
      Age8Schedule16=Age8Schedule16,
      Age8Schedule17=Age8Schedule17,
      Age8Schedule18=Age8Schedule18,
      Age8Schedule19=Age8Schedule19,
      Age8Schedule20=Age8Schedule20,
      Age8Schedule21=Age8Schedule21,
      Age8Schedule22=Age8Schedule22,
      Age8Schedule23=Age8Schedule23,
      Age8Schedule24=Age8Schedule24,
      Age8Schedule25=Age8Schedule25,
      Age8Schedule26=Age8Schedule26,
      Age8Schedule27=Age8Schedule27,
      Age8Schedule28=Age8Schedule28,
      Age8Schedule29=Age8Schedule29,
      Age8Schedule30=Age8Schedule30,
```

```
      Age8Schedule31=Age8Schedule31,
      Age8Schedule32=Age8Schedule32,
      Age8Schedule33=Age8Schedule33,
      Age8Schedule34=Age8Schedule34,
      Age8Schedule35=Age8Schedule35,
      Fit8Schedule1=Fit8Schedule1,
      Fit8Schedule2=Fit8Schedule2,
      Fit8Schedule3=Fit8Schedule3,
      Fit8Schedule4=Fit8Schedule4,
      Fit8Schedule5=Fit8Schedule5,
      Fit8Schedule6=Fit8Schedule6,
      Fit8Schedule7=Fit8Schedule7,
      Fit8Schedule8=Fit8Schedule8,
      Fit8Schedule9=Fit8Schedule9,
      Fit8Schedule10=Fit8Schedule10,
      Fit8Schedule11=Fit8Schedule11,
      Fit8Schedule12=Fit8Schedule12,
      Fit8Schedule13=Fit8Schedule13,
      Fit8Schedule14=Fit8Schedule14,
      Fit8Schedule15=Fit8Schedule15,
      Fit8Schedule16=Fit8Schedule16,
      Fit8Schedule17=Fit8Schedule17,
      Fit8Schedule18=Fit8Schedule18,
      Fit8Schedule19=Fit8Schedule19,
      Fit8Schedule20=Fit8Schedule20,
      Fit8Schedule21=Fit8Schedule21,
      Fit8Schedule22=Fit8Schedule22,
      Fit8Schedule23=Fit8Schedule23,
      Fit8Schedule24=Fit8Schedule24,
      Fit8Schedule25=Fit8Schedule25,
      Fit8Schedule26=Fit8Schedule26,
      Fit8Schedule27=Fit8Schedule27,
      Fit8Schedule28=Fit8Schedule28,
      Fit8Schedule29=Fit8Schedule29,
      Fit8Schedule30=Fit8Schedule30,
      Fit8Schedule31=Fit8Schedule31,
      Fit8Schedule32=Fit8Schedule32,
      Fit8Schedule33=Fit8Schedule33,
      Fit8Schedule34=Fit8Schedule34,
      Fit8Schedule35=Fit8Schedule35
      )

#Save the
saveRDS(Schedules8, file="InputFiles/ScreenSchedules/Schedules8.R
Data")


if(length(Age8Schedule1) ==length(Fit8Schedule1) ){}else{print("E
rror Cohort 1)")}
```

```
if(length(Age8Schedule2) ==length(Fit8Schedule2) ){}else{print("E
rror Cohort 2)")}
if(length(Age8Schedule3) ==length(Fit8Schedule3) ){}else{print("E
rror Cohort 3)")}
if(length(Age8Schedule4) ==length(Fit8Schedule4) ){}else{print("E
rror Cohort 4)")}
if(length(Age8Schedule5) ==length(Fit8Schedule5) ){}else{print("E
rror Cohort 5)")}
if(length(Age8Schedule6) ==length(Fit8Schedule6) ){}else{print("E
rror Cohort 6)")}
if(length(Age8Schedule7) ==length(Fit8Schedule7) ){}else{print("E
rror Cohort 7)")}
if(length(Age8Schedule8) ==length(Fit8Schedule8) ){}else{print("E
rror Cohort 8)")}
if(length(Age8Schedule9) ==length(Fit8Schedule9) ){}else{print("E
rror Cohort 9)")}
if(length(Age8Schedule10)==length(Fit8Schedule10)){}else{print("E
rror Cohort 10")}
if(length(Age8Schedule11)==length(Fit8Schedule11)){}else{print("E
rror Cohort 11")}
if(length(Age8Schedule12)==length(Fit8Schedule12)){}else{print("E
rror Cohort 12")}
if(length(Age8Schedule13)==length(Fit8Schedule13)){}else{print("E
rror Cohort 13")}
if(length(Age8Schedule14)==length(Fit8Schedule14)){}else{print("E
rror Cohort 14")}
if(length(Age8Schedule15)==length(Fit8Schedule15)){}else{print("E
rror Cohort 15")}
if(length(Age8Schedule16)==length(Fit8Schedule16)){}else{print("E
rror Cohort 16")}
if(length(Age8Schedule17)==length(Fit8Schedule17)){}else{print("E
rror Cohort 17")}
if(length(Age8Schedule18)==length(Fit8Schedule18)){}else{print("E
rror Cohort 18")}
if(length(Age8Schedule19)==length(Fit8Schedule19)){}else{print("E
rror Cohort 19")}
if(length(Age8Schedule20)==length(Fit8Schedule20)){}else{print("E
rror Cohort 20")}
if(length(Age8Schedule21)==length(Fit8Schedule21)){}else{print("E
rror Cohort 21")}
if(length(Age8Schedule22)==length(Fit8Schedule22)){}else{print("E
rror Cohort 22")}
if(length(Age8Schedule23)==length(Fit8Schedule23)){}else{print("E
rror Cohort 23")}
if(length(Age8Schedule24)==length(Fit8Schedule24)){}else{print("E
rror Cohort 24")}
if(length(Age8Schedule25)==length(Fit8Schedule25)){}else{print("E
rror Cohort 25")}
if(length(Age8Schedule26)==length(Fit8Schedule26)){}else{print("E
```

```
rror Cohort 26")}
if(length(Age8Schedule27)==length(Fit8Schedule27)){}else{print("E
rror Cohort 27")}
if(length(Age8Schedule28)==length(Fit8Schedule28)){}else{print("E
rror Cohort 28")}
if(length(Age8Schedule29)==length(Fit8Schedule29)){}else{print("E
rror Cohort 29")}
if(length(Age8Schedule30)==length(Fit8Schedule30)){}else{print("E
rror Cohort 30")}
if(length(Age8Schedule31)==length(Fit8Schedule31)){}else{print("E
rror Cohort 31")}
if(length(Age8Schedule32)==length(Fit8Schedule32)){}else{print("E
rror Cohort 32")}
if(length(Age8Schedule33)==length(Fit8Schedule33)){}else{print("E
rror Cohort 33")}
if(length(Age8Schedule34)==length(Fit8Schedule34)){}else{print("E
rror Cohort 34")}
if(length(Age8Schedule35)==length(Fit8Schedule35)){}else{print("E
rror Cohort 35")}



Strategy=Schedules8


#StrategyNumber=1
#Check a strategy
StrategyNumber=4#Read the screening strategy for simulation
Strategy<-readRDS(paste("InputFiles/ScreenSchedules/Schedules",St
rategyNumber,".RData",sep=""))


#Checking lengths of strategies
i=i+1
i
rbind(
length(unlist(Strategy[i])),
length(unlist(Strategy[i+length(Strategy)/2])))



i=i+1
i
rbind(
unlist(Strategy[i]),
unlist(Strategy[i+length(Strategy)/2]))
```

SECTION 2 SAMPLE BIRTH COHORTS AND ADHERENCE ARRAYS

In the PopulationSample file, we developed codes to sample birth cohorts in proportion to population

size and to create the adherence arrays for male and female.

```
#Install and load required packages
#readr is a package to read CSV files
install.packages("readr")
library(readr)
#readr is a package to read excel files
install.packages("readxl")
library(readxl)


#Set the working file directory path

try(setwd("File path"))


FullPopulationFemale<-try(as.data.frame(read.csv("InputFiles/Mill
ionWomen.csv")))
#FullPopulationMale  <-try(as.data.frame(read.csv("InputFiles/Mil
lionMen.csv"  )))


#Import survival data
try(SurvivalFemale<-read_excel("InputFiles/SurvivalProbability.xl
sx", sheet=1))


#Import population size
try(PopulationSizeIreland <- read_excel("InputFiles/PopulationSiz
eIreland.xlsx", sheet=1))

#View(PopulationSizeIreland)

#Assigning highest element number to the crc death element
FullPopulationFemale$element[which(FullPopulationFemale$tag=="crc
_death")]<-FullPopulationFemale$element[which(FullPopulationFemal
e$tag=="crc_death")-1]
#Factor for reducing population size, recommended values of 20, 1
0 and 1, 1 means equal to the population size
PopulationDemoninatorFactor=10


#Redefine the male and female column in PopulationSizeIreland as
numeric.
```

```
PopulationSizeIreland$Female<-
as.numeric(PopulationSizeIreland$Female)


#Curtail the PopulationSizeIreland required rows only. The
minimum age and the maximum age of interest for our screening
policies are 30 and 80 respectively.

PopulationSizeIreland<-PopulationSizeIreland[30:80,]

CohortSequence<-PopulationSizeIreland$Cohort


#Add columns named BirthMale and BirthFemale to
PopulationSizeIreland

PopulationSizeIreland<-cbind(PopulationSizeIreland,
BirthFemale=NA)

#We calculate the population size from age 30 to age 80 at birth
by multiplying the population size with the relative survival
rate (1/SurvivalProbability).

PopulationSizeIreland$BirthFemale<-
round(PopulationSizeIreland$Female*(1/(SurvivalFemale$SurvivalPro
bability[seq(which(SurvivalFemale$Age==30),which(SurvivalFemale$A
ge==80))])),0)


#We add 1 to the population number (to remove individual 0).
#Increase all population numbers by one
FullPopulationFemale$individual<-
FullPopulationFemale$individual+1



for (i in 1:nrow(PopulationSizeIreland)){

#Rescale and round the birth population in accordance with a
scaling factor (PopulationDemoninatorFactor)
PopulationSizeFemale<-
round(PopulationSizeIreland$BirthFemale[PopulationSizeIreland$Coh
ort==i]/PopulationDemoninatorFactor,0)


#Create a vector of individuals to sample from the full
population
FemalePopulationRef<-sample(x =
1:max(FullPopulationFemale$individual),size =
PopulationSizeFemale,replace = FALSE)
```

```
#Sample from the full population
SamplePopulationFemale<-
FullPopulationFemale[FullPopulationFemale$individual %in%
FemalePopulationRef,]

#Re number the sampled individuals from 1 onward sequentially
IndividualIndexFemale=as.data.frame(cbind(Old=unique(SamplePopula
tionFemale$individual),New=seq(1,length(unique(SamplePopulationFe
male$individual)))))

for (x in 1:nrow(IndividualIndexFemale)){
SamplePopulationFemale$individual[SamplePopulationFemale$individu
al==IndividualIndexFemale$Old[x]]<-x}

write.table(SamplePopulationFemale,paste("InputFiles/BirthCohortS
izes/Population_Female", PopulationSizeIreland$Cohort[i],
".txt",sep=""))

}

#Import Adherence proportion
#try(AdherenceAssumptionsProportion <-
read_excel("Filepath/Adherenceassumptions.xlsx", sheet=x))

#Import Adherence probability

#try(AdherenceAssumptionsProbability <- read_excel("Filepath",
sheet=x))



for (i in 1:nrow(PopulationSizeIreland)){

PopulationSizeFemale<-
round(PopulationSizeIreland$BirthFemale[PopulationSizeIreland$Coh
ort==i]/PopulationDemoninatorFactor,0)

NumberSimulated<-PopulationSizeFemale

#Assign proportion value from the excel, this is taking values
from first row which is Male and columns as specified
NonAdherenceProportion      <-
AdherenceAssumptionsProportion[1,"Non"    ]
PerfectAdherenceProportion  <-
AdherenceAssumptionsProportion[1,"Perfect"]
LowAdherenceProportion      <-
AdherenceAssumptionsProportion[1,"Low"    ]
HighAdherenceProportion     <-
AdherenceAssumptionsProportion[1,"High"   ]
```

```r
#Assign age specific probability for non adherence category
NonAdherenceProbability40_44 <-
as.numeric(AdherenceAssumptionsProbability[1, "Non"])
NonAdherenceProbability45_49 <-
as.numeric(AdherenceAssumptionsProbability[2, "Non"])
NonAdherenceProbability50_54 <-
as.numeric(AdherenceAssumptionsProbability[3, "Non"])
NonAdherenceProbability55_59 <-
as.numeric(AdherenceAssumptionsProbability[4, "Non"])
NonAdherenceProbability60_64 <-
as.numeric(AdherenceAssumptionsProbability[5, "Non"])
NonAdherenceProbability65_69 <-
as.numeric(AdherenceAssumptionsProbability[6, "Non"])
NonAdherenceProbability70_74 <-
as.numeric(AdherenceAssumptionsProbability[7, "Non"])
NonAdherenceProbability75_79 <-
as.numeric(AdherenceAssumptionsProbability[8, "Non"])
NonAdherenceProbability80_84 <-
as.numeric(AdherenceAssumptionsProbability[9, "Non"])
NonAdherenceProbability85_89 <-
as.numeric(AdherenceAssumptionsProbability[10,"Non"])
NonAdherenceProbability90_94 <-
as.numeric(AdherenceAssumptionsProbability[11,"Non"])
NonAdherenceProbability95_100<-
as.numeric(AdherenceAssumptionsProbability[12,"Non"])


#Assign age specific probability for low adherence category
LowAdherenceProbability40_44 <-
as.numeric(AdherenceAssumptionsProbability[1, "Low"])
LowAdherenceProbability45_49 <-
as.numeric(AdherenceAssumptionsProbability[2, "Low"])
LowAdherenceProbability50_54 <-
as.numeric(AdherenceAssumptionsProbability[3, "Low"])
LowAdherenceProbability55_59 <-
as.numeric(AdherenceAssumptionsProbability[4, "Low"])
LowAdherenceProbability60_64 <-
as.numeric(AdherenceAssumptionsProbability[5, "Low"])
LowAdherenceProbability65_69 <-
as.numeric(AdherenceAssumptionsProbability[6, "Low"])
LowAdherenceProbability70_74 <-
as.numeric(AdherenceAssumptionsProbability[7, "Low"])
LowAdherenceProbability75_79 <-
as.numeric(AdherenceAssumptionsProbability[8, "Low"])
LowAdherenceProbability80_84 <-
as.numeric(AdherenceAssumptionsProbability[9, "Low"])
LowAdherenceProbability85_89 <-
as.numeric(AdherenceAssumptionsProbability[10,"Low"])
```

```
LowAdherenceProbability90_94 <-
as.numeric(AdherenceAssumptionsProbability[11,"Low"])
LowAdherenceProbability95_100<-
as.numeric(AdherenceAssumptionsProbability[12,"Low"])

#Assign age specific probability for high adherence category
HighAdherenceProbability40_44 <-
as.numeric(AdherenceAssumptionsProbability[1, "High"])
HighAdherenceProbability45_49 <-
as.numeric(AdherenceAssumptionsProbability[2, "High"])
HighAdherenceProbability50_54 <-
as.numeric(AdherenceAssumptionsProbability[3, "High"])
HighAdherenceProbability55_59 <-
as.numeric(AdherenceAssumptionsProbability[4, "High"])
HighAdherenceProbability60_64 <-
as.numeric(AdherenceAssumptionsProbability[5, "High"])
HighAdherenceProbability65_69 <-
as.numeric(AdherenceAssumptionsProbability[6, "High"])
HighAdherenceProbability70_74 <-
as.numeric(AdherenceAssumptionsProbability[7, "High"])
HighAdherenceProbability75_79 <-
as.numeric(AdherenceAssumptionsProbability[8, "High"])
HighAdherenceProbability80_84 <-
as.numeric(AdherenceAssumptionsProbability[9, "High"])
HighAdherenceProbability85_89 <-
as.numeric(AdherenceAssumptionsProbability[10,"High"])
HighAdherenceProbability90_94 <-
as.numeric(AdherenceAssumptionsProbability[11,"High"])
HighAdherenceProbability95_100<-
as.numeric(AdherenceAssumptionsProbability[12,"High"])


#Assign age specific probability for perfect adherence category
PerfectAdherenceProbability40_44 <-
as.numeric(AdherenceAssumptionsProbability[1, "Perfect"])
PerfectAdherenceProbability45_49 <-
as.numeric(AdherenceAssumptionsProbability[2, "Perfect"])
PerfectAdherenceProbability50_54 <-
as.numeric(AdherenceAssumptionsProbability[3, "Perfect"])
PerfectAdherenceProbability55_59 <-
as.numeric(AdherenceAssumptionsProbability[4, "Perfect"])
PerfectAdherenceProbability60_64 <-
as.numeric(AdherenceAssumptionsProbability[5, "Perfect"])
PerfectAdherenceProbability65_69 <-
as.numeric(AdherenceAssumptionsProbability[6, "Perfect"])
PerfectAdherenceProbability70_74 <-
as.numeric(AdherenceAssumptionsProbability[7, "Perfect"])
PerfectAdherenceProbability75_79 <-
as.numeric(AdherenceAssumptionsProbability[8, "Perfect"])
```

```
PerfectAdherenceProbability80_84 <-
as.numeric(AdherenceAssumptionsProbability[9, "Perfect"])
PerfectAdherenceProbability85_89 <-
as.numeric(AdherenceAssumptionsProbability[10,"Perfect"])
PerfectAdherenceProbability90_94 <-
as.numeric(AdherenceAssumptionsProbability[11,"Perfect"])
PerfectAdherenceProbability95_100<-
as.numeric(AdherenceAssumptionsProbability[12,"Perfect"])


# Create a table with number simulated and age from 40 to 100,give
name to the columns from 40 to 100
FemaleAdherence=array(NA, dim = c(NumberSimulated, (101-39)))
colnames(FemaleAdherence) <- c("IndividualSimulated",
seq(40,100,1))

#Assign a sequence of numbers from 1 to PopulationSize to
"IndividualSimulated" column in the FemaleAdherence
FemaleAdherence[, "IndividualSimulated"] <- seq(1,
PopulationSizeFemale)

## This gives total number in each category, there are 4
categories of attendance with 0.25 in each group and we have
rounded them to get the total number in each category
nonattenders<-round(NumberSimulated*NonAdherenceProportion)
perfectattenders<-
round(NumberSimulated*PerfectAdherenceProportion)
lowattenders<-round(NumberSimulated*LowAdherenceProportion)
highattenders<-NumberSimulated-nonattenders-perfectattenders-
lowattenders


#Create correlated random variables
R <- matrix(0.9, nrow = 61, ncol = 61)
diag(R) <- 1
C = t(chol(R))
nvars = dim(C)[1]
n = nrow(FemaleAdherence)
set.seed(1)
random.normal = matrix(rnorm(nvars*n,0,1), nrow=nvars, ncol=n);
U = t(pnorm(C %*% random.normal))


## Assign probability of attendance for low attenders, We use
probability function to return 1 if x is less than
LowAdherenceProbability and 0 otherwise.
probFunction <- function(x) {
ifelse(x<as.numeric(LowAdherenceProbability),1,0)}

LowAdherenceProbability<-LowAdherenceProbability40_44
```

```
FemaleAdherence[as.numeric(nonattenders+perfectattenders+1):as.nu
meric(nonattenders+perfectattenders+lowattenders),2:6] <-
probFunction(U[as.numeric(nonattenders+perfectattenders+1):as.num
eric(nonattenders+perfectattenders+lowattenders),1:5])

LowAdherenceProbability<-LowAdherenceProbability45_49
FemaleAdherence[as.numeric(nonattenders+perfectattenders+1):as.nu
meric(nonattenders+perfectattenders+lowattenders),7:11] <-
probFunction(U[as.numeric(nonattenders+perfectattenders+1):as.num
eric(nonattenders+perfectattenders+lowattenders),6:10])

LowAdherenceProbability<-LowAdherenceProbability50_54
FemaleAdherence[as.numeric(nonattenders+perfectattenders+1):as.nu
meric(nonattenders+perfectattenders+lowattenders),12:16] <-
probFunction(U[as.numeric(nonattenders+perfectattenders+1):as.num
eric(nonattenders+perfectattenders+lowattenders),11:15])

LowAdherenceProbability<-LowAdherenceProbability55_59
FemaleAdherence[as.numeric(nonattenders+perfectattenders+1):as.nu
meric(nonattenders+perfectattenders+lowattenders),17:21] <-
probFunction(U[as.numeric(nonattenders+perfectattenders+1):as.num
eric(nonattenders+perfectattenders+lowattenders),16:20])

LowAdherenceProbability<-LowAdherenceProbability60_64
FemaleAdherence[as.numeric(nonattenders+perfectattenders+1):as.nu
meric(nonattenders+perfectattenders+lowattenders),22:26] <-
probFunction(U[as.numeric(nonattenders+perfectattenders+1):as.num
eric(nonattenders+perfectattenders+lowattenders),21:25])

LowAdherenceProbability<-LowAdherenceProbability65_69
FemaleAdherence[as.numeric(nonattenders+perfectattenders+1):as.nu
meric(nonattenders+perfectattenders+lowattenders),27:31] <-
probFunction(U[as.numeric(nonattenders+perfectattenders+1):as.num
eric(nonattenders+perfectattenders+lowattenders),26:30])

LowAdherenceProbability<-LowAdherenceProbability70_74
FemaleAdherence[as.numeric(nonattenders+perfectattenders+1):as.nu
meric(nonattenders+perfectattenders+lowattenders),32:36] <-
probFunction(U[as.numeric(nonattenders+perfectattenders+1):as.num
eric(nonattenders+perfectattenders+lowattenders),31:35])

LowAdherenceProbability<-LowAdherenceProbability75_79
FemaleAdherence[as.numeric(nonattenders+perfectattenders+1):as.nu
meric(nonattenders+perfectattenders+lowattenders),37:41] <-
probFunction(U[as.numeric(nonattenders+perfectattenders+1):as.num
eric(nonattenders+perfectattenders+lowattenders),36:40])

LowAdherenceProbability<-LowAdherenceProbability80_84
FemaleAdherence[as.numeric(nonattenders+perfectattenders+1):as.nu
meric(nonattenders+perfectattenders+lowattenders),42:46] <-
```

```
probFunction(U[as.numeric(nonattenders+perfectattenders+1):as.num
eric(nonattenders+perfectattenders+lowattenders),41:45])

LowAdherenceProbability<-LowAdherenceProbability85_89
FemaleAdherence[as.numeric(nonattenders+perfectattenders+1):as.nu
meric(nonattenders+perfectattenders+lowattenders),47:51] <-
probFunction(U[as.numeric(nonattenders+perfectattenders+1):as.num
eric(nonattenders+perfectattenders+lowattenders),46:50])

LowAdherenceProbability<-LowAdherenceProbability90_94
FemaleAdherence[as.numeric(nonattenders+perfectattenders+1):as.nu
meric(nonattenders+perfectattenders+lowattenders),52:56] <-
probFunction(U[as.numeric(nonattenders+perfectattenders+1):as.num
eric(nonattenders+perfectattenders+lowattenders),51:55])

LowAdherenceProbability<-LowAdherenceProbability95_100
FemaleAdherence[as.numeric(nonattenders+perfectattenders+1):as.nu
meric(nonattenders+perfectattenders+lowattenders),57:62] <-
probFunction(U[as.numeric(nonattenders+perfectattenders+1):as.num
eric(nonattenders+perfectattenders+lowattenders),56:61])

## Assign probability of attendance for non attenders

probFunction <- function(x) {
ifelse(x<as.numeric(NonAdherenceProbability),1,0)}

NonAdherenceProbability<-NonAdherenceProbability40_44
FemaleAdherence[as.numeric(1:as.numeric(nonattenders)),2:6] <-
probFunction(U[1:as.numeric(nonattenders),1:5])

NonAdherenceProbability<-NonAdherenceProbability45_49
FemaleAdherence[as.numeric(1:as.numeric(nonattenders)),7:11] <-
probFunction(U[1:as.numeric(nonattenders),6:10])

NonAdherenceProbability<-NonAdherenceProbability50_54
FemaleAdherence[as.numeric(1:as.numeric(nonattenders)),12:16] <-
probFunction(U[1:as.numeric(nonattenders),11:15])

NonAdherenceProbability<-NonAdherenceProbability55_59
FemaleAdherence[as.numeric(1:as.numeric(nonattenders)),17:21] <-
probFunction(U[1:as.numeric(nonattenders),16:20])

NonAdherenceProbability<-NonAdherenceProbability60_64
FemaleAdherence[as.numeric(1:as.numeric(nonattenders)),22:26] <-
probFunction(U[1:as.numeric(nonattenders),21:25])

NonAdherenceProbability<-NonAdherenceProbability65_69
FemaleAdherence[as.numeric(1:as.numeric(nonattenders)),27:31] <-
probFunction(U[1:as.numeric(nonattenders),26:30])
```

```
NonAdherenceProbability<-NonAdherenceProbability70_74
FemaleAdherence[as.numeric(1:as.numeric(nonattenders)),32:36] <-
probFunction(U[1:as.numeric(nonattenders),31:35])

NonAdherenceProbability<-NonAdherenceProbability75_79
FemaleAdherence[as.numeric(1:as.numeric(nonattenders)),37:41] <-
probFunction(U[1:as.numeric(nonattenders),36:40])

NonAdherenceProbability<-NonAdherenceProbability80_84
FemaleAdherence[as.numeric(1:as.numeric(nonattenders)),42:46] <-
probFunction(U[1:as.numeric(nonattenders),41:45])

LowAdherenceProbability<-LowAdherenceProbability85_89
FemaleAdherence[as.numeric(1:as.numeric(nonattenders)),47:51] <-
probFunction(U[1:as.numeric(nonattenders),46:50])

NonAdherenceProbability<-NonAdherenceProbability90_94
FemaleAdherence[as.numeric(1:as.numeric(nonattenders)),52:56] <-
probFunction(U[1:as.numeric(nonattenders),51:55])

NonAdherenceProbability<-NonAdherenceProbability95_100
FemaleAdherence[as.numeric(1:as.numeric(nonattenders)),57:62] <-
probFunction(U[1:as.numeric(nonattenders),56:61])

## Assign probability of attendance for perfect attenders
probFunction <- function(x) {
ifelse(x<as.numeric(PerfectAdherenceProbability),1,0)}

PerfectAdherenceProbability<-PerfectAdherenceProbability40_44
FemaleAdherence[as.numeric(nonattenders+1):as.numeric(nonattender
s+perfectattenders),2:6] <-
probFunction(U[as.numeric(nonattenders+1):as.numeric(nonattenders
+perfectattenders),1:5])

PerfectAdherenceProbability<-PerfectAdherenceProbability45_49
FemaleAdherence[as.numeric(nonattenders+1):as.numeric(nonattender
s+perfectattenders),7:11] <-
probFunction(U[as.numeric(nonattenders+1):as.numeric(nonattenders
+perfectattenders),6:10])

PerfectAdherenceProbability<-PerfectAdherenceProbability50_54
FemaleAdherence[as.numeric(nonattenders+1):as.numeric(nonattender
s+perfectattenders),12:16] <-
probFunction(U[as.numeric(nonattenders+1):as.numeric(nonattenders
+perfectattenders),11:15])

PerfectAdherenceProbability<-PerfectAdherenceProbability55_59
FemaleAdherence[as.numeric(nonattenders+1):as.numeric(nonattender
s+perfectattenders),17:21] <-
probFunction(U[as.numeric(nonattenders+1):as.numeric(nonattenders
```

```
+perfectattenders),16:20])

PerfectAdherenceProbability<-PerfectAdherenceProbability60_64
FemaleAdherence[as.numeric(nonattenders+1):as.numeric(nonattender
s+perfectattenders),22:26] <-
probFunction(U[as.numeric(nonattenders+1):as.numeric(nonattenders
+perfectattenders),21:25])

PerfectAdherenceProbability<-PerfectAdherenceProbability65_69
FemaleAdherence[as.numeric(nonattenders+1):as.numeric(nonattender
s+perfectattenders),27:31] <-
probFunction(U[as.numeric(nonattenders+1):as.numeric(nonattenders
+perfectattenders),26:30])

PerfectAdherenceProbability<-PerfectAdherenceProbability70_74
FemaleAdherence[as.numeric(nonattenders+1):as.numeric(nonattender
s+perfectattenders),32:36] <-
probFunction(U[as.numeric(nonattenders+1):as.numeric(nonattenders
+perfectattenders),31:35])

PerfectAdherenceProbability<-PerfectAdherenceProbability75_79
FemaleAdherence[as.numeric(nonattenders+1):as.numeric(nonattender
s+perfectattenders),37:41] <-
probFunction(U[as.numeric(nonattenders+1):as.numeric(nonattenders
+perfectattenders),36:40])

PerfectAdherenceProbability<-PerfectAdherenceProbability80_84
FemaleAdherence[as.numeric(nonattenders+1):as.numeric(nonattender
s+perfectattenders),42:46] <-
probFunction(U[as.numeric(nonattenders+1):as.numeric(nonattenders
+perfectattenders),41:45])

PerfectAdherenceProbability<-PerfectAdherenceProbability85_89
FemaleAdherence[as.numeric(nonattenders+1):as.numeric(nonattender
s+perfectattenders),47:51] <-
probFunction(U[as.numeric(nonattenders+1):as.numeric(nonattenders
+perfectattenders),46:50])

PerfectAdherenceProbability<-PerfectAdherenceProbability90_94
FemaleAdherence[as.numeric(nonattenders+1):as.numeric(nonattender
s+perfectattenders),52:56] <-
probFunction(U[as.numeric(nonattenders+1):as.numeric(nonattenders
+perfectattenders),51:55])

PerfectAdherenceProbability<-PerfectAdherenceProbability95_100
FemaleAdherence[as.numeric(nonattenders+1):as.numeric(nonattender
s+perfectattenders),57:62] <-
probFunction(U[as.numeric(nonattenders+1):as.numeric(nonattenders
+perfectattenders),56:61])
```

```
## Assign probability of attendance for high attenders

probFunction <- function(x) {
ifelse(x<as.numeric(HighAdherenceProbability),1,0)}

HighAdherenceProbability<-HighAdherenceProbability40_44
FemaleAdherence[as.numeric(nonattenders+perfectattenders+lowatten
ders+1):as.numeric(nonattenders+perfectattenders+lowattenders+hig
hattenders),2:6] <-
probFunction(U[as.numeric(nonattenders+perfectattenders+lowattend
ers+1):as.numeric(nonattenders+perfectattenders+lowattenders+high
attenders),1:5])

HighAdherenceProbability<-HighAdherenceProbability45_49
FemaleAdherence[as.numeric(nonattenders+perfectattenders+lowatten
ders+1):as.numeric(nonattenders+perfectattenders+lowattenders+hig
hattenders),7:11] <-
probFunction(U[as.numeric(nonattenders+perfectattenders+lowattend
ers+1):as.numeric(nonattenders+perfectattenders+lowattenders+high
attenders),6:10])

HighAdherenceProbability<-HighAdherenceProbability50_54
FemaleAdherence[as.numeric(nonattenders+perfectattenders+lowatten
ders+1):as.numeric(nonattenders+perfectattenders+lowattenders+hig
hattenders),12:16] <-
probFunction(U[as.numeric(nonattenders+perfectattenders+lowattend
ers+1):as.numeric(nonattenders+perfectattenders+lowattenders+high
attenders),11:15])

HighAdherenceProbability<-HighAdherenceProbability55_59
FemaleAdherence[as.numeric(nonattenders+perfectattenders+lowatten
ders+1):as.numeric(nonattenders+perfectattenders+lowattenders+hig
hattenders),17:21] <-
probFunction(U[as.numeric(nonattenders+perfectattenders+lowattend
ers+1):as.numeric(nonattenders+perfectattenders+lowattenders+high
attenders),16:20])

HighAdherenceProbability<-HighAdherenceProbability60_64
FemaleAdherence[as.numeric(nonattenders+perfectattenders+lowatten
ders+1):as.numeric(nonattenders+perfectattenders+lowattenders+hig
hattenders),22:26] <-
probFunction(U[as.numeric(nonattenders+perfectattenders+lowattend
ers+1):as.numeric(nonattenders+perfectattenders+lowattenders+high
attenders),21:25])

HighAdherenceProbability<-HighAdherenceProbability65_69
FemaleAdherence[as.numeric(nonattenders+perfectattenders+lowatten
ders+1):as.numeric(nonattenders+perfectattenders+lowattenders+hig
hattenders),27:31] <-
```

```
probFunction(U[as.numeric(nonattenders+perfectattenders+lowattend
ers+1):as.numeric(nonattenders+perfectattenders+lowattenders+high
attenders),26:30])

HighAdherenceProbability<-HighAdherenceProbability70_74
FemaleAdherence[as.numeric(nonattenders+perfectattenders+lowatten
ders+1):as.numeric(nonattenders+perfectattenders+lowattenders+hig
hattenders),32:36] <-
probFunction(U[as.numeric(nonattenders+perfectattenders+lowattend
ers+1):as.numeric(nonattenders+perfectattenders+lowattenders+high
attenders),31:35])

HighAdherenceProbability<-HighAdherenceProbability75_79
FemaleAdherence[as.numeric(nonattenders+perfectattenders+lowatten
ders+1):as.numeric(nonattenders+perfectattenders+lowattenders+hig
hattenders),37:41] <-
probFunction(U[as.numeric(nonattenders+perfectattenders+lowattend
ers+1):as.numeric(nonattenders+perfectattenders+lowattenders+high
attenders),36:40])

HighAdherenceProbability<-HighAdherenceProbability80_84
FemaleAdherence[as.numeric(nonattenders+perfectattenders+lowatten
ders+1):as.numeric(nonattenders+perfectattenders+lowattenders+hig
hattenders),42:46] <-
probFunction(U[as.numeric(nonattenders+perfectattenders+lowattend
ers+1):as.numeric(nonattenders+perfectattenders+lowattenders+high
attenders),41:45])

HighAdherenceProbability<-HighAdherenceProbability85_89
FemaleAdherence[as.numeric(nonattenders+perfectattenders+lowatten
ders+1):as.numeric(nonattenders+perfectattenders+lowattenders+hig
hattenders),47:51] <-
probFunction(U[as.numeric(nonattenders+perfectattenders+lowattend
ers+1):as.numeric(nonattenders+perfectattenders+lowattenders+high
attenders),46:50])

HighAdherenceProbability<-HighAdherenceProbability90_94
FemaleAdherence[as.numeric(nonattenders+perfectattenders+lowatten
ders+1):as.numeric(nonattenders+perfectattenders+lowattenders+hig
hattenders),52:56] <-
probFunction(U[as.numeric(nonattenders+perfectattenders+lowattend
ers+1):as.numeric(nonattenders+perfectattenders+lowattenders+high
attenders),51:55])

HighAdherenceProbability<-HighAdherenceProbability95_100
FemaleAdherence[as.numeric(nonattenders+perfectattenders+lowatten
ders+1):as.numeric(nonattenders+perfectattenders+lowattenders+hig
hattenders),57:62] <-
probFunction(U[as.numeric(nonattenders+perfectattenders+lowattend
```

```
ers+1):as.numeric(nonattenders+perfectattenders+lowattenders+high
attenders),56:61])


#This is for cross check, this extracts values from every 1000th
row of the first column of the FemaleAdherence data frame
#(FemaleAdherence[seq(1,nrow(FemaleAdherence),1000),2])

write.table(FemaleAdherence,paste("InputFiles/AdherenceArrays/Adh
erence_Female", PopulationSizeIreland$Cohort[i], ".txt",sep=""))

}
```

SECTION 3 MAIN SIMULATION

We developed two versions of main simulation file for men and women. In the main simulation file, we have code for the preparation for simulation such as for setting working directory, loading required packages and importing datasets required. The required packages were readr, readxl to read excel files and CSV files. We imported the natural history simulation file for male and female, survival probability, adherence probability and proportion for male and female.

```
#This is the main file for calling all other components in the mo
del
#This section is preparation for simulation with setting working
directories, loading required packages and importing data


# Delete everything that is in R's memory
rm(list = ls())

#To time a process

time=proc.time()


#Create a file marker for debugging
File="ScreeningSimulation V23.R"

#Install and load required packages
#readr is a package to read CSV files
#install.packages("readr")
try(library(readr),silent=TRUE)
#readr is a package to read excel files
#install.packages("readxl")
try(library(readxl),silent=TRUE)

#Set the working file directory path
```

```
try(setwd("Filepath"))


#Import surival data
try(SurvivalFemale <- read_excel("InputFiles/SurvivalProbability.
xlsx", sheet=1))
try(SurvivalMale   <- read_excel("InputFiles/SurvivalProbability.
xlsx", sheet=2))

#Define the sex simulated
#Sex="Female"
Sex="Male"
TestSex="NotSpecific"


#TestSex=Sex

#Select the number of strategies to loop over
StrategyNumbers=c(1:1)

#Select which strategy to simulate
#StrategyNumber=1

for(StrategyNumber in StrategyNumbers){
#Read the screening strategy for simulation
Strategy<-readRDS(paste("InputFiles/ScreenSchedules/Schedules",St
rategyNumber,".RData",sep=""))

#Set out the Cohorts for simulation
Cohorts<-seq(1,length(Strategy)/2)

#Define the stop age for cohorts
SurveillanceStopAge=80


#Loop over the simulated cohorts
for (b in 1:length(Cohorts)){
#for (b in 26:26){
ScreenAges=unlist(Strategy[b])
FitCutOffStrategy=unlist(Strategy[b+length(Cohorts)])
Rounds=length(ScreenAges)


#Load the sex and cohort-specific population for simulation
if(Sex=="Female"){
CompleteData<-read.table(paste("InputFiles/BirthCohortSizes/Popul
ation_Female", Cohorts[b], ".txt",sep=""))}else{
CompleteData<-read.table(paste("InputFiles/BirthCohortSizes/Popul
ation_Male",   Cohorts[b], ".txt",sep=""))}

#Add a column for the lesion being present initially
```

```
CompleteData <-cbind(CompleteData,"LesionPresent"=1)

#Load the sex and cohort-specific adherence array
if(Sex=="Female"){
AdherenceArray<-read.table(paste("InputFiles/AdherenceArrays/Adhe
rence_Female", Cohorts[b], ".txt",sep=""))}else{
AdherenceArray<-read.table(paste("InputFiles/AdherenceArrays/Adhe
rence_Male",   Cohorts[b], ".txt",sep=""))}

#Define the number to be simulated with reference to the length o
f the adherence array
NumberSimulated=nrow(AdherenceArray)

#INVITATION AND ACTUAL ATTENDANCE

#Create Invite array with current policy, This array has 41 colum
ns; the first column is named IndividualInvited and rest of the c
olumns are named from 40 to 100 corresponding to age.

Invite <- array(0, dim = c(NumberSimulated, (101-39)))


#Give name to the columns from 40 to 100
colnames(Invite) <- c("IndividualInvited", seq(40,100,1))

#Assign value 1 to invited individuals as per screening ages
for (i in 1:length(ScreenAges)){
Invite[,as.character(ScreenAges[i])]<-1}

#Assign value 1 to the size of population simulated to Individual
Invited column
Invite[, "IndividualInvited"] <- seq(1, NumberSimulated

# Converting invite to dataframe
Invite <- as.data.frame(Invite)

#We use a loop function to iterate over all the screening ages to
create different subsets of data from CompleteData based on
individual's age and information on death from CRC death age
(crc_death) and death from other causes (oc_death). First it
identifies individuals who are older than the given screening age
and those who died from CRC or other causes. Then it creates
subsets of these individuals from the complete data. These are
the population not eligible for screening.

for (i in 1:length(ScreenAges)){
AlivePopulationRef <-subset(CompleteData, age > ScreenAges[i] &
(tag %in% c("oc_death", "crc_death")))$individual

AlivePopulation <-subset(CompleteData, individual %in%
```

```
AlivePopulationRef)

PopulationDeadBeforeScreeningAge <-
Invite$IndividualInvited[!(Invite$IndividualInvited %in%
AlivePopulation$individual)]


matching_rows <- which(Invite$IndividualInvited %in%
PopulationDeadBeforeScreeningAge)
Invite[matching_rows,(which(colnames(Invite)==ScreenAges[i])):nco
l(Invite)]<-0}


#Use adherence array if people respond to the invitation
ActualAttendance<-(array(0, dim = c(NumberSimulated, (101-39))))


#Give column names
colnames(ActualAttendance) <- c("IndividualReference",
seq(40,100,1))

# Assign values from 1 to the size of NumberSimulated
ActualAttendance[, "IndividualReference"] <- seq(1,
NumberSimulated)


#Converting all array as list
Invite <- as.data.frame(Invite)
AdherenceArray<- as.data.frame(AdherenceArray)
ActualAttendance <- as.data.frame(ActualAttendance)

#This gives value 1 when individuals invited adhere
ActualAttendance[(Invite == 1) & (AdherenceArray == 1)] <- 1


# DEFINE AND APPLY SCREENING POLICY
Cohort=Cohorts[b]


#Set objects to Null prior to running the loop
TruePositivesColonoscopy    <-NULL
FalsePositivesColonoscopy   <-NULL
SurveillanceColonoscopy     <-NULL
TotalColonoscopy            <-NULL
PrimaryScreens              <-NULL


#Run the model from the start of the screen age to the max of
surveillance age
ModelYears<-seq(from=min(ScreenAges),to=SurveillanceStopAge,by=1)
```

```
#Loop over the model years in the strategy
for (ModelYear in ModelYears){

  if(ModelYear%in%ScreenAges)
    {ScreenAge=ModelYear
  # Run the primary screening round with respect to test
sensitivity
  source("ScreeningCode4.R")
  # Determine false positives from primary screening
  source("Specificity2.R")
  # Determine the disease stage at triage for those positively
identified
  DiseaseStageScreen <-
LesionAtScreeningAge[LesionAtScreeningAge$TruePositivesTriage ==
1, c("individual","age", "tag", "TruePositivesTriage")]

  # Combine with the Screen Age to determine the age at screen
detection
  DiseaseStageScreen<-cbind
(DiseaseStageScreen,"ScreenAge"=ScreenAge)

  # Update objects within the loop
  TruePositivesColonoscopy          <-
rbind(TruePositivesColonoscopy,DiseaseStageScreen)
  FalsePositivesColonoscopy         <-
rbind(FalsePositivesColonoscopy,IndividualsFalselyReferred)
  SurveillanceColonoscopy           <-
rbind(SurveillanceColonoscopy,PerRoundSurveillanceColonscopy)
  PrimaryScreens                    <-
rbind(PrimaryScreens,PerRoundPrimaryScreens)
  #Isolating those who are the true positive and removing
duplicates
  TruePositivesColonoscopyVolume    <-
as.data.frame(cbind("individual"=unique(TruePositivesColonoscopy$
individual),ModelYear,"Indication"="TriageTruePositives"))


#intersect(TruePositivesColonoscopy$individual,FalsePositivesColo
noscopy[,"individual"])


  TotalColonoscopy<-
rbind(TotalColonoscopy,TruePositivesColonoscopyVolume)
  TotalColonoscopy<-
rbind(TotalColonoscopy,cbind(individual=IndividualsFalselyReferre
d,"Indication"="TriageFalsePositives"))

if(ModelYear==SurveillanceStopAge){}else{source("ScreeningReferre
dSurveillance.R")}}
```

```
if(ModelYear==ScreenAges[1]|ModelYear==SurveillanceStopAge){}else
{source("SurveillanceImplementation3.R")

if(is.null(RoundSpecificSurveillanceVolume)){}else{colnames(Round
SpecificSurveillanceVolume)=colnames(TotalColonoscopy)}

    TotalColonoscopy<-
rbind(TotalColonoscopy,as.data.frame(RoundSpecificSurveillanceVol
ume))
  }
}#Close the loop over the years simulated in the model

#Count up the outcomes within the model
ClinicallyIndicatedColonoscopy<-
DataAfterCensoring[DataAfterCensoring$tag=="cl1"|DataAfterCensori
ng$tag=="cl2"|DataAfterCensoring$tag=="cl3"|DataAfterCensoring$ta
g=="cl4",c("individual","age" )]
ClinicallyIndicatedColonoscopy<-
cbind(ClinicallyIndicatedColonoscopy,"Clinical")
colnames(ClinicallyIndicatedColonoscopy)=colnames(TotalColonoscop
y)
TotalColonoscopy<-
rbind(TotalColonoscopy,ClinicallyIndicatedColonoscopy)
TotalColonoscopy$ModelYear=floor(as.numeric(TotalColonoscopy$Mode
lYear))
write.table(TruePositivesColonoscopy,
file="TruePositivesColonoscopy.txt")
write.table(FalsePositivesColonoscopy,
file="FalsePositivesColonoscopy.txt")
write.table(ClinicallyIndicatedColonoscopy,
file="ClinicallyIndicatedColonoscopy.txt")
write.table(SurveillanceColonoscopy,
file="SurveillanceColonoscopy.txt")
write.table(TotalColonoscopy,
file="TotalColonoscopy.txt")



  #Total volume by age
  table(TotalColonoscopy$ScreenAge)

  #Generate the table of counts
  SummaryTable<-table(TotalColonoscopy$ModelYear,
  TotalColonoscopy$Indication)

  #Add an age column
  SummaryTable<-
  as.data.frame(cbind(Age=as.numeric(rownames(SummaryTable)),Yea
  r=NA,Alive=NA,PrimaryScreens=0,SummaryTable))
```

```
SummaryTableYear<-
as.data.frame(array(0,dim=c(71,ncol(SummaryTable))))
colnames(SummaryTableYear)<-colnames(SummaryTable)

#Write in the ages of the cohorts
SummaryTableYear$Age<-seq(20,90)

#Curtail the summary table within the range of the ages of
interest
SummaryTable<-
SummaryTable[SummaryTable$Age>=min(SummaryTableYear$Age),]
SummaryTable<-
SummaryTable[SummaryTable$Age<=max(SummaryTableYear$Age),]

#Write in the relevant year data
SummaryTableYear[SummaryTableYear$Age %in%
SummaryTable$Age,]=SummaryTable[c(seq(1,nrow(SummaryTable))),]

#Write in the number or primary screens within each round
SummaryTableYear$PrimaryScreens[SummaryTableYear$Age %in%
ScreenAges]<-PrimaryScreens

SummaryTableYear$Year<-seq(1985,2055)

#State a reference to the index cohort-set to be the cohort
aged 60 in 2025
IndexCohort=21

YearAdjustmentFactor<-Cohort-IndexCohort

SummaryTableYear$Year <-SummaryTableYear$Year
+YearAdjustmentFactor


#Write in a year by year total of who is alive
for(j in 1:nrow(SummaryTableYear)){
SummaryTableYear$Alive[j]=length(unique(CompleteData$individua
l))-
sum(CompleteData$age[CompleteData$tag=="oc_death"]<SummaryTabl
eYear$Age[j])-
sum(CompleteData$age[CompleteData$tag=="crc_death"]<SummaryTab
leYear$Age[j])
}



if (nrow(SummaryTableYear) > 0) {
 write.table(SummaryTableYear, file =
```

```
  paste("OutputFiles/","Scenario",StrategyNumber,"/",
  "SummaryTable_", Sex,"_", Cohort,"Strategy",StrategyNumber,
  ".txt", sep = ""))}

  #Pause between cohorts
  Sys.sleep(1)
  }

  #Pause between scenarios
  Sys.sleep(1)
  }
  t=proc.time()-time
  t
```

SECTION 4 SCREENING

In this file, we identify the population with disease, identify if their lesions developed before a particular screening age, identify if they are attending screening for the first time and apply sensitivity if they actually attend the screening based on their adherence probability. We defined the sensitivity of FIT test and colonoscopy test based on the adenomas size. We removed the lesions identified from each screening round before simulating the next round.

```
# The purpose of this file is to run each round of screening
# For the first screening round we work with CompleteData and the
subsequent screening round we work with modified dataset

#Create a file marker for debugging
File="ScreeningCode4.R"


# Implement an if statement in order to define the correct data d
epending on whether this is the first round of screening or not
if (ScreenAge==ScreenAges[1]) {

  #IDENTIFY TRUE DISEASE STAGE

  #Identifying individuals with disease and no disease, creates a
frequency table and returns indices with count greater than 2
  Disease       =as.numeric(which((table(CompleteData$individual)
>=2)==TRUE))

  #Subset StageData with individuals with disease
  StageDataDisease<-CompleteData[(which(CompleteData$individual %
in% Disease)),]
```

```
  } else {

# Remove existing objects to avoid errors
  rm(CompleteData)
  rm(Disease)
  rm(StageDataDisease)


  #Define the data as that following censoring from a previous ro
und of screening
  CompleteData <- DataAfterCensoring

  #Identifying individuals with disease and no disease, create a
frequency table and returns indices with count greater than 2
  Disease       =as.numeric(which((table(CompleteData$individual)
>=2)==TRUE))

  #Subset StageData with individuals with disease
  StageDataDisease<-CompleteData[(which(CompleteData$individual %
in% Disease)),]

}

#This gives data frame with individuals with disease that started
before screening age
StageDataDiseaseBeforeScreeningAge <- StageDataDisease[StageDataD
isease$age < ScreenAge, ]


#Following is the nested loop, the first loop creates subset of d
ata with rows for each individual with lesions that developed bef
ore screening age and finds the number of lesions, the second loo
p creates a array with maximum age by selecting the tail of the l
esion array, rbind combines the rows in

# Identify the individuals to loop over
Individuals<-unique(StageDataDiseaseBeforeScreeningAge$individual
)
# Create an empty object prior to the loop
LesionAtScreeningAge=NULL
for (j in Individuals){
  IndividualArray<-StageDataDiseaseBeforeScreeningAge[StageDataDi
seaseBeforeScreeningAge$individual==j,]
  NumberOfLesion<-max(IndividualArray$element)

  Lesions<-unique( IndividualArray$element)
  for (i in Lesions){
    LesionArray<-IndividualArray[IndividualArray$element==i,]
```

```
    LesionAtMaxAge<- tail(LesionArray, n=1)
    LesionAtScreeningAge=rbind(LesionAtScreeningAge,LesionAtMaxAg
e)}}



#Individuals attending screening round
RoundAttendees<-ActualAttendance$IndividualReference[ActualAttend
ance[,which(colnames(ActualAttendance)==ScreenAge)]==1]


#Print a warning that there are no screening attendees
if(length(RoundAttendees)==0){print("Warning, there are no screen
ing attendees")}

#Define which tags relate to clinical desease states
ClinicalTags<-c("cl2",  "cl1" ,"cl3", "cl4" )


#Identify which individuals have clinical disease at the time of
screening
ClinicalCases<-StageDataDiseaseBeforeScreeningAge$individual[(Sta
geDataDiseaseBeforeScreeningAge$tag%in%ClinicalTags)]


#Remove all those with clinical disease as they are not eligible
for screening
RoundAttendees=RoundAttendees[!RoundAttendees%in%ClinicalCases]

#Skip excluding those from surveillance if it is the first screen
ing round
if (ScreenAge==ScreenAges[1]) {}else{
#Exclude those currently in screening from surveillance
#Read the surveillance file
InSurveillance<-read.table("ContinuousSurveillanceRegistry.txt")
#Refine it back to those in surveillance at this screening round
CurrentlyInSurveillance<-InSurveillance$individual[InSurveillance
$years==ScreenAge]


#Remove from round attendees
RoundAttendees=RoundAttendees[!RoundAttendees%in%CurrentlyInSurve
illance]
}

#APPLY SENSITIVITY TO TRUE DISEASE STAGE

#Add three columns to LesionAtScreeningAge
LesionAtScreeningAge <- cbind(LesionAtScreeningAge, Participation
=NA, Sensitivity = NA, RandomNumber = NA,TruePositives = NA)
```

```r
#Censor back to those attending screening
LesionAtScreeningAge <- LesionAtScreeningAge[LesionAtScreeningAge
$individual %in% RoundAttendees,]


# Define the disease states in the natural history model
DiseaseStates <- c(
"ad51",
"ad52",
"ad53",
"ad54",
"np_ad6_9",
"npl_ad6_9",
"np_ad10",
"pl_ad6_9",
"p_ad6_9",
"p_ad10",
"pcl1a",
"pcl1b",
"pcl2a",
"pcl2b",
"pcl3a",
"pcl3b",
"pcl4")


#Create table of sensitivity values
SensitivityTable <- array(0, dim = c(1, length(DiseaseStates)))

#Give names to the columns and rows
colnames(SensitivityTable) <- DiseaseStates
rownames(SensitivityTable) <- c("SensitivityValue")

FITCutOffs<- c(10,15,20,30,40)

FITCutoff=10

FITRef=which(FITCutOffs==FITCutoff)

#Assign values to sensitivity table columns
SensitivityTable[,"ad51"]       <-c(0,0,0,0,0)[FITRef]
SensitivityTable[,"ad52"]       <-c(0,0,0,0,0)[FITRef]
SensitivityTable[,"ad53"]       <-c(0,0,0,0,0)[FITRef]
SensitivityTable[,"ad54"]       <-c(0,0,0,0,0)[FITRef]

SensitivityTable[,"np_ad6_9"]   <-c(0.10,   0.057,  0.044,  0.029
,  0.025)[FITRef]
SensitivityTable[,"npl_ad6_9"]  <-c(0.10,   0.057,  0.044,  0.029
,  0.025)[FITRef]
```

```
SensitivityTable[,"np_ad10"]    <-c(0.10,   0.057,  0.044,  0.029
,  0.025)[FITRef]

SensitivityTable[,"pl_ad6_9"]   <-c(0.161,  0.144,  0.131,  0.123
,  0.103)[FITRef]

SensitivityTable[,"p_ad6_9"]    <-c(0.161,  0.144,  0.131,  0.123
,  0.103)[FITRef]
SensitivityTable[,"p_ad10"]     <-c(0.161,  0.144,  0.131,  0.123
,  0.103)[FITRef]

SensitivityTable[,"pcl1a"]      <-0.9
SensitivityTable[,"pcl1b"]      <-0.9
SensitivityTable[,"pcl2a"]      <-0.9
SensitivityTable[,"pcl2b"]      <-0.9
SensitivityTable[,"pcl3a"]      <-0.9
SensitivityTable[,"pcl3b"]      <-0.9
SensitivityTable[,"pcl4"]       <-0.9



#The value from SensitivityTable is assigned to rows in LesionAtS
creeningAge where the corresponding "tag" matches with in Sensiti
vityTable
for (i in 1:ncol(SensitivityTable)){
  LesionAtScreeningAge[LesionAtScreeningAge$tag==colnames(Sensiti
vityTable)[i],"Sensitivity"]<-SensitivityTable[i]}

#Assign random number to RandomNumber column
LesionAtScreeningAge$RandomNumber<-runif(nrow(LesionAtScreeningAg
e))


#Assign 1 to TruePositives column if sensitivity value is less th
e random number or 0 if higher
LesionAtScreeningAge$TruePositives<-{ifelse(LesionAtScreeningAge$
RandomNumber<(LesionAtScreeningAge$Sensitivity),1,0)}

sum(LesionAtScreeningAge$TruePositives == 1)
table(LesionAtScreeningAge$TruePositives)


LesionAtScreeningAge        <- LesionAtScreeningAge[!is.na(Lesion
AtScreeningAge$Sensitivity), ]

#Create dataset with truepositives from primary test
ScreenTestTruePositivesData <-LesionAtScreeningAge[LesionAtScreen
ingAge$TruePositives == 1, ]
```

```r
#================================================================
================================================

#APPLY TRIAGE SENSITIVITY

#Add columns to LesionAtScreeningAge
LesionAtScreeningAge    <- cbind(LesionAtScreeningAge,TriageSensi
tivity = NA, RandomNumber3 = NA,TruePositivesTriage = NA, Size=NA
, Risk=NA)


#Create table to store triage sensitivity values
SensitivityTableTriage  <- array(0, dim = c(1, length(DiseaseStat
es)))


#Give name to the columns and rows
colnames(SensitivityTableTriage) <- DiseaseStates
rownames(SensitivityTableTriage) <- c("SensitivityValue")


#Assign values to sensitivity table columns
SensitivityTableTriage[,"ad51"]     <-0.75
SensitivityTableTriage[,"ad52"]     <-0.75
SensitivityTableTriage[,"ad53"]     <-0.75
SensitivityTableTriage[,"ad54"]     <-0.75

SensitivityTableTriage[,"np_ad6_9"] <-0.85
SensitivityTableTriage[,"npl_ad6_9"]<-0.85
SensitivityTableTriage[,"np_ad10"]  <-0.85

SensitivityTableTriage[,"pl_ad6_9"] <-0.95
SensitivityTableTriage[,"p_ad6_9"]  <-0.95
SensitivityTableTriage[,"p_ad10"]   <-0.95

SensitivityTableTriage[,"pcl1a"]    <-0.95
SensitivityTableTriage[,"pcl1b"]    <-0.95
SensitivityTableTriage[,"pcl2a"]    <-0.95
SensitivityTableTriage[,"pcl2b"]    <-0.95
SensitivityTableTriage[,"pcl3a"]    <-0.95
SensitivityTableTriage[,"pcl3b"]    <-0.95
SensitivityTableTriage[,"pcl4"]     <-0.95



#The value from SensitivityTableTriage is assigned to rows in Les
ionAtScreeningAge where the corresponding "tag" matches with in S
ensitivityTableTriage
for (m in 1:ncol(SensitivityTableTriage)){
```

```
  LesionAtScreeningAge[LesionAtScreeningAge$tag==colnames(Sensiti
vityTableTriage)[m],"TriageSensitivity"]<-SensitivityTableTriage[
m]}

TriageParticipation<-0.8

#Applying triage participation
TriageParticipationSchedule<-as.data.frame(cbind("Individual"=uni
que(LesionAtScreeningAge$individual),"Participation"= rbinom(n=le
ngth(unique(LesionAtScreeningAge$individual)), size=1, prob=Triag
eParticipation)))


#Assigning participation
for(k in LesionAtScreeningAge$individual ){
LesionAtScreeningAge$Participation[LesionAtScreeningAge$individua
l==k]<-TriageParticipationSchedule$Participation[TriageParticipat
ionSchedule$Individual==k]}

#Assign random number to RandomNumber3 column
LesionAtScreeningAge$RandomNumber3      <-runif(nrow(LesionAtScre
eningAge))



#Assign 1 to TruePositivesTriage column if the sensitivity value
is less than 1 or 0 if it's higher
LesionAtScreeningAge$TruePositivesTriage<-{ifelse(LesionAtScreeni
ngAge$RandomNumber3<(LesionAtScreeningAge$TriageSensitivity),1,0)
}



LesionAtScreeningAge$Size=LesionAtScreeningAge$tag


#CENSORING

#Create lesion-specific identifier
LesionAtScreeningAge=cbind(LesionAtScreeningAge,"LesionIdentifier
"=c(paste(LesionAtScreeningAge$individual,LesionAtScreeningAge$el
ement,sep=".")))


#Subset age, tag and TruePositivesTriage
#DiseaseStagePerScreening <- LesionAtScreeningAge[LesionAtScreeni
ngAge$TruePositivesTriage == 1, c("age", "tag", "TruePositivesTri
age")]
```

```
#Identify lesions referred for treatment
#LesionsReferredtoTreatment <-unique(LesionAtScreeningAge$LesionI
dentifier[which(LesionAtScreeningAge$TruePositivesTriage == 1)])

LesionsReferredtoTreatment <-unique(LesionAtScreeningAge$LesionId
entifier[which((LesionAtScreeningAge$TruePositivesTriage == 1)& (
LesionAtScreeningAge$Participation==1))])


#Adding lesion specific identifier
if (ScreenAge==ScreenAges[1]) {
 #Create lesion-specific identifier in CompleteData
CompleteData=cbind(CompleteData,"IndividualLesion"=c(paste(Comple
teData$individual,CompleteData$element,sep=".")))


#Assign value to lesionpresent column
CompleteData$LesionPresent[(CompleteData$IndividualLesion %in% Le
sionsReferredtoTreatment)]<-0


#Define DataAfterCensoring as the CompleteData
DataAfterCensoring=CompleteData


} else {


  #Edit to remove unnecessary data after censoring

  #Data after removing lesions that got detected
  #DataAfterCensoring <-DataAfterCensoring[!(DataAfterCensoring$I
ndividualLesion %in% LesionsReferredtoTreatment),]

  #Assign value to lesionpresent column
  CompleteData$LesionPresent[(CompleteData$IndividualLesion %in%
LesionsReferredtoTreatment)]<-0
  #Define DataAfterCensoring as the CompleteData
  DataAfterCensoring=CompleteData
}


#Categorizing adenomas based on size
Small=c("ad51", "ad52","ad53",  "ad54", "pl_ad6_9","npl_ad6_9", "
p_ad6_9" , "np_ad6_9" )
Large=c("p_ad10","np_ad10")

#Assigning category based on size
LesionAtScreeningAge$Size[LesionAtScreeningAge$tag %in% Small]<-"
```

```
Small"
LesionAtScreeningAge$Size[LesionAtScreeningAge$tag %in% Large]<-"
Large"


# Loop over all individuals identified in triage in order to cate
gorise their triage findings as low, intermediate or high
for (s in unique(LesionAtScreeningAge$individual)){

  # Select the per round person lesion characteristics
  PerPersonLesionAtScreeningAge<-LesionAtScreeningAge[LesionAtScr
eeningAge$individual==s, c("Size", "TruePositivesTriage" )]

  # Subset to those correctly identified at screening
  PerPersonLesionAtScreeningAge=PerPersonLesionAtScreeningAge[Per
PersonLesionAtScreeningAge$TruePositivesTriage==1,]

  # Categorise those with large adenomas as being of high risk
  if (sum(PerPersonLesionAtScreeningAge$Size=="Large")>=1) {
  Risk="High"

  # If adenomas are small, count those that are three or more in
number and classify as intermediate risk
} else {
  if (sum(PerPersonLesionAtScreeningAge$Size=="Small")>=3) {
    Risk="Intermediate"



# Finally, if the number of small lesions is 1 or 2, then the are
categorised as low risk
  } else {if (sum(PerPersonLesionAtScreeningAge$Size=="Small")==1
|sum(PerPersonLesionAtScreeningAge$Size=="Small")==2) {
    Risk="Low"} else{
    Risk=NA}}}

 # Write the risk categorisation into the array
 LesionAtScreeningAge$Risk [LesionAtScreeningAge$individual %in%
s]<-Risk}


#Censoring preclinical cancer: all of those cases that are not ad
enomas have NA inserted in their risk classification
LesionAtScreeningAge$Risk[!LesionAtScreeningAge$Size %in% c("Smal
l","Large")]<-NA

#Create a round specific array of individuals newly referred to s
urveillance directly from Screening
PerRoundSurveillanceColonscopy<-cbind(LesionAtScreeningAge[,c("in
dividual", "Risk")], ScreenAge, "Referral"="Screening" )[LesionAt
```

```
ScreeningAge$Participation==1,]

#Individuals arriving for surveillance per round
PerRoundSurveillanceColonscopy=PerRoundSurveillanceColonscopy[!is
.na(PerRoundSurveillanceColonscopy$Risk),]
```

SECTION 5 SPECIFICITY

```
# The purpose of this file is to apply the imperfect test specifi
city to generate false negatives from screening

# Run an if statement to use the correct modified file of patient
history
if (ScreenAge==ScreenAges[1]) {

} else {

# Remove the existing complete data file
  rm(CompleteData)

# Redefine complete data with respect to the file following censo
ring of cured lesions
  CompleteData <- DataAfterCensoring

}

# Remove prior objects to avoid errors
rm(Disease)
rm(StageDataDisease)

#Using the pre-censoring data of those with disease from the sens
itivity file
DiseaseAtScreenAge=unique(StageDataDiseaseBeforeScreeningAge$indi
vidual)
NewNoDiseaseAtScreenAge=unique(CompleteData$individual[!CompleteD
ata$individual %in% DiseaseAtScreenAge])


## Identifying individuals with disease and no disease,creates a
frequency table and returns indices with count greater than 2
##Disease       =as.numeric(which((table(CompleteData$individual)
>=2)==TRUE))
##NoDisease =as.numeric(which((table(CompleteData$individual)>=2)
==FALSE))
#
#
#
## Subset StageData with individuals with disease
```

```r
#StageDataDisease<-CompleteData[(which(CompleteData$individual %in% Disease)),]
#
## No disease ever, they died of other cause
#StageDataNoDisease<-CompleteData[(which(CompleteData$individual %in% NoDisease)),]
#
## This gives data frame with individuals with disease that started before screening age
##StageDataDiseaseBeforeScreeningAge <- StageDataDisease[StageDataDisease$age < ScreenAge, ]
#
## No disease yet at screen age
#StageDataNoDiseaseBeforeScreeningAge <- StageDataDisease[!(StageDataDisease$age < ScreenAge), ]
#
## No disease at screen age
#NoDiseaseAtScreenAge<-rbind(StageDataNoDisease,StageDataNoDiseaseBeforeScreeningAge)
#
## Identify individual reference identities
#IndividualsNoDiseaseAtScreenAge<-c(StageDataNoDisease$individual,unique(StageDataNoDiseaseBeforeScreeningAge$individual))

##################################


# Add three columns to NoDiseaseDataBeforeScreeningAge
#NoDiseaseAtScreenAge <- cbind(IndividualsNoDiseaseAtScreenAge, Specificity = NA, RandomNumber2 = NA, FalsePositives = NA)
NoDiseaseAtScreenAge <- cbind(NewNoDiseaseAtScreenAge, Specificity = NA, RandomNumber2 = NA, TriageAttendanceRandom=NA, FalsePositives = NA)


# Convert to a data frame
NoDiseaseAtScreenAge<-as.data.frame(NoDiseaseAtScreenAge)

#Censor those not attending screening
NoDiseaseAtScreenAge=NoDiseaseAtScreenAge[NoDiseaseAtScreenAge$NewNoDiseaseAtScreenAge %in% RoundAttendees,]

# Assign values - basecase non sex specific - Source McFerran
NoDiseaseAtScreenAge$Specificity<-c(0.9579, 0.9705, 0.9776, 0.9834, 0.9870)[FITRef]

if(TestSex=="NotSpecific"){
# Assign values - basecase non sex specific - Source McFerran
NoDiseaseAtScreenAge$Specificity<-c(0.9579, 0.9705, 0.9776, 0.983
```

```
4, 0.9870)[FITRef]}

if(TestSex=="Male"){
#Specifiity values at various cut-offs from Vandeer Meulen for me
n (updated)
NoDiseaseAtScreenAge$Specificity<-c(0.959,  0.971,  0.977,  0.985
,  0.987)[FITRef]}

if(TestSex=="Female"){
#Specifiity values at various cut-offs from Vandeer Meulen for wo
men
NoDiseaseAtScreenAge$Specificity<-c(0.959,  0.971,  0.978,  0.983
,  0.987)[FITRef]}


#FITCutOffs<- c(10,15,20,30,40)
#FITCutOffs<- c(50,75,100,150,225)

NoDiseaseAtScreenAge$RandomNumber2<-runif(nrow(NoDiseaseAtScreenA
ge))
NoDiseaseAtScreenAge$FalsePositives<-{ifelse(NoDiseaseAtScreenAge
$RandomNumber2<(1-NoDiseaseAtScreenAge$Specificity),1,0)}

#Generate random uniforms for to determine triage participation
NoDiseaseAtScreenAge$TriageAttendanceRandom=runif(nrow(NoDiseaseA
tScreenAge))

#Censor any non attendance back to zero
NoDiseaseAtScreenAge$FalsePositives[NoDiseaseAtScreenAge$TriageAt
tendanceRandom>TriageParticipation]=0

# Identify the individuals referred falsely
IndividualsFalselyReferred<-cbind(NoDiseaseAtScreenAge[NoDiseaseA
tScreenAge$FalsePositives==1, c("NewNoDiseaseAtScreenAge")],Scree
nAge)

# Apply column names
colnames(IndividualsFalselyReferred) <- c("individual", "ModelYea
r")
```

SECTION 6 SCREEN REFERRED SURVEILLANCE

```
# This file generates the initial surveillance schedule for those
individuals referred to surveillance following primary screening
tirage colonosocopy

#Create a file marker for debugging
```

```
File="ScreeningReferredSurveillance.R"

1
#Define the policy variables of the Surveillance stop age and the
surveillance intervals for both high and intermediate groups
HighRiskInitialSurveillanceInterval         <-1
IntermediateRiskInitialSurveillanceInterval <-3
#SurveillanceStopAge                            <-80

#SURVEILLANCE SCHEDULE HIGH

#Individuals identified from screening for high risk surveillance
#Are we bringing in anyone unnecessarily?
#SurveillanceScheduleHigh<- SurveillanceColonoscopy[(Surveillance
Colonoscopy$Risk=="High"),]
SurveillanceScheduleHigh<- PerRoundSurveillanceColonscopy[(PerRou
ndSurveillanceColonscopy$Risk=="High"),]



#Determine the age at which the first surveillance event will occ
ur
SurveillanceScheduleHigh$ScreenAge<-SurveillanceScheduleHigh$Scre
enAge+HighRiskInitialSurveillanceInterval

#Add columns for which surveillance round it is and other cause d
eath age
SurveillanceScheduleHigh<-cbind(SurveillanceScheduleHigh, "Round"
=1, "OC_Death"=NA)


#================================================================
================================================================
====

#Censor repeated individuals from surveillance schedule

#Create an empty vector before running a loop
SurveillanceScheduleHighWithoutRep<-NULL

#Loop over all the possible surveillance ages within the schedule
- maybe this should be modified to only run surveillance at a giv
en age
for (l in unique(SurveillanceScheduleHigh$ScreenAge)){

  #Subset that part of the array specific to a given round of sur
veillance
  SurveillanceScheduleHighWithoutRepRoundSpecific=SurveillanceSch
eduleHigh[SurveillanceScheduleHigh$ScreenAge==l,]
```

```
  #Limit to the first instance of each individual who features mo
re than once in the array
  SurveillanceScheduleHighWithoutRepRoundSpecific <-SurveillanceS
cheduleHighWithoutRepRoundSpecific[!duplicated(SurveillanceSchedu
leHighWithoutRepRoundSpecific$individual), ]
  #Bind over the possible loops of different screening ages
  SurveillanceScheduleHighWithoutRep<-rbind(SurveillanceScheduleH
ighWithoutRep,SurveillanceScheduleHighWithoutRepRoundSpecific)

}

#Return a warning if there is an empty vector
if(length(nrow(SurveillanceScheduleHighWithoutRep))==0){cat("Warn
ing, no individuals referred to high risk surveillance at age",Su
rveillanceScheduleHigh$ScreenAge[1])}


#=================================================================
=================================================================
===

#Find other cause death age for individuals

OtherCause_Death    <-CompleteData[CompleteData$tag=="oc_death",
c("individual","age")]
CRC_Death           <-CompleteData[CompleteData$tag=="crc_death",
c("individual","age")]




#Placeholder for counterfactual other cause death age for people
who died of crc
#This will be updated when correctly estimate the counterfactual
death age using survival curves
CRC_Death$age       =CRC_Death$age+5

OtherCause_Death    =rbind(OtherCause_Death,CRC_Death)

#=================================================================
=========================================================

#Assign values to SurveillanceScheduleHigh$OC_Death

#Write in the other cause death age into the surveillance schedul
e
for (y in 1:nrow(SurveillanceScheduleHighWithoutRep)){Surveillanc
eScheduleHighWithoutRep[y,"OC_Death"]<-
  OtherCause_Death$age[OtherCause_Death$individual==SurveillanceS
```

```
cheduleHighWithoutRep[y,"individual"]]}


#Add in the surveillance schedule upper age bound
SurveillanceScheduleHighWithoutRep<-cbind(SurveillanceScheduleHig
hWithoutRep,"SurveillanceCutOffAge"=NA)

#Ad-hoc limitation to the first 6 columns to avoid adding additio
nal columns within a loop
SurveillanceScheduleHighWithoutRep=SurveillanceScheduleHighWithou
tRep[,c(1:6)]

#Write in the other cause death age
SurveillanceScheduleHighWithoutRep$SurveillanceCutOffAge<-Surveil
lanceScheduleHighWithoutRep$OC_Death

#Assign the SurveillanceStopAge to those who died above that age
SurveillanceScheduleHighWithoutRep[SurveillanceScheduleHighWithou
tRep$SurveillanceCutOffAge>SurveillanceStopAge,"SurveillanceCutOf
fAge"]=SurveillanceStopAge

#Remove those who died before the surveillance age
SurveillanceScheduleHighWithoutRep<-SurveillanceScheduleHighWitho
utRep[SurveillanceScheduleHighWithoutRep$SurveillanceCutOffAge>Su
rveillanceScheduleHighWithoutRep$ScreenAge,]

#Round integer SurveillanceCutOffAge
SurveillanceScheduleHighWithoutRep$SurveillanceCutOffAge<-round(S
urveillanceScheduleHighWithoutRep$SurveillanceCutOffAge)

#================================================================
================================================================
======
#Generate vector of ages based on the difference between surveill
ance initiation age and cut-off age  of screening for each indivi
dual using loop function

#Create an empty object outside the loop
SurveillanceSchedule=NULL

#Loop over the individuals referred for surveillance
for (r in 1:length(SurveillanceScheduleHighWithoutRep$individual)
){

  # Create a sequence of surveillance ages based on start and sto
p ages
  IndividualSurveillanceAgeInterval<-seq(SurveillanceScheduleHigh
WithoutRep$ScreenAge[r], SurveillanceScheduleHighWithoutRep$Surve
illanceCutOffAge[r],by=HighRiskInitialSurveillanceInterval)
```

```
  # Add columns for the risk and the round of screening
  #Code the referral pathway as 0 to indicate individuals referre
d to from primary screening
  IndividualSurveillanceAgeInterval <-cbind("individual"=Surveill
anceScheduleHighWithoutRep$individual[r], IndividualSurveillanceA
geInterval, "Referral"=0, "InitialReferralAge"=ScreenAge,"Initial
Risk"="High","Risk"="High", "StopAge"=SurveillanceScheduleHighWit
houtRep$SurveillanceCutOffAge[r],"NegativeCount"=0,"AppliedStopAg
e"=NA)
  SurveillanceSchedule<-rbind(SurveillanceSchedule,IndividualSurv
eillanceAgeInterval)

}

write.table(SurveillanceSchedule,file="SurveillanceSchedule.txt")



#=================================================================
===

#SURVEILLANCE SCHEDULE INTERMEDIATE

#Individuals identified from screening for intermediate risk surv
eillance
#SurveillanceScheduleIntermediate<- SurveillanceColonoscopy[(Surv
eillanceColonoscopy$Risk=="Intermediate"),]

SurveillanceScheduleIntermediate<- PerRoundSurveillanceColonscopy
[(PerRoundSurveillanceColonscopy$Risk=="Intermediate"),]

nrow(SurveillanceScheduleIntermediate)

#Removing old code

if(nrow(SurveillanceScheduleIntermediate)==0){}else{
#write.table(NA,file="SurveillanceScheduleIntermediate.txt")

#file.size("SurveillanceScheduleIntermediate.txt")
#}else{


SurveillanceScheduleIntermediate$ScreenAge<-SurveillanceScheduleI
ntermediate$ScreenAge+IntermediateRiskInitialSurveillanceInterval

SurveillanceScheduleIntermediate<-cbind(SurveillanceScheduleInter
mediate, "Round"=1, "OC_Death"=NA)
```

```r
#================================================================
===

#Censor repeated individuals from surveillance schedule
SurveillanceScheduleIntermediateWithoutRep<-NULL


for (q in unique(SurveillanceScheduleIntermediate$ScreenAge)){

  SurveillanceScheduleIntermediateWithoutRepRoundSpecific=Surveil
lanceScheduleIntermediate[SurveillanceScheduleIntermediate$Screen
Age==q,]
  SurveillanceScheduleIntermediateWithoutRepRoundSpecific <-Surve
illanceScheduleIntermediateWithoutRepRoundSpecific[!duplicated(Su
rveillanceScheduleIntermediateWithoutRepRoundSpecific$individual)
, ]
  SurveillanceScheduleIntermediateWithoutRep<-rbind(SurveillanceS
cheduleIntermediateWithoutRep,SurveillanceScheduleIntermediateWit
houtRepRoundSpecific)

}

nrow(SurveillanceScheduleIntermediateWithoutRep)


#Find other cause death age for individuals

OtherCause_Death<-CompleteData[CompleteData$tag=="oc_death",c("in
dividual","age")]
CRC_Death<-CompleteData[CompleteData$tag=="crc_death",c("individu
al","age")]

#Generate death age for people who died from crc from survival pr
obability
SurvivalFunction <- function(x) {
  (approx(SurvivalFemale$SurvivalProbability,SurvivalFemale$Age,r
unif(n=1, min = 0, max = approx(SurvivalFemale$Age,SurvivalFemale
$SurvivalProbability,x)$y))$y)
}


#counterfactual other cause death age for people who died of crc
CRC_Death$age=unlist(lapply(CRC_Death$age,SurvivalFunction))

OtherCause_Death=rbind(OtherCause_Death,CRC_Death)

#================================================================
===
```

```r
#Assign values to SurveillanceScheduleHigh$OC_Death

for (y in 1:nrow(SurveillanceScheduleIntermediateWithoutRep)){Sur
veillanceScheduleIntermediateWithoutRep[y,"OC_Death"]<-
  OtherCause_Death$age[OtherCause_Death$individual==SurveillanceS
cheduleIntermediateWithoutRep[y,"individual"]]}



#Add SurveillanceCutOffAge to SurveillanceScheduleIntermediateWit
houtRep using if else function

SurveillanceScheduleIntermediateWithoutRep<-cbind(SurveillanceSch
eduleIntermediateWithoutRep,"SurveillanceCutOffAge"=NA)


SurveillanceScheduleIntermediateWithoutRep$SurveillanceCutOffAge<
-SurveillanceScheduleIntermediateWithoutRep$OC_Death

SurveillanceStopAge<-80

#Assign 80 to those who died above 80
SurveillanceScheduleIntermediateWithoutRep[SurveillanceScheduleIn
termediateWithoutRep$SurveillanceCutOffAge>SurveillanceStopAge,"S
urveillanceCutOffAge"]=80


#Remove those who died before ScreenAge

SurveillanceScheduleIntermediateWithoutRep<-SurveillanceScheduleI
ntermediateWithoutRep[SurveillanceScheduleIntermediateWithoutRep$
SurveillanceCutOffAge>SurveillanceScheduleIntermediateWithoutRep$
ScreenAge,]

#Round integer SurveillanceCutOffAge

SurveillanceScheduleIntermediateWithoutRep$SurveillanceCutOffAge<
-round(SurveillanceScheduleIntermediateWithoutRep$SurveillanceCut
OffAge)


#Generate vector of ages based on the difference between surveill
ance initiation age and cut-off age  of screening for each inidiv
idual using loop function

SurveillanceScheduleIntermediate=NULL


if(length(SurveillanceScheduleIntermediateWithoutRep$individual)=
```

```
=0){}else{

for (r in 1:length(SurveillanceScheduleIntermediateWithoutRep$ind
ividual)){

  IndividualSurveillanceAgeInterval<-seq(SurveillanceScheduleInte
rmediateWithoutRep$ScreenAge[r], SurveillanceScheduleIntermediate
WithoutRep$SurveillanceCutOffAge[r],by=IntermediateRiskInitialSur
veillanceInterval)
  # Add columns for the risk and the round of screening
  # Code the referral pathway as 0 to indicate individuals referr
ed to from primary screening
  IndividualSurveillanceAgeInterval <-cbind("individual"=Surveill
anceScheduleIntermediateWithoutRep$individual[r], IndividualSurve
illanceAgeInterval,"Referral"=0,"InitialReferralAge"=ScreenAge,"I
nitialRisk"="Intermediate", "Risk"="Intermediate", "StopAge"=Surv
eillanceScheduleIntermediateWithoutRep$SurveillanceCutOffAge[r],
"NegativeCount"=0,"AppliedStopAge"=NA)
  SurveillanceScheduleIntermediate<-rbind(SurveillanceScheduleInt
ermediate,IndividualSurveillanceAgeInterval)

}

#Removing old code
#write.table(SurveillanceScheduleIntermediate,file="SurveillanceS
cheduleIntermediate.txt")
}
}

# Join the high risk and intermediate risk surveillance schedule
into one object
OverallSurveillance<-as.data.frame(rbind(SurveillanceSchedule,Sur
veillanceScheduleIntermediate))


# Write in the effective maximum surveillance age by looping over
each individual
for (u in unique(OverallSurveillance$individual)){
OverallSurveillance$AppliedStopAge[OverallSurveillance$individual
==u]<-max(OverallSurveillance$IndividualSurveillanceAgeInterval[O
verallSurveillance$individual==u])
}


#Write the Surveillance schedule, either as a new file if it is t
he first screening round, or by appending the new cases if it's a
subsequent screening round.

if(ModelYear==ScreenAges[1]){
```

```
CombinedSurveillance=OverallSurveillance
write.table(OverallSurveillance,file="OverallSurveillance.txt")}e
lse{
ExistingSurveillance=read.table("OverallSurveillance.txt")
CombinedSurveillance=rbind(OverallSurveillance,ExistingSurveillan
ce)
write.table(CombinedSurveillance, file="OverallSurveillance.txt")
}


#Create the continuous span of being in surveillance at any point
in time
#Set the empty object outside the loop
ContinuousSurveillanceRegistry=NULL
#Iterate over everyone in surveillance
for (v in unique(CombinedSurveillance$individual)){
ContinuousSurveillanceRegistry=rbind(ContinuousSurveillanceRegist
ry,cbind(v,seq(from=CombinedSurveillance$InitialReferralAge[Combi
nedSurveillance$individual==v][1],to=CombinedSurveillance$Applied
StopAge[CombinedSurveillance$individual==v][1],by=1)))
}
colnames(ContinuousSurveillanceRegistry)=c("individual","years")
#Save this as the new OverallSurveillance file
write.table(ContinuousSurveillanceRegistry, file="ContinuousSurve
illanceRegistry.txt")
```

SECTION 7 SURVEILLANCE

This file generates surveillance schedule following first surveillance round

```
#Create a file marker for debugging
File="SurveillanceImplementation3.R"

#Remove prior objects
rm(OverallSurveillance,LowIndividuals,IntermediateIndividuals,Neg
ativeIndividuals,HighIndividuals)


#setwd("G:/.shortcut-targets-by-id/10LP8txkt0YSb4Mcy9EEN5n0V7RYZz
-CN/MISCAN Simulation/ModellingTemplate/")

#Surveillance for high risk
OverallSurveillance=read.table("OverallSurveillance.txt")
#OverallSurveillance=read.table("ModifiedSurveillance.txt")

SurveillanceParticipation<-0.45

Debug=19

#Subsetting in the current model year
OverallSurveillanceRoundSpecificIndividual<-OverallSurveillance$i
ndividual[OverallSurveillance$IndividualSurveillanceAgeInterval==
ModelYear]
#sample(x=c(OverallSurveillanceRoundSpecificIndividual),size=1,re
place=FALSE, prob=SurveillanceParticipation)

#Applying surveillance participation
ParticipationSchedule<-as.data.frame(cbind("Individual"=OverallSu
rveillanceRoundSpecificIndividual,"Participation"= rbinom(n=lengt
h(OverallSurveillanceRoundSpecificIndividual), size=1, prob=Surve
illanceParticipation)))

#Censor round specific surveillance based on participation
OverallSurveillanceRoundSpecificIndividual<-OverallSurveillanceRo
undSpecificIndividual[ParticipationSchedule$Participation==1]

#Generte volume for each round

if(identical(OverallSurveillanceRoundSpecificIndividual,integer(0
))){RoundSpecificSurveillanceVolume=NULL}else{
RoundSpecificSurveillanceVolume<-cbind(OverallSurveillanceRoundSp
ecificIndividual,ModelYear,"Surveillance")}

UnModified<-OverallSurveillance$individual[!OverallSurveillance$i
ndividual%in%OverallSurveillanceRoundSpecificIndividual]
```

```
UnModifiedSurveillance<-OverallSurveillance[OverallSurveillance$i
ndividual%in%UnModified,]

#Subset of individuals going for surveillance
OverallSurveillanceIndividualData<-CompleteData[CompleteData$indi
vidual%in%OverallSurveillanceRoundSpecificIndividual,]
#Subset to those lesions still present following censoring follow
ing lesion removal
OverallSurveillanceIndividualData<-OverallSurveillanceIndividualD
ata[(OverallSurveillanceIndividualData$LesionPresent==1),]
if (nrow(OverallSurveillanceIndividualData)==0){}else{
OverallSurveillanceIndividualData<-cbind(OverallSurveillanceIndiv
idualData, "Participation"=NA)}


#Identifying the individuals with disease present
DiseaseAtSurveillance=unique(OverallSurveillanceIndividualData$in
dividual)[as.numeric(which((table(OverallSurveillanceIndividualDa
ta$individual)>=2)==TRUE))]

Debug=50

#if statement to skip surveillance if there are no individuals wi
th disease at the time of surveillance
if(identical(DiseaseAtSurveillance, numeric(0))){
OverallSurveillance=NULL}else{

  #Finding disease present in those individuals at the time of su
rveillance
StageDataDiseaseSurveillance<-OverallSurveillanceIndividualData[(
which(OverallSurveillanceIndividualData$individual %in% DiseaseAt
Surveillance)),]
StageDataDiseaseSurveillance<-StageDataDiseaseSurveillance[!Stage
DataDiseaseSurveillance$tag=="location",]


#Finding the relevant disease state before the moment of surveill
ance
StageDataDiseaseBeforeSurveillance <- StageDataDiseaseSurveillanc
e[StageDataDiseaseSurveillance$age < ModelYear, ]

if(nrow(StageDataDiseaseBeforeSurveillance)==0){}else{

# Identifying the unique individuals to investigate
Individuals<-unique(StageDataDiseaseBeforeSurveillance$individual
)
# Setting an empty object before the loop
LesionAtScreeningAge=NULL
```

```
for (j in Individuals){
  # Retrieve the disease array per individual
  IndividualArray<-StageDataDiseaseBeforeSurveillance[StageDataDi
seaseBeforeSurveillance$individual==j,]
  # Identify the lesions the individual has
  Lesions<-unique( IndividualArray$element)
  # Loop over these lesions
  for (i in Lesions){
  #Get the lesion-specific data
  LesionArray<-IndividualArray[IndividualArray$element==i,]
  #Strip out the location tags
  LesionArray<-LesionArray[!LesionArray$tag=="location",]
  #Select the latest lesion
  LesionAtMaxAge<- tail(LesionArray, n=1)
  #Gather the latest lesions over the loop
  LesionAtScreeningAge=rbind(LesionAtScreeningAge,LesionAtMaxAge)
  }}

Debug=87

#=================================================================
===
#Apply sensitivity to those on surveillance
#Add columns to LesionAtScreeningAge
LesionAtScreeningAge <- cbind(LesionAtScreeningAge,TriageSensitiv
ity = NA, RandomNumber3 = NA,TruePositivesTriage = NA, Size=NA, R
isk=NA)

#Identify those referred for surveillance but disease free at the
point of surveillance
DiseaseFreeAtSurveillance<-OverallSurveillanceRoundSpecificIndivi
dual[!OverallSurveillanceRoundSpecificIndividual%in%LesionAtScree
ningAge$individual]


# Define the disease states in the natural history model
DiseaseStates <- c(
"ad51",
"ad52",
"ad53",
"ad54",
"np_ad6_9",
"npl_ad6_9",
"np_ad10",
"pl_ad6_9",
"p_ad6_9",
"p_ad10",
"pcl1a",
"pcl1b",
```

```
"pcl2a",
"pcl2b",
"pcl3a",
"pcl3b",
"pcl4")


#Create table to store triage sensitivity values
SensitivityTableTriage <- array(0, dim = c(1, length(DiseaseState
s)))

#Give names to the columns and rows
colnames(SensitivityTableTriage) <- DiseaseStates
rownames(SensitivityTableTriage) <- c("SensitivityValue")


#Assign values to sensitivity table columns
SensitivityTableTriage[,"ad51"]     <-0.7
SensitivityTableTriage[,"ad52"]     <-0.7
SensitivityTableTriage[,"ad53"]     <-0.7
SensitivityTableTriage[,"ad54"]     <-0.7

SensitivityTableTriage[,"np_ad6_9"] <-0.9
SensitivityTableTriage[,"npl_ad6_9"]<-0.9
SensitivityTableTriage[,"np_ad10"]  <-0.9

SensitivityTableTriage[,"pl_ad6_9"] <-0.9
SensitivityTableTriage[,"p_ad6_9"]  <-0.9
SensitivityTableTriage[,"p_ad10"]   <-0.9

SensitivityTableTriage[,"pcl1a"]    <-0.9
SensitivityTableTriage[,"pcl1b"]    <-0.9
SensitivityTableTriage[,"pcl2a"]    <-0.9
SensitivityTableTriage[,"pcl2b"]    <-0.9
SensitivityTableTriage[,"pcl3a"]    <-0.9
SensitivityTableTriage[,"pcl3b"]    <-0.9
SensitivityTableTriage[,"pcl4"]     <-0.9


Debug=150
#The value from SensitivityTableTriage is assigned to rows in Les
ionAtScreeningAge where the corresponding "tag" matches with in S
ensitivityTableTriage
for (m in 1:ncol(SensitivityTableTriage)){
  LesionAtScreeningAge[LesionAtScreeningAge$tag==colnames(Sensiti
vityTableTriage)[m],"TriageSensitivity"]<-SensitivityTableTriage[
m]}
```

```
#Assign random number to RandomNumber3 column
LesionAtScreeningAge$RandomNumber3<-runif(nrow(LesionAtScreeningA
ge))


#Assign 1 to TruePositivesTriage column if the sensitivity value
is less than 1 or 0 if it's higher
LesionAtScreeningAge$TruePositivesTriage<-{ifelse(LesionAtScreeni
ngAge$RandomNumber3<(LesionAtScreeningAge$TriageSensitivity),1,0)
}

#Categories
Small=c("ad51", "ad52","ad53",  "ad54", "pl_ad6_9","npl_ad6_9", "
p_ad6_9" , "np_ad6_9" )
Large=c("p_ad10","np_ad10")
PCA=c("pcl1b", "pcl2b","pcl3b","pcl4", "pcl1a","pcl2a","pcl3a" )
Other=c("cl1","cl3",  "cl2", "cl4", "oc_death","crc_death")


#Assigning category based on size
LesionAtScreeningAge$Size[LesionAtScreeningAge$tag %in% Small]<-"
Small"
LesionAtScreeningAge$Size[LesionAtScreeningAge$tag %in% Large]<-"
Large"

LesionAtScreeningAge$Size[LesionAtScreeningAge$tag %in% PCA]<-"PC
A"
LesionAtScreeningAge$Size[LesionAtScreeningAge$tag %in% Other]<-"
Other"

Debug=177

for (s in unique(LesionAtScreeningAge$individual)){
 #Line needs additional markup
  PerPersonLesionAtScreeningAge<-LesionAtScreeningAge[LesionAtScr
eeningAge$individual==s, c("Size", "TruePositivesTriage" )]

  LesionsReferredtoTreatmentSurveillance <-unique(LesionAtScreeni
ngAge$IndividualLesion[which(LesionAtScreeningAge$TruePositivesTr
iage == 1)])

  CompleteData$LesionPresent[(CompleteData$IndividualLesion %in%
LesionsReferredtoTreatmentSurveillance)]<-0

  PerPersonLesionAtScreeningAge=PerPersonLesionAtScreeningAge[Per
PersonLesionAtScreeningAge$TruePositivesTriage==1,]

  #Remove NA rows arrising from other non-adenoma outcomes
  PerPersonLesionAtScreeningAge<-PerPersonLesionAtScreeningAge[!i
```

```
s.na(PerPersonLesionAtScreeningAge$TruePositivesTriage),]



  if (sum(PerPersonLesionAtScreeningAge$Size=="Large")>=1) {
    Risk="High"

  } else {
    if (sum(PerPersonLesionAtScreeningAge$Size=="Small")>=3) {
      Risk="Intermediate"

    } else {if (sum(PerPersonLesionAtScreeningAge$Size=="Small")==
=1|sum(PerPersonLesionAtScreeningAge$Size=="Small")==2) {
      Risk="Low"} else{
        Risk=NA}}}


LesionAtScreeningAge$Risk [LesionAtScreeningAge$individual %in% s
]<-Risk}

Debug=208

#colnames(AnnualSurveilalnceVolume)=c("Year", "High", "Intermedia
te")

#AnnualSurveilalnceVolume[,"Year"]=ModelYear

#AnnualSurveilalnceVolume[,"High"]=sum(HighRiskSurveillance$Indiv
idualSurveillanceAgeInterval==ModelYear)
#================================================================
===

#Subsetting to the round-specific individuals
OverallSurveillance<-as.data.frame(OverallSurveillance[OverallSur
veillance$individual %in% OverallSurveillanceRoundSpecificIndivid
ual,])


# Write in the categories of individuals according to risk
OverallSurveillance[OverallSurveillance[,"individual"]%in%Disease
FreeAtSurveillance,"Risk"]
<-"negative"
OverallSurveillance[OverallSurveillance[,"individual"]%in%LesionA
tScreeningAge$individual[LesionAtScreeningAge$Risk=="Low"],"Risk"
]         <-"Low"
OverallSurveillance[OverallSurveillance[,"individual"]%in%LesionA
tScreeningAge$individual[LesionAtScreeningAge$Risk=="Intermediate
"],"Risk"]<-"Intermediate"
OverallSurveillance[OverallSurveillance[,"individual"]%in%LesionA
```

```
tScreeningAge$individual[LesionAtScreeningAge$Risk=="High"],"Risk
"]        <-"High"

Debug=227
# Identify the individuals in each categories
LowIndividuals          <-unique(OverallSurveillance[,"individual
"][OverallSurveillance$Risk=="Low"])
NegativeIndividuals     <-unique(OverallSurveillance[,"individual
"][OverallSurveillance$Risk=="negative"])
IntermediateIndividuals <-unique(OverallSurveillance[,"individual
"][OverallSurveillance$Risk=="Intermediate"])
HighIndividuals         <-unique(OverallSurveillance[,"individual
"][OverallSurveillance$Risk=="High"])

Debug=234

#Neg, Low, intermediate needs to be dis intensified to 3 yearly

# Set the surveillance strategy
IntermediateInterval    =3
LongerInterval          =5

#Creating the updated sequences based on risk
if(identical(LowIndividuals,integer(0))){}else{
for(s in LowIndividuals){

#Identify the individual target surveillance stop year
SurveillanceStopYear<-max(OverallSurveillance$IndividualSurveilla
nceAgeInterval[OverallSurveillance$individual==s], na.rm = TRUE)

# Create a sequence of surveillance years: this needs to be neste
d with an if statement to skip instances when individuals die bef
ore the next surveillance moment
 if (is.na(OverallSurveillance$IndividualSurveillanceAgeInterval[
OverallSurveillance$individual==s][1])){ IndividualSchedule=NA

 #Blanking the previous surveillance schedule back to NA
OverallSurveillance$IndividualSurveillanceAgeInterval[OverallSurv
eillance$individual==s] <-NA}else
{IndividualSchedule<-seq(ModelYear,SurveillanceStopYear,by=Interm
ediateInterval)[-1]

  #Blanking the previous surveillance schedule back to NA
  OverallSurveillance$IndividualSurveillanceAgeInterval[OverallSu
rveillance$individual==s] <-NA
  Debug=258
  #Add a conditional to skip schedules that can't be completed
  if(identical(IndividualSchedule,numeric(0))){}else{
  #Writing in the new surveillance schedule
```

```
  OverallSurveillance$IndividualSurveillanceAgeInterval[OverallSu
rveillance$individual==s][c(1:length(IndividualSchedule))] <-Indi
vidualSchedule}}}}


#OverallSurveillance$IndividualSurveillanceAgeInterval[OverallSur
veillance$individual==s]=c(74)


if(identical(NegativeIndividuals,integer(0))){}else{
for(s in NegativeIndividuals){

#Identify the individual target surveillance stop year
SurveillanceStopYear<-max(OverallSurveillance$IndividualSurveilla
nceAgeInterval[OverallSurveillance$individual==s], na.rm = TRUE)

  # Create a sequence of surveillance years: this needs to be nes
ted with an if statement to skip instances when individuals die b
efore the next surveillance moment
  if (is.na(OverallSurveillance$IndividualSurveillanceAgeInterval
[OverallSurveillance$individual==s][1])){ IndividualSchedule=NA

  #Blanking the previous surveillance schedule back to NA
  #This is where we need a condition to only lengthen the interva
l if there are two consecutive negatives. I think we should not d
o any change to the interval yet, rather, simply inflate the nega
tive count and let the conditional changes below take effect

  OverallSurveillance$IndividualSurveillanceAgeInterval[OverallSu
rveillance$individual==s] <-NA}else{
    # If the model year is the maximum surveillance year, then ab
andon surveillance: this might need to be added to the other risk
outcomes
  if(max(OverallSurveillance$IndividualSurveillanceAgeInterval[Ov
erallSurveillance$individual==s],na.rm=TRUE)==ModelYear){
  OverallSurveillance$IndividualSurveillanceAgeInterval[OverallSu
rveillance$individual==s] <-NA }else{
    IndividualSchedule<-seq(ModelYear,SurveillanceStopYear,by=Int
ermediateInterval)[-1]}

    #Blanking the previous surveillance schedule back to NA
    OverallSurveillance$IndividualSurveillanceAgeInterval[Overall
Surveillance$individual==s] <-NA
    Debug=288
    #Writing in the new surveillance schedule
    if(identical(IndividualSchedule,numeric(0))){}else{
      OverallSurveillance$IndividualSurveillanceAgeInterval[Overa
llSurveillance$individual==s][c(1:length(IndividualSchedule))] <-
IndividualSchedule}
```

```
      # Add one to the counter of how many negative tests the ind
ividual has had
      OverallSurveillance$NegativeCount[OverallSurveillance$indiv
idual==s]<-OverallSurveillance$NegativeCount[OverallSurveillance$
individual==s]+1

    if(OverallSurveillance$InitialRisk[OverallSurveillance$indivi
dual==s][1]=="Intermediate"
       & OverallSurveillance$NegativeCount[OverallSurveillance$in
dividual==s][1]==1) {

        if(max(OverallSurveillance$IndividualSurveillanceAgeInter
val[OverallSurveillance$individual==s],na.rm=TRUE)==ModelYear){
  OverallSurveillance$IndividualSurveillanceAgeInterval[OverallSu
rveillance$individual==s] <-NA }else{
    IndividualSchedule<-seq(ModelYear,SurveillanceStopYear,by=Lon
gerInterval)[-1]}


      #Blanking the previous surveillance schedule back to NA
      OverallSurveillance$IndividualSurveillanceAgeInterval[Overa
llSurveillance$individual==s] <-NA

      #Add a conditional to skip schedules that can't be complete
d
      if(identical(IndividualSchedule, numeric(0))){}else{
      #Writing in the new surveillance schedule
      OverallSurveillance$IndividualSurveillanceAgeInterval[Overa
llSurveillance$individual==s][c(1:length(IndividualSchedule))] <-
IndividualSchedule}} else{}

    if(OverallSurveillance$InitialRisk[OverallSurveillance$indivi
dual==s][1]=="Intermediate"
       & OverallSurveillance$NegativeCount[OverallSurveillance$in
dividual==s][1]==2) {

      #Blanking the previous surveillance schedule back to NA
      OverallSurveillance$IndividualSurveillanceAgeInterval[Overa
llSurveillance$individual==s] <-NA

      #Writing in the new surveillance schedule
      } else{}


    if(OverallSurveillance$InitialRisk[OverallSurveillance$indivi
dual==s][1]=="High"
      & OverallSurveillance$NegativeCount[OverallSurveillance$ind
ividual==s][1]==2) {
```

```
      Debug=326

      IndividualSchedule<-seq(ModelYear,SurveillanceStopYear,by=L
ongerInterval)[-1]
      #Blanking the previous surveillance schedule back to NA
      OverallSurveillance$IndividualSurveillanceAgeInterval[Overa
llSurveillance$individual==s] <-NA

      #Add a conditional to skip schedules that can't be complete
d
      if(identical(IndividualSchedule, numeric(0))){}else{
      #Writing in the new surveillance schedule
      OverallSurveillance$IndividualSurveillanceAgeInterval[Overa
llSurveillance$individual==s][c(1:length(IndividualSchedule))] <-
IndividualSchedule}} else{}

    }}}

if(identical(IntermediateIndividuals,integer(0))){}else{
for(s in IntermediateIndividuals){

#Identify the individual target surveillance stop year
SurveillanceStopYear<-max(OverallSurveillance$IndividualSurveilla
nceAgeInterval[OverallSurveillance$individual==s], na.rm = TRUE)

  # Create a sequence of surveillance years: this needs to be nes
ted with an if statement to skip instances when individuals die b
efore the next surveillance moment
  if (is.na(OverallSurveillance$IndividualSurveillanceAgeInterval
[OverallSurveillance$individual==s][1])){ IndividualSchedule=NA

  #Blanking the previous surveillance schedule back to NA
  OverallSurveillance$IndividualSurveillanceAgeInterval[OverallSu
rveillance$individual==s] <-NA}else
  {IndividualSchedule<-seq(ModelYear,SurveillanceStopYear,by=Inte
rmediateInterval)[-1]

    #Blanking the previous surveillance schedule back to NA
    OverallSurveillance$IndividualSurveillanceAgeInterval[Overall
Surveillance$individual==s] <-NA

    #Add a conditional to skip schedules that can't be completed
    if(identical(IndividualSchedule,numeric(0))){}else{
    #Writing in the new surveillance schedule
    OverallSurveillance$IndividualSurveillanceAgeInterval[Overall
Surveillance$individual==s][c(1:length(IndividualSchedule))] <-In
dividualSchedule}}}}}
```

```
# Update the Referral round reference
#OverallSurveillance$Referral=OverallSurveillance$Referral+1
Debug=362
#Remove NA rows
OverallSurveillance     <-OverallSurveillance[!is.na(OverallSurve
illance$IndividualSurveillanceAgeInterval), ]}


#Create the combined surveillance array of both those with modifi
ed and unmodified surveillance strategies
CombinedSurveillance    <-rbind(OverallSurveillance,UnModifiedSur
veillance)

# Write in the effective maximum surveillance age by looping over
each individual
for (u in unique(CombinedSurveillance$individual)){
CombinedSurveillance$AppliedStopAge[CombinedSurveillance$individu
al==u]<-max(CombinedSurveillance$IndividualSurveillanceAgeInterva
l[CombinedSurveillance$individual==u])
}

Debug=375
#Save this as the new OverallSurveillance file
write.table(CombinedSurveillance, file="OverallSurveillance.txt")



#Create the continuous span of being in surveillance at any point
in time
#Set the empty object outside the loop
ContinuousSurveillanceRegistry=NULL

if(nrow(CombinedSurveillance)==0){}else{
#Iterate over everyone in surveillance
for (v in unique(CombinedSurveillance$individual)){
ContinuousSurveillanceRegistry=rbind(ContinuousSurveillanceRegist
ry,cbind(v,seq(from=CombinedSurveillance$InitialReferralAge[Combi
nedSurveillance$individual==v][1],to=CombinedSurveillance$Applied
StopAge[CombinedSurveillance$individual==v][1],by=1)))
}
colnames(ContinuousSurveillanceRegistry)=c("individual","years")}
#Save this as the new OverallSurveillance file
write.table(ContinuousSurveillanceRegistry, file="ContinuousSurve
illanceRegistry.txt")
Debug=391
```

SECTION 8 POST PROCESSING

The purpose of this file is to process men and women separately to check the files.

```
#Set the working file directory path
try(setwd("FilePath”)


#Define scenario
Scenarios=seq(1, 1)


#Define cohort
Cohorts =seq(1,45)


#Years selected for output generation
YearsSelected<-seq(2013,2034)


#Loop over all Scenarios and all cohorts to generate all summary
tables
for (Scenario in Scenarios){

#Loop over all simulated cohorts
for (Cohort in Cohorts){

assign("FemaleSummaryTable",
read.table(paste("Scenario",Scenario,"/SummaryTable_Female_",Coho
rt,"Strategy",Scenario,".txt",sep="")))

assign("MaleSummaryTable",
read.table(paste("Scenario",Scenario,"/SummaryTable_Male_",  Coho
rt,"Strategy",Scenario,".txt",sep="")))

FemaleSummaryTable=FemaleSummaryTable[FemaleSummaryTable$Year%in%
YearsSelected,]
MaleSummaryTable  =MaleSummaryTable  [MaleSummaryTable  $Year%in%
YearsSelected,]


assign(paste("FemaleSummaryTable",Cohort,sep=""),FemaleSummaryTab
le)
assign(paste("MaleSummaryTable",  Cohort,sep=""),MaleSummaryTable
)

#colnames(TotalTable)=colnames(FemaleSummaryTable)[-1]
}
```

```
TotalTableWomen<-as.data.frame(array(NA,c(length(YearsSelected),n
col(FemaleSummaryTable)-1)))

colnames(TotalTableWomen)<-colnames(FemaleSummaryTable[-1])
TotalTableMen<-TotalTableWomen

    TotalTableWomen[,c("Alive","PrimaryScreens","Clinical","Surve
illance", "TriageFalsePositives", "TriageTruePositives")]=(
    FemaleSummaryTable1[,c("Alive","PrimaryScreens","Clinical","S
urveillance", "TriageFalsePositives", "TriageTruePositives")]+
    FemaleSummaryTable2[,c("Alive","PrimaryScreens","Clinical","S
urveillance", "TriageFalsePositives", "TriageTruePositives")]+
    FemaleSummaryTable3[,c("Alive","PrimaryScreens","Clinical","S
urveillance", "TriageFalsePositives", "TriageTruePositives")]+
    FemaleSummaryTable4[,c("Alive","PrimaryScreens","Clinical","S
urveillance", "TriageFalsePositives", "TriageTruePositives")]+
    FemaleSummaryTable5[,c("Alive","PrimaryScreens","Clinical","S
urveillance", "TriageFalsePositives", "TriageTruePositives")]+
    FemaleSummaryTable6[,c("Alive","PrimaryScreens","Clinical","S
urveillance", "TriageFalsePositives", "TriageTruePositives")]+
    FemaleSummaryTable7[,c("Alive","PrimaryScreens","Clinical","S
urveillance", "TriageFalsePositives", "TriageTruePositives")]+
    FemaleSummaryTable8[,c("Alive","PrimaryScreens","Clinical","S
urveillance", "TriageFalsePositives", "TriageTruePositives")]+
    FemaleSummaryTable9[,c("Alive","PrimaryScreens","Clinical","S
urveillance", "TriageFalsePositives", "TriageTruePositives")]+
    FemaleSummaryTable10[,c("Alive","PrimaryScreens","Clinical","
Surveillance", "TriageFalsePositives", "TriageTruePositives")]+
    FemaleSummaryTable11[,c("Alive","PrimaryScreens","Clinical","
Surveillance", "TriageFalsePositives", "TriageTruePositives")]+
    FemaleSummaryTable12[,c("Alive","PrimaryScreens","Clinical","
Surveillance", "TriageFalsePositives", "TriageTruePositives")]+
    FemaleSummaryTable13[,c("Alive","PrimaryScreens","Clinical","
Surveillance", "TriageFalsePositives", "TriageTruePositives")]+
    FemaleSummaryTable14[,c("Alive","PrimaryScreens","Clinical","
Surveillance", "TriageFalsePositives", "TriageTruePositives")]+
    FemaleSummaryTable15[,c("Alive","PrimaryScreens","Clinical","
Surveillance", "TriageFalsePositives", "TriageTruePositives")]+
    FemaleSummaryTable16[,c("Alive","PrimaryScreens","Clinical","
Surveillance", "TriageFalsePositives", "TriageTruePositives")]+
    FemaleSummaryTable17[,c("Alive","PrimaryScreens","Clinical","
Surveillance", "TriageFalsePositives", "TriageTruePositives")]+
    FemaleSummaryTable18[,c("Alive","PrimaryScreens","Clinical","
Surveillance", "TriageFalsePositives", "TriageTruePositives")]+
    FemaleSummaryTable19[,c("Alive","PrimaryScreens","Clinical","
Surveillance", "TriageFalsePositives", "TriageTruePositives")]+
    FemaleSummaryTable20[,c("Alive","PrimaryScreens","Clinical","
Surveillance", "TriageFalsePositives", "TriageTruePositives")]+
    FemaleSummaryTable21[,c("Alive","PrimaryScreens","Clinical","
```

```
Surveillance", "TriageFalsePositives", "TriageTruePositives")]+
    FemaleSummaryTable22[,c("Alive","PrimaryScreens","Clinical","
Surveillance", "TriageFalsePositives", "TriageTruePositives")]+
    FemaleSummaryTable23[,c("Alive","PrimaryScreens","Clinical","
Surveillance", "TriageFalsePositives", "TriageTruePositives")]+
    FemaleSummaryTable24[,c("Alive","PrimaryScreens","Clinical","
Surveillance", "TriageFalsePositives", "TriageTruePositives")]+
    FemaleSummaryTable25[,c("Alive","PrimaryScreens","Clinical","
Surveillance", "TriageFalsePositives", "TriageTruePositives")]+
    FemaleSummaryTable26[,c("Alive","PrimaryScreens","Clinical","
Surveillance", "TriageFalsePositives", "TriageTruePositives")]+
    FemaleSummaryTable27[,c("Alive","PrimaryScreens","Clinical","
Surveillance", "TriageFalsePositives", "TriageTruePositives")]+
    FemaleSummaryTable28[,c("Alive","PrimaryScreens","Clinical","
Surveillance", "TriageFalsePositives", "TriageTruePositives")]+
    FemaleSummaryTable29[,c("Alive","PrimaryScreens","Clinical","
Surveillance", "TriageFalsePositives", "TriageTruePositives")]+
    FemaleSummaryTable30[,c("Alive","PrimaryScreens","Clinical","
Surveillance", "TriageFalsePositives", "TriageTruePositives")]+
    FemaleSummaryTable31[,c("Alive","PrimaryScreens","Clinical","
Surveillance", "TriageFalsePositives", "TriageTruePositives")]+
    FemaleSummaryTable32[,c("Alive","PrimaryScreens","Clinical","
Surveillance", "TriageFalsePositives", "TriageTruePositives")]+
    FemaleSummaryTable33[,c("Alive","PrimaryScreens","Clinical","
Surveillance", "TriageFalsePositives", "TriageTruePositives")]+
    FemaleSummaryTable34[,c("Alive","PrimaryScreens","Clinical","
Surveillance", "TriageFalsePositives", "TriageTruePositives")]+
    FemaleSummaryTable35[,c("Alive","PrimaryScreens","Clinical","
Surveillance", "TriageFalsePositives", "TriageTruePositives")]+
    FemaleSummaryTable36[,c("Alive","PrimaryScreens","Clinical","
Surveillance", "TriageFalsePositives", "TriageTruePositives")]+
    FemaleSummaryTable37[,c("Alive","PrimaryScreens","Clinical","
Surveillance", "TriageFalsePositives", "TriageTruePositives")]+
    FemaleSummaryTable38[,c("Alive","PrimaryScreens","Clinical","
Surveillance", "TriageFalsePositives", "TriageTruePositives")]+
    FemaleSummaryTable39[,c("Alive","PrimaryScreens","Clinical","
Surveillance", "TriageFalsePositives", "TriageTruePositives")]+
    FemaleSummaryTable40[,c("Alive","PrimaryScreens","Clinical","
Surveillance", "TriageFalsePositives", "TriageTruePositives")]+
    FemaleSummaryTable41[,c("Alive","PrimaryScreens","Clinical","
Surveillance", "TriageFalsePositives", "TriageTruePositives")]+
    FemaleSummaryTable42[,c("Alive","PrimaryScreens","Clinical","
Surveillance", "TriageFalsePositives", "TriageTruePositives")]+
    FemaleSummaryTable43[,c("Alive","PrimaryScreens","Clinical","
Surveillance", "TriageFalsePositives", "TriageTruePositives")]+
    FemaleSummaryTable44[,c("Alive","PrimaryScreens","Clinical","
Surveillance", "TriageFalsePositives", "TriageTruePositives")]+
    FemaleSummaryTable45[,c("Alive","PrimaryScreens","Clinical","
Surveillance", "TriageFalsePositives", "TriageTruePositives")])
```

```
    TotalTableMen[,c("Alive","PrimaryScreens","Clinical","Surveil
lance", "TriageFalsePositives", "TriageTruePositives")]=(
    MaleSummaryTable1   [,c("Alive","PrimaryScreens","Clinical","
Surveillance", "TriageFalsePositives", "TriageTruePositives")]+
    MaleSummaryTable2   [,c("Alive","PrimaryScreens","Clinical","
Surveillance", "TriageFalsePositives", "TriageTruePositives")]+
    MaleSummaryTable3   [,c("Alive","PrimaryScreens","Clinical","
Surveillance", "TriageFalsePositives", "TriageTruePositives")]+
    MaleSummaryTable4   [,c("Alive","PrimaryScreens","Clinical","
Surveillance", "TriageFalsePositives", "TriageTruePositives")]+
    MaleSummaryTable5   [,c("Alive","PrimaryScreens","Clinical","
Surveillance", "TriageFalsePositives", "TriageTruePositives")]+
    MaleSummaryTable6   [,c("Alive","PrimaryScreens","Clinical","
Surveillance", "TriageFalsePositives", "TriageTruePositives")]+
    MaleSummaryTable7   [,c("Alive","PrimaryScreens","Clinical","
Surveillance", "TriageFalsePositives", "TriageTruePositives")]+
    MaleSummaryTable8   [,c("Alive","PrimaryScreens","Clinical","
Surveillance", "TriageFalsePositives", "TriageTruePositives")]+
    MaleSummaryTable9   [,c("Alive","PrimaryScreens","Clinical","
Surveillance", "TriageFalsePositives", "TriageTruePositives")]+
    MaleSummaryTable10  [,c("Alive","PrimaryScreens","Clinical","
Surveillance", "TriageFalsePositives", "TriageTruePositives")]+
    MaleSummaryTable11  [,c("Alive","PrimaryScreens","Clinical","
Surveillance", "TriageFalsePositives", "TriageTruePositives")]+
    MaleSummaryTable12  [,c("Alive","PrimaryScreens","Clinical","
Surveillance", "TriageFalsePositives", "TriageTruePositives")]+
    MaleSummaryTable13  [,c("Alive","PrimaryScreens","Clinical","
Surveillance", "TriageFalsePositives", "TriageTruePositives")]+
    MaleSummaryTable14  [,c("Alive","PrimaryScreens","Clinical","
Surveillance", "TriageFalsePositives", "TriageTruePositives")]+
    MaleSummaryTable15  [,c("Alive","PrimaryScreens","Clinical","
Surveillance", "TriageFalsePositives", "TriageTruePositives")]+
    MaleSummaryTable16  [,c("Alive","PrimaryScreens","Clinical","
Surveillance", "TriageFalsePositives", "TriageTruePositives")]+
    MaleSummaryTable17  [,c("Alive","PrimaryScreens","Clinical","
Surveillance", "TriageFalsePositives", "TriageTruePositives")]+
    MaleSummaryTable18  [,c("Alive","PrimaryScreens","Clinical","
Surveillance", "TriageFalsePositives", "TriageTruePositives")]+
    MaleSummaryTable19  [,c("Alive","PrimaryScreens","Clinical","
Surveillance", "TriageFalsePositives", "TriageTruePositives")]+
    MaleSummaryTable20  [,c("Alive","PrimaryScreens","Clinical","
Surveillance", "TriageFalsePositives", "TriageTruePositives")]+
    MaleSummaryTable21  [,c("Alive","PrimaryScreens","Clinical","
Surveillance", "TriageFalsePositives", "TriageTruePositives")]+
    MaleSummaryTable22  [,c("Alive","PrimaryScreens","Clinical","
Surveillance", "TriageFalsePositives", "TriageTruePositives")]+
    MaleSummaryTable23  [,c("Alive","PrimaryScreens","Clinical","
Surveillance", "TriageFalsePositives", "TriageTruePositives")]+
```

```
    MaleSummaryTable24  [,c("Alive","PrimaryScreens","Clinical","
Surveillance", "TriageFalsePositives", "TriageTruePositives")]+
    MaleSummaryTable25  [,c("Alive","PrimaryScreens","Clinical","
Surveillance", "TriageFalsePositives", "TriageTruePositives")]+
    MaleSummaryTable26  [,c("Alive","PrimaryScreens","Clinical","
Surveillance", "TriageFalsePositives", "TriageTruePositives")]+
    MaleSummaryTable27  [,c("Alive","PrimaryScreens","Clinical","
Surveillance", "TriageFalsePositives", "TriageTruePositives")]+
    MaleSummaryTable28  [,c("Alive","PrimaryScreens","Clinical","
Surveillance", "TriageFalsePositives", "TriageTruePositives")]+
    MaleSummaryTable29  [,c("Alive","PrimaryScreens","Clinical","
Surveillance", "TriageFalsePositives", "TriageTruePositives")]+
    MaleSummaryTable30  [,c("Alive","PrimaryScreens","Clinical","
Surveillance", "TriageFalsePositives", "TriageTruePositives")]+
    MaleSummaryTable31  [,c("Alive","PrimaryScreens","Clinical","
Surveillance", "TriageFalsePositives", "TriageTruePositives")]+
    MaleSummaryTable32  [,c("Alive","PrimaryScreens","Clinical","
Surveillance", "TriageFalsePositives", "TriageTruePositives")]+
    MaleSummaryTable33  [,c("Alive","PrimaryScreens","Clinical","
Surveillance", "TriageFalsePositives", "TriageTruePositives")]+
    MaleSummaryTable34  [,c("Alive","PrimaryScreens","Clinical","
Surveillance", "TriageFalsePositives", "TriageTruePositives")]+
    MaleSummaryTable35  [,c("Alive","PrimaryScreens","Clinical","
Surveillance", "TriageFalsePositives", "TriageTruePositives")]+
    MaleSummaryTable36  [,c("Alive","PrimaryScreens","Clinical","
Surveillance", "TriageFalsePositives", "TriageTruePositives")]+
    MaleSummaryTable37  [,c("Alive","PrimaryScreens","Clinical","
Surveillance", "TriageFalsePositives", "TriageTruePositives")]+
    MaleSummaryTable38  [,c("Alive","PrimaryScreens","Clinical","
Surveillance", "TriageFalsePositives", "TriageTruePositives")]+
    MaleSummaryTable39  [,c("Alive","PrimaryScreens","Clinical","
Surveillance", "TriageFalsePositives", "TriageTruePositives")]+
    MaleSummaryTable40  [,c("Alive","PrimaryScreens","Clinical","
Surveillance", "TriageFalsePositives", "TriageTruePositives")]+
    MaleSummaryTable41  [,c("Alive","PrimaryScreens","Clinical","
Surveillance", "TriageFalsePositives", "TriageTruePositives")]+
    MaleSummaryTable42  [,c("Alive","PrimaryScreens","Clinical","
Surveillance", "TriageFalsePositives", "TriageTruePositives")]+
    MaleSummaryTable43  [,c("Alive","PrimaryScreens","Clinical","
Surveillance", "TriageFalsePositives", "TriageTruePositives")]+
    MaleSummaryTable44  [,c("Alive","PrimaryScreens","Clinical","
Surveillance", "TriageFalsePositives", "TriageTruePositives")]+
    MaleSummaryTable45  [,c("Alive","PrimaryScreens","Clinical","
Surveillance", "TriageFalsePositives", "TriageTruePositives")])


#Add a total column
TotalTableWomen <-cbind(TotalTableWomen,Total=rowSums(TotalTableW
omen[,c("Clinical","Surveillance", "TriageFalsePositives", "Triag
```

```
eTruePositives")]))
TotalTableMen   <-cbind(TotalTableMen,  Total=rowSums(TotalTableM
en  [,c("Clinical","Surveillance", "TriageFalsePositives", "Triag
eTruePositives")]))

TotalTableWomen$Year<-YearsSelected
TotalTableMen$Year  <-YearsSelected


#Write the summary table to the respective files
#write.table(TotalTable, file = paste("Scenario",Scenario,"/", "T
otalTable_Strategy",Scenario, ".txt", sep = ""))

assign(paste("TotalTableWomen",Scenario,sep=""),TotalTableWomen)
assign(paste("TotalTableMen",  Scenario,sep=""),TotalTableMen  )

}




MaxCountWomen=max(pretty(max(c(TotalTableWomen1$Total,TotalTableW
omen2$Total,TotalTableWomen3$Total,TotalTableWomen4$Total,TotalTa
bleWomen5$Total,TotalTableWomen6$Total,TotalTableWomen7$Total,Tot
alTableWomen8$Total))))
MaxCountMen  =max(pretty(max(c(TotalTableMen1$Total,TotalTableMen
2$Total,TotalTableMen3$Total,TotalTableMen4$Total,TotalTableMen5$
Total,TotalTableMen6$Total,TotalTableMen7$Total,TotalTableMen8$To
tal))))
MaxCount     =max(MaxCountWomen,MaxCountMen )


plot(
  x=TotalTableWomen1$Year,
  y=TotalTableWomen1$Total,
  type="l",
  ylim=c(0,MaxCount),
  xlim=c(2012,2036),
  xlab="Year",
  ylab="Annual colonoscopy volume",
  lwd=2
)
text(x=2035,y=TotalTableWomen1$Total[length(TotalTableWomen1$Tota
l)],"1")

lines(
  x=TotalTableWomen2$Year,
  y=TotalTableWomen2$Total,
  col="grey",
```

```
  lwd=2)

text(x=2035,y=TotalTableWomen2$Total[length(TotalTableWomen2$Tota
l)],"2")

lines(
  x=TotalTableWomen3$Year,
  y=TotalTableWomen3$Total,
  col="grey",
  lwd=2)

text(x=2035,y=TotalTableWomen3$Total[length(TotalTableWomen3$Tota
l)],"3")


lines(
  x=TotalTableWomen4$Year,
  y=TotalTableWomen4$Total,
  col="grey",
  lwd=2)

text(x=2035,y=TotalTableWomen4$Total[length(TotalTableWomen4$Tota
l)],"4")

lines(
  x=TotalTableWomen5$Year,
  y=TotalTableWomen5$Total,
  col="grey",
  lwd=2)

text(x=2035,y=TotalTableWomen5$Total[length(TotalTableWomen5$Tota
l)],"5")

lines(
  x=TotalTableWomen6$Year,
  y=TotalTableWomen6$Total,
  col="grey",
  lwd=2)

text(x=2035,y=TotalTableWomen6$Total[length(TotalTableWomen6$Tota
l)],"6")

lines(
  x=TotalTableWomen7$Year,
  y=TotalTableWomen7$Total,
  col="grey",
  lwd=2)

text(x=2035,y=TotalTableWomen7$Total[length(TotalTableWomen7$Tota
```

```
l)],"7")

lines(
  x=TotalTableWomen8$Year,
  y=TotalTableWomen8$Total,
  col="grey",
  lwd=2)

text(x=2035,y=TotalTableWomen8$Total[length(TotalTableWomen8$Tota
l)],"8")

lines(
  x=TotalTableMen1$Year,
  y=TotalTableMen1$Total,
  col="blue",
  lwd=2)

lines(
  x=TotalTableMen2$Year,
  y=TotalTableMen2$Total,
  col="blue",
  lwd=2)

text(x=2035,y=TotalTableMen2$Total[length(TotalTableMen2$Total)],
"2")

lines(
  x=TotalTableMen3$Year,
  y=TotalTableMen3$Total,
  col="blue",
  lwd=2)

text(x=2035,y=TotalTableMen3$Total[length(TotalTableMen3$Total)],
"3")


lines(
  x=TotalTableMen4$Year,
  y=TotalTableMen4$Total,
  col="blue",
  lwd=2)

text(x=2035,y=TotalTableMen4$Total[length(TotalTableMen4$Total)],
"4")

lines(
  x=TotalTableMen5$Year,
  y=TotalTableMen5$Total,
  col="blue",
```

```
  lwd=2)

text(x=2035,y=TotalTableMen5$Total[length(TotalTableMen5$Total)],
"5")

lines(
  x=TotalTableMen6$Year,
  y=TotalTableMen6$Total,
  col="blue",
  lwd=2)

text(x=2035,y=TotalTableMen6$Total[length(TotalTableMen6$Total)],
"6")

lines(
  x=TotalTableMen7$Year,
  y=TotalTableMen7$Total,
  col="blue",
  lwd=2)

text(x=2035,y=TotalTableMen7$Total[length(TotalTableMen7$Total)],
"7")

lines(
  x=TotalTableMen8$Year,
  y=TotalTableMen8$Total,
  col="blue",
  lwd=2)

text(x=2035,y=TotalTableMen8$Total[length(TotalTableMen7$Total)],
"8")



Years=seq(from=2013,to=2021,by=1)
Ages =seq(from=68,to=60,by=-2)

Counts=array(NA,dim=c(length(Ages),length(Years)))

colnames(Counts)=Years
rownames(Counts)=Ages

#SimpleStack of output files
MaleSummaryTableCombined=rbind(
MaleSummaryTable1,
MaleSummaryTable2,
MaleSummaryTable3,
MaleSummaryTable4,
MaleSummaryTable5,
```

```
MaleSummaryTable6,
MaleSummaryTable7,
MaleSummaryTable8,
MaleSummaryTable9,
MaleSummaryTable10,
MaleSummaryTable11,
MaleSummaryTable12,
MaleSummaryTable13,
MaleSummaryTable14,
MaleSummaryTable15,
MaleSummaryTable16,
MaleSummaryTable17,
MaleSummaryTable18,
MaleSummaryTable19,
MaleSummaryTable20,
MaleSummaryTable21,
MaleSummaryTable22,
MaleSummaryTable23,
MaleSummaryTable24,
MaleSummaryTable25,
MaleSummaryTable26,
MaleSummaryTable27,
MaleSummaryTable28,
MaleSummaryTable29,
MaleSummaryTable30,
MaleSummaryTable31,
MaleSummaryTable32,
MaleSummaryTable33,
MaleSummaryTable34,
MaleSummaryTable35,
MaleSummaryTable36,
MaleSummaryTable37,
MaleSummaryTable38,
MaleSummaryTable39,
MaleSummaryTable30,
MaleSummaryTable41,
MaleSummaryTable42,
MaleSummaryTable43,
MaleSummaryTable44,
MaleSummaryTable45)

#SimpleStack of output files
FemaleSummaryTableCombined=rbind(
FemaleSummaryTable1,
FemaleSummaryTable2,
FemaleSummaryTable3,
FemaleSummaryTable4,
FemaleSummaryTable5,
FemaleSummaryTable6,
```

```
FemaleSummaryTable7,
FemaleSummaryTable8,
FemaleSummaryTable9,
FemaleSummaryTable10,
FemaleSummaryTable11,
FemaleSummaryTable12,
FemaleSummaryTable13,
FemaleSummaryTable14,
FemaleSummaryTable15,
FemaleSummaryTable16,
FemaleSummaryTable17,
FemaleSummaryTable18,
FemaleSummaryTable19,
FemaleSummaryTable20,
FemaleSummaryTable21,
FemaleSummaryTable22,
FemaleSummaryTable23,
FemaleSummaryTable24,
FemaleSummaryTable25,
FemaleSummaryTable26,
FemaleSummaryTable27,
FemaleSummaryTable28,
FemaleSummaryTable29,
FemaleSummaryTable30,
FemaleSummaryTable31,
FemaleSummaryTable32,
FemaleSummaryTable33,
FemaleSummaryTable34,
FemaleSummaryTable35,
FemaleSummaryTable36,
FemaleSummaryTable37,
FemaleSummaryTable38,
FemaleSummaryTable39,
FemaleSummaryTable30,
FemaleSummaryTable41,
FemaleSummaryTable42,
FemaleSummaryTable43,
FemaleSummaryTable44,
FemaleSummaryTable45)


#Count how many are alive
for (Year in Years){
for (Age in Ages){

Counts[rownames(Counts)==Age,colnames(Counts)==Year]=MaleSummaryT
ableCombined$Alive [MaleSummaryTableCombined$Age==Age & MaleSumma
ryTableCombined$Year==Year]}}
```

```
#Count how many primary screens
for (Year in Years){
for (Age in Ages){

Counts[rownames(Counts)==Age,colnames(Counts)==Year]=MaleSummaryT
ableCombined$PrimaryScreens [MaleSummaryTableCombined$Age==Age &
MaleSummaryTableCombined$Year==Year]}}


#Count how many colonoscopies
for (Year in Years){
for (Age in Ages){

Counts[rownames(Counts)==Age,colnames(Counts)==Year]=MaleSummaryT
ableCombined$PrimaryScreens [MaleSummaryTableCombined$Age==Age &
MaleSummaryTableCombined$Year==Year]}}


#Count how many are alive
for (Year in Years){
for (Age in Ages){

Counts[rownames(Counts)==Age,colnames(Counts)==Year]=FemaleSummar
yTableCombined$Alive [FemaleSummaryTableCombined$Age==Age & Femal
eSummaryTableCombined$Year==Year]}}


#Count how many primary screens
for (Year in Years){
for (Age in Ages){

Counts[rownames(Counts)==Age,colnames(Counts)==Year]=FemaleSummar
yTableCombined$PrimaryScreens [FemaleSummaryTableCombined$Age==Ag
e & FemaleSummaryTableCombined$Year==Year]}}


#Count how many colonoscopies
for (Year in Years){
for (Age in Ages){

Counts[rownames(Counts)==Age,colnames(Counts)==Year]=FemaleSummar
yTableCombined$PrimaryScreens [FemaleSummaryTableCombined$Age==Ag
e & FemaleSummaryTableCombined$Year==Year]}}


#Checking Sex-specific participation

ScreenYearsWomen=FemaleSummaryTableCombined[FemaleSummaryTableCom
```

```
bined$PrimaryScreens>0,]
ScreenYearsMen  =MaleSummaryTableCombined  [MaleSummaryTableCombi
ned$PrimaryScreens>0,]

ScreenYearsWomen$PrimaryScreens/ScreenYearsWomen$Alive
ScreenYearsMen$PrimaryScreens/ScreenYearsMen$Alive


#Checking adherence from adherence files
setwd("Filename")

#Dropping first column
AdherenceMale1=read.table("Adherence_Male1.txt",header=TRUE)[,-1]
AdherenceFemale1=read.table("Adherence_Female1.txt",header=TRUE)[
,-1]
sum(AdherenceMale1)/(nrow(AdherenceMale1)*ncol(AdherenceMale1))
sum(AdherenceFemale1)/(nrow(AdherenceFemale1)*ncol(AdherenceFemal
e1))
```

Appendix 6 Details of Recalibration targets

T1: Total number of CRC cases and population size (Person-years) for the five most recent years prior to introduction of screening by 5-year age group and sex

Male				Female		
Age Group	2007-2011			2007-2011		
	Cases	Population size	Rate (x100,000 PYs)	Cases	Population size	Rate (x100,000 PYs)
0-19	18	3129088	0.575247484	28	2991047	0.936127048
20-24	23	856407	2.685638954	19	868204	2.188425762
25-29	33	966897	3.412979873	31	986243	3.143241574
30-34	32	944146	3.389306315	45	935753	4.808961339
35-39	62	892129	6.949667593	71	870876	8.152710604
40-44	109	799902	13.62666927	102	789576	12.91832578
45-49	235	734675	31.986933	182	735654	24.73989131
50-54	362	658811	54.94747355	320	655807	48.7948436
55-59	619	593200	104.349292	397	585951	67.75310564
60-64	911	518837	175.5850103	546	510472	106.9598333
65-69	1095	391434	279.7406459	541	394726	137.0570978
70-74	1140	299457	380.6890472	702	324333	216.4442101
75-79	1094	218594	500.4711932	762	265587	286.9116335
80-84	787	132314	594.7972248	659	204194	322.7323036
85+	443	83994	527.4186251	634	185650	341.5028279
Total	6963	11219885	62.05945961	5039	11304073	44.57685296

T2: Number of deaths due to CRC and population size for the five most recent years prior to introduction of screening by 5-year age group and sex

Male				Female		
Age Group	2007-2011			2007-2011		
	# deaths	population size	rate (x100,000 PYs)	# deaths	population size	Rate (x100,000 PYs)
0-19	0	3129088	0		2991047	0
20-24	2	856407	0.233533822		868204	0
25-29	5	966897	0.517118163	1	986243	0.101394889
30-34	7	944146	0.741410756	7	935753	0.748060653
35-39	12	892129	1.345096953	20	870876	2.296538198
40-44	29	799902	3.625444117	27	789576	3.419556825
45-49	54	734675	7.350188859	51	735654	6.932606905
50-54	98	658811	14.8752829	70	655807	10.67387204
55-59	184	593200	31.01820634	101	585951	17.23693619
60-64	272	518837	52.42494271	173	510472	33.89020358
65-69	364	391434	92.99141107	181	394726	45.85459281

70-74	469	299457	156.6168098	237	324333	73.0730453
75-79	479	218594	219.1276979	315	265587	118.6052028
80-84	437	132314	330.274952	362	204194	177.2823883
85+	346	83994	411.9341858	453	185650	244.0075411
Total	2758	11219885	24.58135712	1998	11304073	17.67504509

T3: Number of CRC cases for the five most recent years prior to introduction of screening by location, stage and sex.

Male						
Localization	2007-2011					
	Stage I	Stage II	Stage III	Stage IV	Unknown	Total
Right	200	690	562	483	127	2062
Left	337	569	651	533	180	2270
Rectum	303	396	754	394	266	2113
Unknown	42	56	60	113	92	363
Total	882	1711	2027	1523	665	6808

Female						
Localization	2007-2011					
	Stage I	Stage II	Stage III	Stage IV	Unknown	Total
Right	194	659	534	425	128	1940
Left	236	436	405	337	128	1542
Rectum	227	186	366	167	157	1103
Unknown	38	37	30	77	84	266
Total	695	1318	1335	1006	497	4851

Right = Cecum, Ascending colon, Transverse colon
Left = Descending colon, Sigmoid, Rectosigmoid junction
Rectum = Rectum

T4: Number of CRC cases for the five most recent years prior to introduction of screening by 5-year age group, stage and sex.

Male						
Age Group	2005-2009					
	Stage I	Stage II	Stage III	Stage IV	Unknown	Total
0-19	1	1	2		14	18
20-24	0	0	3	2	12	17
25-29	4	4	5	6	15	34
30-34	5	3	11	4	18	41
35-39	8	10	20	18	11	67
40-44	11	34	43	30	13	131

45-49	32	46	93	64	25	260
50-54	48	91	144	98	42	423
55-59	80	156	215	169	55	675
60-64	132	236	308	198	72	946
65-69	153	255	345	274	93	1120
70-74	148	296	324	252	96	1116
75-79	146	309	272	219	94	1040
80-84	84	197	182	147	101	711
85+	34	94	73	60	92	353
Total	886	1732	2040	1541	753	6952

Female						
Age Group	2005-2009					
	Stage I	Stage II	Stage III	Stage IV	Unknown	Total
0-19	1				25	26
20-24	0	0	2	0	14	16
25-29	3	1	3	3	17	27
30-34	3	8	8	8	15	42
35-39	8	4	24	22	13	71
40-44	13	21	34	18	16	102
45-49	13	37	71	45	16	182
50-54	54	67	98	71	30	320
55-59	67	93	123	87	27	397
60-64	80	128	182	115	41	546
65-69	89	141	165	106	40	541
70-74	108	195	192	158	49	702
75-79	91	253	199	156	63	762
80-84	97	199	141	137	85	659
85+	67	160	119	105	183	634
Total	694	1307	1361	1031	634	5027

Appendix 7 Categorization of aim/objective stated in the studies included in the review

Study	Title	Stated Aim/Objective	Categorisation of the objective
Aeria et al, 2019	Cost-utility analysis of colonoscopy or faecal immunochemical test for population-based organised colorectal cancer screening	“Primary aim of our analysis was to perform a cost utility analysis in a European country, to compare a population-based CRC screening programme with FIT or primary colonoscopy versus no screening. Secondary aims were to explore the influence of adherence rates and costs on such cost-utility ratio, and to evaluate its impact on health resources, namely on the annual capacity for performing colonoscopies.”	Broad
Aronsson et al, 2017	Cost-effectiveness of high-sensitivity faecal immunochemical test and colonoscopy screening for colorectal cancer	“The primary aim of the present study was to estimate the long-term costs and health outcomes of four strategies for colorectal cancer screening compared with no screening. A secondary aim was to calculate the uncertainties in the cost-effectiveness results and single-model inputs, such as the importance of the participation rate, age at initiation of screening and disease progression.”	Narrow
Arrospide et al, 2018	Cost-effectiveness and budget impact analyses of a colorectal cancer screening programme in a high adenoma prevalence scenario using MISCAN-Colon microsimulation model	"The object of our study was to economically evaluate the programme compared to no screening via cost-effectiveness and budget impact analyses with microsimulation models calibrated to the Basque epidemiological features of CRC incidence and adenoma prevalence.”	Broad
Babela et al, 2021	Cost-effectiveness of colorectal cancer screening in Slovakia	“The study aims to analyze the comparative effectiveness and cost-effectiveness of two most often used strategies in Europe and the USA, annual and biennial FIT, in reducing CRC incidence and mortality in the Slovak population of 50–75 years of age using the microsimulation screening analysis model.”	Narrow
Barre et al, 2020	Cost-effectiveness analysis of alternative colon cancer screening strategies in the context of the French national screening programme	“The objective of this work is to compare the cost-effectiveness of screening alternatives currently available for average-risk individuals taking real-world participation rates into account.”	Broad
Berchi et al, 2004	Cost-e¡ectiveness analysis of two strategies for mass screening for colorectal cancer in France	“The aim of the present study was to use a simulation model to analyse the costs and the effectiveness of 20 years of biennial CRC screening with an automated immunological test (Magstream) and to compare its results to those obtained with a guaiac stool test (Haemoccult).”	Narrow
Chauvin 2012	Incremental net benefit and acceptability of alternative health policies: a case study of mass screening for colorectal cancer	“Our cost-effectiveness analysis aimed at assessing the potential of alternative mass screening strategies when biennial guaiac FOBT is already implemented in average risk population. We considered three alternative screening policies: biennial immunological FOBT, CTC every 10 years, and CTC every 5 years.”	Broad
Coretti et al, 2020	Economic evaluation of colorectal cancer screening programs: Affordability for the health service	“We aimed to investigate the cost-effectiveness of the Abruzzo CRC screening programme, and to determine which variables most affect its success. The results may provide a generalizable decisional support tool to steer any revision of the current programme.”	Narrow
Currais et al, 2021	Should Colorectal Cancer Screening in Portugal Start at the Age of 45 Years? A Cost-Utility Analysis	“We aimed to evaluate if the changes in the CRC incidence/mortality observed in the USA and the rest of Europe also occur in Portugal, and then perform a cost-utility analysis of CRC screening that starts at 45 years of age.”	Broad
Goede et al, 2013	Cost-effectiveness of one versus two sample faecal immunochemical testing for colorectal cancer screening	“The aim of this study was to evaluate the cost-effectiveness of one-sample and two-sample FIT screening strategies with variable intervals, age ranges and cut-off levels in order to assess whether the increased performance of a second FIT sample outweighs the increased costs compared with one-sample FIT screening.”	Broad

Greuter et al, 2016	The potential of imaging techniques as a screening tool for colorectal cancer: a cost-effectiveness analysis	"We aimed to compare CTC and MRC screening with no screening and colonoscopy screening in terms of effectiveness, costs and cost-effectiveness using the Adenoma and Serrated pathway to Colorectal CAncer (ASCCA) model."	Broad
Gyrd Hansen 1998a	Fecal Occult Blood Tests A cost-effectiveness Analysis	"The aim of this paper is to compare the cost-effectiveness of the unhydrated H-II test based on the experience of the Danish randomized trial with the potential cost-effectiveness of alternative FOB tests if these were to be used as a test in a similar population screening programme."	Broad
Gyrd Hansen 1998b	Colorectal cancer screening: efficiency and effectiveness	"The aim of this analysis was to build upon the knowledge acquired from this screening programme, in order to give a basis on which to evaluate the cost-effectiveness of alternative colorectal cancer screening programmes using the unhydrated H-II test."	Broad
Hassan et al, 2011	Cost-effectiveness and projected national impact of colorectal cancer screening in France	"The aim of the current cost-effectiveness analysis was to assess the efficacy and costs of different CRC screening modalities, including endoscopic modalities, in a simulated cohort of average-risk French subjects, to project the health and economic outcomes on the French population, and to quantify the potential loss associated with decision uncertainty."	Broad
Heinävaara et al, 2022	Optimizing screening with faecal immunochemical test for both sexes - Cost-effectiveness analysis from Finland	"This study aims to model cost-effectiveness of sex-specific strategies for the whole population, and to assess whether the current strategies are optimal."	Broad
Heresbach et al, 2010	Cost-effectiveness of colorectal cancer screening with computed tomography colonography or fecal blood tests	"The aim of our study was thus to assess the cost-effectiveness of CTC and iFOBTstrategies compared with no screening or FOBT over a 30-year horizon with sex distinction."	Broad

Idigoras et al, 2018	Evaluation of the colorectal cancer screening Programme in the Basque Country (Spain) and its effectiveness based on the MISCAN-Colon model	"The aim of our study was to determine possible scenarios in terms of incidence, mortality and reduction of Life-years-Lost (L-y-L) in the medium and long term of CRC. The objectives of this study were to predict future scenarios and outcomes for the Basque population and to determine the epidemiological benefits of the screening programme in terms of incidence, mortality and years of life lost (L-y-L)."	Narrow
Jahn et al, 2019	Effectiveness, benefit harm and cost-effectiveness of colorectal cancer screening in Austria	"We aim to systematically evaluate the long-term effectiveness, harms and cost-effectiveness of different organized CRC screening strategies in Austria."	Broad
Ladabum et al, 2014	Cost-effectiveness of colorectal cancer screening in Germany: current endoscopic and fecal testing strategies versus plasma mSEPT9 DNA	"We performed a cost-effectiveness analysis of current and emerging CRC screening strategies in Germany."	Broad
Lansdorp-Vogelaar et al, 2018	Cost-effectiveness of High-performance Biomarker Tests vs Fecal Immunochemical Test for Noninvasive Colorectal Cancer Screening	"Therefore the aim of this study was to provide insight in the requirements for test sensitivity, specificity and unit cost in order for new technologies to be cost-effective compared to FIT screening in population-based screening programs."	Broad
Lee 2010	Cost-effectiveness of CT Colonography for UK NHS Colorectal Cancer Screening of Asymptomatic Adults Aged 60–69 Years	"The current study extends this previous work and uses updated data on disease staging and progression to estimate the cost-effectiveness of CRC screening technologies (CTC, OC, FOBT,FSIG) from the perspective of the UK NHS."	Broad
Lejeune et al, 2004	Cost-effectiveness analysis of fecal occult blood screening for colorectal cancer	"The objective of this study was to assess the cost-effectiveness of screening for colorectal cancer using a fecal occult blood screening test, the Hemoccult-II, in a cohort of 100,000 asymptomatic individuals 50–74 years of age."	Narrow
Lejeune et al, 2010	Cost-effectiveness of screening for colorectal cancer in France using a guaiac test versus an immunochemical test	"The aim of this study was to compare the cost and the effectiveness of two biennial fecal occult blood screening tests for colorectal cancer: a guaiac nonrehydrated test (G-FOBT) and an immunochemical test (I-FOBT) with the absence of screening."	Narrow
Lejeune et al, 2014	The cost-effectiveness of immunochemical tests for colorectal cancer screening	"To compare the cost and effectiveness in biennial screening for colorectal cancer of fifteen strategies consisting of the three-stool sample un-rehydrated guaiac faecal occult blood test and three immunochemical tests: Magstream, FOB-Gold and OC-Sensor, at different positivity cut-off levels and stool-sample collection."	Narrow
Macafee et al, 2008	Population screening for colorectal cancer: the implications of an ageing population	"The aim of this study was to simulate a population-based screening setting using a Markov model and assess the effect of increasing life expectancy on CRC screening cost-effectiveness."	Broad
McFerran et al, 2022	Colorectal Cancer Screening within Colonoscopy Capacity Constraints: Can FIT-Based Programs Save More Lives by Trading off More Sensitive Test Cutoffs against Longer Screening Intervals?	"The objective of this study is to further explore the potential for improved effectiveness and cost-effectiveness within a capacity-constrained system."	Broad
Murphy et al, 2017	Cost-effectiveness of the faecal immunochemical test at a range of positivity thresholds compared with the guaiac faecal occult blood test in the NHS Bowel Cancer Screening Programme in England	"The aim of this analysis was to estimate the cost–utility of the faecal immunochemical test for haemoglobin (FIT) compared with FOBT for a cohort beginning screening aged 60 years at a range of FIT positivity thresholds."	Broad
Pil et al, 2016	Cost-effectiveness and budget impact analysis of a population-based screening programme for colorectal cancer	"This study assessed the cost-effectiveness and budget impact of the colorectal population-based screening programme in Flanders (Belgium)."	Broad
Senore et al, 2019	Cost-effectiveness of colorectal cancer screening programmes using sigmoidoscopy and immunochemical faecal occult blood test	"This analysis aimed to compute the actual cost of organized FS and/or FIT programmes, and to assess their cost-effectiveness, based on real data extracted from an established screening programme."	Broad

Sharp et al, 2012	Cost-effectiveness of population-based screening for colorectal cancer: a comparison of guaiac-based faecal occult blood testing, faecal immunochemical testing and flexible sigmoidoscopy	"The aim of this study was to estimate the incremental cost-effectiveness of a population-based colorectal cancer-screening programme using primary FIT, FOBT with reflex FIT testing, or once-only FSIG compared with no screening."	Broad
Sobhani et al, 2011	Cost-effectiveness of mass screening for colorectal cancer: choice of fecal occult blood test and screening strategy.	"The aim was to improve the sensitivity of the test by choosing an accurate format (1- to 3-sample and optimum hemoglobin concentration) while maintaining acceptable specificity and avoiding alteration of the screening programme in terms of quality of life and economic outputs."	Narrow
Tappenden et al, 2007	Option appraisal of population-based colorectal cancer screening programmes in England	"The aim of this study was to estimate the likely effectiveness, cost-effectiveness and resource impact resulting from the implementation of alternative CRC screening programmes using FOBT, FSIG or a combination of both tests."	Broad
Thomas et al, 2021	Should colorectal cancer screening start at different agesfor males and females? Cost-effectiveness analysis for aresource-constrained service	"This analysis investigates whether, in a resource-constrained setting, it would be more effective and cost-effective for males and females to start screening for CRC at different ages."	Broad
Van der Meulen et al, 2017	Do Males and Females Need to Be Screened Differently with Fecal Immunochemical Testing? A Cost-Effectiveness Analysis	"We used the microsimulation model MISCAN-Colon model to evaluate whether screening stratified by sex is cost-effective."	Broad
Van Rossum et al, 2011	Colorectal cancer screening comparing no screening, immunochemical and guaiac fecal occult blood tests: a cost-effectiveness analysis	"We analyzed prospective empirical data from a randomized-controlled trial to compare cost-effectiveness of screening with either one round of immunochemical fecal occult blood testing (I-FOBT; OC-SensorVR), one round of guaiac FOBT (G-FOBT; Hemoccult-IIVR) or no screening in Dutch aged 50 to 75 years, completed with cancer registry and literature data, from a third-party payer perspective in a Markov model with first- and second-order Monte Carlo simulation."	Narrow

Whyte et al, 2012	Reappraisal of the options for colorectal cancer screening in England	"The aim was to use newly available data to estimate the cost-effectiveness and endoscopy requirements of screening options for colorectal cancer (CRC) to inform screening policy in England."	Broad
Whyte et al, 2021	Optimizing the Design of a Repeated Fecal Immunochemical Test Bowel Cancer Screening Programme With a Limited Endoscopy Capacity From a Health Economic Perspective	"The aim was to determine the optimal strategy in terms of screening age range, screening frequency, and FIT threshold to inform policy making."	Broad
Wilschut et al, 2011a	Cost-effectiveness Analysis of a Quantitative Immunochemical Test for Colorectal Cancer Screening	"We assessed which are the most clinically effective and cost-effective FOBT screening alternatives under different colonoscopy capacity levels with the validated MISCAN-Colon microsimulation model, using attendance rates, costs, positivity, and detection rates of FOBT and FIT at varying hemoglobin cutoff levels from two implementation trials in the Netherlands."	Broad
Wilschut et al, 2011b	Fecal Occult Blood Testing When Colonoscopy Capacity is Limited	"We aimed to identify the most cost-effective FIT cut off level for referral to colonoscopy based on data from these trials and allowing for differences in screening ages."	Narrow

Appendix 8 The detailed results of quality appraisal of studies.

Authors, year of publication	Question 1	Question 2	Question 3	Question 4	Question 5	Question 6	Question 7	Question 8	Question 9	Question 10	TOTAL SCORE
Aeria et al, 2019	1.0	0.5	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0	9.5
Aronsson et al, 2017	1.0	0.5	1.0	1.0	1.0	1.0	1.0	0.5	1.0	1.0	9.0
Arrospide et al, 2018	1.0	0.5	1.0	1.0	1.0	1.0	0.5	1.0	1.0	0.5	8.5
Babela et al, 2021	1.0	1.0	1.0	1.0	1.0	1.0	0.5	1.0	1.0	0.5	9.0
Barre et al, 2020	1.0	1.0	1.0	1.0	0.0	1.0	1.0	1.0	1.0	0.5	8.5
Berchi et al, 2004	0.5	1.0	1.0	1.0	1.0	1.0	0.5	1.0	1.0	0.5	8.5
Chauvin et al, 2012	1.0	0.5	1.0	0.5	0.5	1.0	0.5	1.0	1.0	0.5	7.5
Coretti et al, 2020	0.5	1.0	1.0	0.0	1.0	1.0	0.5	1.0	1.0	0.5	7.5
Currais et al,2021	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0	10.0
Goede et al, 2013	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0	0.5	9.5
Greuter et al, 2016	1.0	0.5	1.0	1.0	1.0	1.0	1.0	1.0	0.5	0.5	8.5
Gyrd Hansen et al, 1998a	1.0	1.0	1.0	0.5	1.0	1.0	0.5	1.0	0.0	0.5	7.5
Gyrd Hansen et al, 1998b	1.0	1.0	1.0	1.0	1.0	1.0	0.5	1.0	1.0	0.5	9.0
Hassan et al, 2011	1.0	0.5	1.0	1.0	1.0	1.0	0.5	1.0	1.0	0.5	8.5
Heinävaara et al, 2022	1.0	1.0	1.0	1.0	1.0	1.0	0.5	1.0	1.0	0.5	9.0
Heresbach et al, 2010	1.0	1.0	1.0	1.0	1.0	1.0	0.5	1.0	0.5	0.5	8.5
Jahn et al, 2019	1.0	0.5	1.0	1.0	1.0	1.0	0.5	1.0	1.0	0.5	8.5
Ladabum et al, 2014	1.0	0.5	1.0	1.0	1.0	1.0	1.0	1.0	1.0	0.5	9.0
Lansdorp-Vogelaar et al, 2018	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0	0.5	9.5
Lee et al, 2010	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0	10.0
Leujene et al, 2004	1.0	0.5	1.0	1.0	1.0	0.5	0.5	0.5	1.0	0.5	7.5
Lejeune et al, 2010	1.0	1.0	1.0	0.5	1.0	1.0	1.0	1.0	0.5	0.5	8.5
Lejeune et al, 2014	1.0	1.0	1.0	0.5	1.0	1.0	0.5	1.0	1.0	0.5	8.5
Macafee et al, 2008	1.0	0.5	1.0	1.0	1.0	1.0	1.0	0.0	0.5	0.5	7.5
McFerran et al, 2022	0.5	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0	0.5	9.0
Murphy et al, 2017	1.0	0.5	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0	9.5
Pil et al, 2016	0.5	0.5	1.0	1.0	1.0	1.0	1.0	0.0	1.0	1.0	8.0
Senore et al, 2019	1.0	0.5	0.5	0.5	1.0	1.0	0.5	1.0	1.0	0.5	7.5
Sharp et al, 2012	1.0	1.0	0.5	1.0	1.0	1.0	1.0	1.0	1.0	0.5	9.0
Sobhani et al, 2011	1.0	0.5	1.0	0.5	1.0	1.0	1.0	1.0	0.5	0.5	8.0
Tappenden et al, 2007	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0	0.5	0.5	9.0
Thomas 2021	1.0	0.5	1.0	1.0	1.0	1.0	0.5	1.0	1.0	0.5	8.5
Van der Meulen, 2017	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0	0.5	1.0	9.5
Van Rosum et al, 2011	0.5	1.0	1.0	1.0	1.0	0.5	1.0	1.0	1.0	0.5	8.5
Whyte et al, 2012	1.0	1.0	0.0	1.0	1.0	1.0	1.0	1.0	0.5	0.5	8.0
Whyte et al, 2021	1.0	1.0	1.0	0.5	1.0	1.0	1.0	1.0	1.0	1.0	9.5
Wilschut et al, 2011a	1.0	1.0	1.0	1.0	1.0	1.0	0.5	1.0	1.0	0.5	9.0
Wilschut 2011b	1.0	1.0	1.0	1.0	1.0	1.0	0.5	1.0	1.0	0.5	9.0

Appendix 9 The detailed results of alternative scenarios

Scenario 2: Biennial, 55- 74 years, FIT cut-off 225 ng Hb/mL

Year	Eligible Population	Primary Screens	Clinical	Surveillance	Triage False Positives	Triage True Positives	Total
2013	223570	77650	1380	0	770	1500	3650
2014	227060	79230	1560	300	460	1160	3480
2015	268750	80450	1670	520	420	2200	4810
2016	271810	80950	1770	480	380	2160	4790
2017	311900	81600	1640	770	530	2580	5520
2018	316220	82190	2160	1060	470	2790	6480
2019	355650	84150	2340	860	460	2860	6520
2020	359530	83790	2230	1040	410	3110	6790
2021	367230	86480	2250	1200	550	3020	7020
2022	369530	85940	2980	1210	420	3640	8250
2023	378040	89230	2900	1740	590	3060	8290
2024	379600	109930	3280	1720	650	3850	9500
2025	448100	220400	3100	1550	1390	7600	13640
2026	390350	156860	3410	1820	1010	7580	13820
2027	458490	225460	3470	2430	1180	9320	16400
2028	401750	163070	3830	2360	960	8330	15480
2029	470950	230720	3900	2430	1290	10220	17840
2030	418970	170680	3890	2620	950	8620	16080
2031	485070	235600	4120	2580	1400	11230	19330
2032	435510	176970	4080	2680	910	8880	16550
2033	499400	240870	4060	2610	1350	12380	20400
2034	450940	184730	4130	2880	1020	9380	17410

Scenario 3 Annual, 59-59 years, FIT cut-off 225 ng Hb/mL

Year	Eligible Population	Primary Screens	Clinical	Surveillance	Triage False Positives	Triage True Positives	Total
2013	223570	77650	1400	0	760	1700	3860
2014	227060	79230	1540	310	500	1130	3480
2015	231880	80520	1670	480	390	2300	4840
2016	232340	81000	1770	520	530	1980	4800
2017	236400	81570	1660	860	430	2560	5510
2018	237260	82300	2170	910	430	2870	6380
2019	243190	84100	2280	850	410	2920	6460
2020	243300	83770	2190	1030	350	3270	6840
2021	250740	86430	2340	1170	360	3070	6940
2022	250210	85940	2930	1530	520	3350	8330
2023	257800	89230	2880	1610	410	2940	7840
2024	258700	110100	3280	1340	680	3380	8680
2025	580570	199990	3220	1530	1060	7760	13570
2026	587990	201840	3500	1950	1030	8510	14990
2027	596100	204860	3580	1600	1160	9680	16020
2028	603940	207330	3890	2120	1160	10300	17470
2029	613800	210960	4040	2050	1320	11200	18610
2030	626250	215170	4020	2130	1080	11830	19060
2031	636590	218490	4250	2150	1210	12470	20080
2032	649370	222460	4050	2850	1240	13250	21390
2033	659570	226390	4150	2500	1370	13750	21770
2034	669810	229950	4080	2420	1260	14310	22070

Scenario 4: Annual, 55-74 years, FIT cut-off 100ng Hb/mL

Year	Eligible Population	Primary Screens	Clinical	Surveillance	Triage False Positives	Triage True Positives	Total
2013	223570	77650	1380	0	930	1350	3660
2014	227060	79230	1580	260	590	1290	3720
2015	231880	80540	1660	510	410	2160	4740
2016	232340	81050	1730	600	440	2210	4980
2017	236400	81480	1680	880	370	2680	5610
2018	237260	82320	2110	770	340	2850	6070
2019	243190	84070	2370	880	530	3040	6820
2020	243300	83770	2170	1060	610	3390	7230
2021	250740	86390	2330	1440	410	3170	7350
2022	250210	85780	2880	1150	540	3650	8220
2023	257800	89170	2820	1210	530	3160	7720
2024	258700	110010	3270	1710	620	3810	9410
2025	1033770	355950	3070	1390	3210	16340	24010
2026	1051800	360920	3240	2520	3200	20510	29470
2027	1068590	365000	3380	3170	3760	23380	33690
2028	1085570	369750	3630	3400	3600	26020	36650
2029	1103330	375960	3810	3470	3460	28260	39000
2030	1120010	380730	3720	3910	3970	30400	42000
2031	1138260	386190	3970	4080	3890	32050	43990
2032	1154570	391210	3790	4370	3590	34000	45750
2033	1172290	397270	3860	4090	4260	35410	47620
2034	1192260	403770	3900	4840	4020	37100	49860

Scenario 5: Annual, 45-80 years, FIT cut-off 50 ng Hb/mL

Year	Eligible Population	Primary Screens	Clinical	Surveillance	Triage False Positives	Triage True Positives	Total
2013	223570	77650	1400	0	660	1510	3570
2014	227060	79230	1550	240	420	1160	3370
2015	231880	80540	1640	570	530	2210	4950
2016	232340	80990	1790	590	430	1980	4790
2017	236400	81620	1670	930	470	2620	5690
2018	237260	82340	2190	930	510	2510	6140
2019	243190	84070	2340	850	430	2940	6560
2020	243300	83860	2160	930	620	2900	6610
2021	250740	86450	2360	1240	380	3310	7290
2022	250210	86050	2900	1070	500	2950	7420
2023	257800	89190	2890	1440	530	3250	8110
2024	258700	110280	3310	1490	580	3180	8560
2025	1957260	679900	2820	1540	12440	29030	45830
2026	1991280	688360	2870	3900	12280	40860	59910
2027	2020150	692660	2940	5280	13070	51150	72440
2028	2046500	698510	3240	5690	12900	58800	80630
2029	2068600	704200	3260	6250	12740	65620	87870
2030	2086930	709540	3310	6450	13220	71500	94480
2031	2104630	713370	3460	6950	13200	76410	100020
2032	2117860	716710	3320	6900	14020	81450	105690
2033	2126010	717960	3290	6720	13540	85160	108710
2034	2137060	721210	3600	7340	13420	88690	113050

Scenario 6: Annual, 55-74 years, FIT cut-off 50 ng Hb/mL

Year	Eligible Population	Primary Screens	Clinical	Surveillance	Triage False Positives	Triage True Positives	Total
2013	223570	77650	1390	0	800	1620	3810
2014	227060	79230	1550	360	400	1050	3360
2015	231880	80470	1660	360	420	2300	4740
2016	232340	81020	1790	580	410	2050	4830
2017	236400	81570	1630	770	460	2760	5620
2018	237260	82440	2200	790	460	2720	6170
2019	243190	84010	2330	1150	390	2990	6860
2020	243300	83880	2190	1270	420	3200	7080
2021	250740	86390	2310	1040	530	3130	7010
2022	250210	85960	2970	1310	450	3670	8400
2023	257800	89230	2840	1350	570	3210	7970
2024	258700	109900	3270	1590	530	3570	8960
2025	1033770	355790	2970	1720	6460	19650	30800
2026	1051800	360380	3220	2700	6730	25920	38570
2027	1068590	363750	3180	3380	6590	30520	43670
2028	1085570	367940	3550	3990	6780	34060	48380
2029	1103330	374090	3660	4420	7150	37230	52460
2030	1120010	378860	3660	4870	6840	40390	55760
2031	1138260	384020	3860	4380	7400	42910	58550
2032	1154570	388980	3700	4940	6560	45330	60530
2033	1172290	395000	3690	5550	7390	47510	64140
2034	1192260	400890	3840	5270	6830	49300	65240

Scenario 7: Biennial, 59-69 years, FIT cut-off 50 ng Hb/mL

Year	Eligible Population	Primary Screens	Clinical	Surveillance	Triage False Positives	Triage True Positives	Total
2013	223570	77650	1380	0	760	1500	3640
2014	227060	79230	1520	260	470	1210	3460
2015	231880	80600	1710	440	380	2130	4660
2016	232340	80960	1800	480	540	1980	4800
2017	236400	81570	1690	790	480	2820	5780
2018	237260	82410	2190	890	460	2650	6190
2019	243190	83960	2320	930	500	3160	6910
2020	243300	83890	2220	1070	530	3130	6950
2021	250740	86400	2350	1340	380	3200	7270
2022	250210	85870	2930	1160	450	3260	7800
2023	257800	89210	2790	1290	520	3190	7790
2024	258700	110030	3280	1430	620	3600	8930
2025	325010	91720	3270	1420	1780	4270	10740
2026	267090	111940	3520	1440	1900	5190	12050
2027	332220	94260	3550	2040	1740	5430	12760
2028	275610	114700	3930	1920	2230	6670	14750
2029	341560	98110	4020	1940	1760	6070	13790
2030	288830	118680	4080	2210	2190	7860	16340
2031	296140	101800	4280	2450	2010	6440	15180
2032	301860	122170	4120	2260	2420	9030	17830
2033	361290	106230	4210	2210	1970	6990	15380
2034	366510	125550	4110	2540	2340	9800	18790

Scenario 8: Annual, 55-74 years, FIT cut-off 225 ng Hb/mL

Year	Eligible Population	Primary Screens	Clinical	Surveillance	Triage False Positives	Triage True Positives	Total
2013	223570	77650	1380	0	700	1670	3750
2014	227060	79230	1580	250	440	1090	3360
2015	231880	80510	1650	510	570	2350	5080
2016	232340	80920	1800	530	390	1870	4590
2017	236400	81460	1680	740	570	2790	5780
2018	237260	82400	2130	930	380	2580	6020
2019	243190	83880	2340	930	460	2950	6680
2020	243300	84000	2130	840	390	3130	6490
2021	250740	86370	2360	1380	520	3260	7520
2022	250210	85930	2900	1390	410	3300	8000
2023	257800	89040	2870	1390	510	3210	7980
2024	258700	110110	3230	1770	590	3770	9360
2025	1033770	355850	3000	1590	2070	14880	21540
2026	1051800	361430	3250	2460	2040	17820	25570
2027	1068590	365710	3380	3040	1840	19640	27900
2028	1085570	370850	3610	2950	2190	21760	30510
2029	1103330	377170	3820	3400	1980	23380	32580
2030	1120010	382150	3750	3600	2200	24610	34160
2031	1138260	387590	4020	3460	2180	26140	35800
2032	1154570	392630	3750	3980	2520	27730	37980
2033	1172290	399130	3910	3880	2270	29260	39320
2034	1192260	405750	3950	3950	2640	30350	40890