Cost-Effectiveness Analysis of Colorectal Cancer screening :

Artificial Intelligence Assisted Colonoscopy and Standard Colonoscopy compared with No screening.

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Abstract

Introduction

Colorectal cancer is a significant public health concern. Implementation of screening can prevent future cancer incidences by early detection of the precancerous polyps. Artificial intelligence assisted colonoscopy offers promising improvement in adenoma detection. The aim of this study is to assess the cost-effectiveness of colorectal cancer screening including AI-assisted colonoscopy and standard colonoscopy compared with no screening strategy in improving health outcomes.

Methods

A Markov model simulation with one -year cycle length, and time horizon up to 100 years was performed on a hypothetical cohort consisting of 100,000 men and women with average risk of colorectal cancer, aged 50, 55 and 60 years at the first invitation. The primary health outcome was quality-adjusted life years (QALY) gained. The study included three main analyses, focusing on the implementation of screening at 50 years, 55 years, and 60 years. The examined strategies were no screening at age 50, 55 and 60 years, population-based standard colonoscopy and AI-assisted colonoscopy screening every 10 years starting at 55 years and 60 years and once in a lifetime screening at age 50 years and 60 years. In the scenario analysis, the study explored the impact of 70% participation rates to capture a more realistic effect of screening, as opposed to the assumption of 100% participation in main analyses. All the strategies were compared according to their implementation age, while optimal strategy was chosen based on highest health gain at lowest cost among all the strategies. Furthermore, sensitivity analysis was performed to assess the uncertainty around the result.

Results

Implementation of a 10-year interval population-based screening at age 50 years resulted in an ICER of € 2171 per QALY gained for AI-assisted colonoscopy and € 2050 per QALY gained for standard colonoscopy, compared with no screening. Once in a lifetime screening at

the same year resulted in ICER of € 886 for colonoscopy with AI and € 409 per QALY gained for standard colonoscopy. Implementation of every 10-year AI-assisted colonoscopy at age 55 years resulted in an ICER of € 2,507 per QALY gained, while for standard colonoscopy ICER was € 2,379 per QALY gained. Implementation of AI-assisted colonoscopy at age 60 years resulted in an ICER of € 3,732 per QALY gained for 10-year interval screening and € 2038 for single screening. While for standard colonoscopy, the respective ICERs were € 3,534 and € 2,578 per QALY gained. Scenario analysis considering 70% participation exhibited less favourable outcome, however AI-assisted colonoscopy remained the cost-effective strategy. Among all the strategies, implementation of AI-assisted colonoscopy at 50 years showed highest gain at lowest cost, indicating it as the optimal strategy.

Conclusion

AI-assisted colonoscopy is a cost-effective strategy, irrespective of the age of implementation, participation rate and frequency of screening. While all the screening strategies are cost-effective compared with no screening, early implementation of AI-assisted colonoscopy holds the potential for greater health gain.

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Abbreviations

ADR	**Adenoma detection rate**
AI	Artificial Intelligence
AJCC	American Joint Committee on Cancer
APR	Abdominoperineal resection
CADe	Computer aided diagnosis for detection
CADx	Computer aided diagnosis for classification
CBA	Cost benefit analysis
CEA	Cost-effectiveness analysis
CEAC	Cost-effectiveness acceptability curve
CRC	Colorectal cancer
CRN	Cancer Registry Norway
CUA	Cost-utility analysis
HRA	High risk adenoma
FIT	Faecal immunochemical test
FS	Flexible Sigmoidoscopy
gFOBT	guaiac based faecal occult blood test
ICD	International Classification of Disease
ICER	incremental cost-effectiveness ratio
ICD	International Classification of Disease
ICER	Incremental cost-effectiveness ratio
ICUR	Incremental cost-utility ratio
LAR	Low anterior resection
LRA	Low risk adenoma
LY	Life years
RCT	Randomized controlled trial

SC	Standard colonoscopy
TNM	Tumour-node-metastasis
UICC	International Union Against Cancer
TME	Total mesorectal excision
QALY	Quality-adjusted life year
WTP	Willingness to pay

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1. Introduction

Colorectal cancer is the third most prevalent cancer and the second leading cause of cancer-related death worldwide, contributing to around 1 million deaths yearly (Morgan et al., 2022). Among all the countries, Norway has one of the highest incidences of colorectal cancer, with 4745 new cases (156 cases per 100000 individuals) in 2022, which contributes to a considerable financial and emotional burden on the patients, family members as well as society (Cancer Registry of Norway, 2023).

Most colorectal cancers begin as a growth on the rectum or colon's inner lining, named as polyp. Although most polyps are benign, certain types, such as some adenomas and traditional serrated adenomas can grow and develop to cancer over time, thus these adenomas are defined as precancerous lesions. Symptoms of colorectal cancer often start to manifest in the later stage of the disease when the prognosis of treatment is uncertain or poor. Therefore, early detection of adenomas will provide health gains by reducing future cancer incidences.

In order to mitigate the risk of colorectal cancer incidence and mortality, Norway started implementing population-based screening for colorectal cancer detection in 2022. There are several available screening procedures including guaiac faecal occult blood test (gFOBT), faecal immunochemical test (FIT), sigmoidoscopy, colonoscopy, CT colonography. Colonoscopy is a diagnostic tool used to examine the inner lining of the colon and rectum, in order to detect any abnormalities such as polyps, cancer or other signs of diseases. It is considered the gold standard of colorectal cancer screening due to higher sensitivity and accuracy than other screening options. In a screening setting, colonoscopy is used to remove polyps and adenomas in order to reduce the future risk of cancer. However, a limitation of conventional colonoscopy is the substantial but variable chance of miss rate in polyp and adenoma detection. This is primarily attributed to human errors arising from insufficient time spent for cleaning the mucosa during bowel preparation, limited optical diagnostic abilities in identifying small flat polyps, and potential impact of fatigue or distraction of the endoscopists (Ahmad et al., 2023).

Recently, artificial intelligence (AI) has been receiving a lot of interest as a solution to the problem of detecting adenomas. AI software tools have been developed to improve the visual abilities of endoscopists in detecting precancerous adenomas during colonoscopy procedure through real-time pattern recognition. Artificial intelligence (AI)-based systems employ algorithms to perform activities and these algorithms can be trained to carry out tasks by identifying patterns in data instead of following specific instructions (machine learning). Computer-aided polyp detection systems (CADe) have been created with the use of this technology to automatically detect polyps in real time during colonoscopy (Ahmad et al., 2023).

AI assisted colonoscopy has shown promising outcomes in detecting polyps and reducing human related errors in adenoma detection. Adenoma detection rate (ADR) is considered a quality indicator of colonoscopy screening which can be defined as the percentage of screening colonoscopies performed by an endoscopist that successfully identify at least one or more adenomas, (Corley et al., 2014). According to recent evidence, the implementation of AI-assisted colonoscopy remarkably improves the overall ADR compared to conventional colonoscopy (Xu et al.,2022). Sensitivity is another important diagnostic measure that can be referred to as the ability of a test to correctly detect individuals with a disease. AI assisted colonoscopy significantly enhances the sensitivity for detecting and classifying colorectal polyps, outperforming conventional colonoscopy for both early career and experienced endoscopists (Ainechi et al., 2022).
However, a limitation of AI assisted colonoscopy is lower specificity that refers to the ability of identifying individuals that do not have the disease. Lower specificity results in higher false positive results, which might lead to unnecessary biopsies of non-neoplastic polyps as well as may contribute to endoscopist fatigue, distraction and need for refocusing during the procedure (YH et al., 2021). Furthermore, AI-assisted colonoscopy may lead to additional costs of polypectomy and the requirement of post-polypectomy surveillance due to increased adenoma detection. To the best of our knowledge, AI-assisted colonoscopy is not reimbursed by public payers or health insurance systems yet, due to a lack of evidence regarding cost-effectiveness of this procedure, which is limiting its widespread usage.

The aim of this research is to assess the cost-effectiveness of AI-assisted colonoscopy and standard colonoscopy strategies for colorectal cancer screening compared to no screening in reducing CRC incidence and mortality.

The following chapter will elaborate on the background, treatment, and screening methods for colorectal cancer. The third chapter will provide the underlying theory and conceptual framework behind this analysis. The fourth chapter will discuss an overview of all the material and methods required for this analysis. The fifth chapter will present the results, while the last chapter will discuss the obtained results and compare them to other available studies. This research will end with suggestions for further research and conclusion.

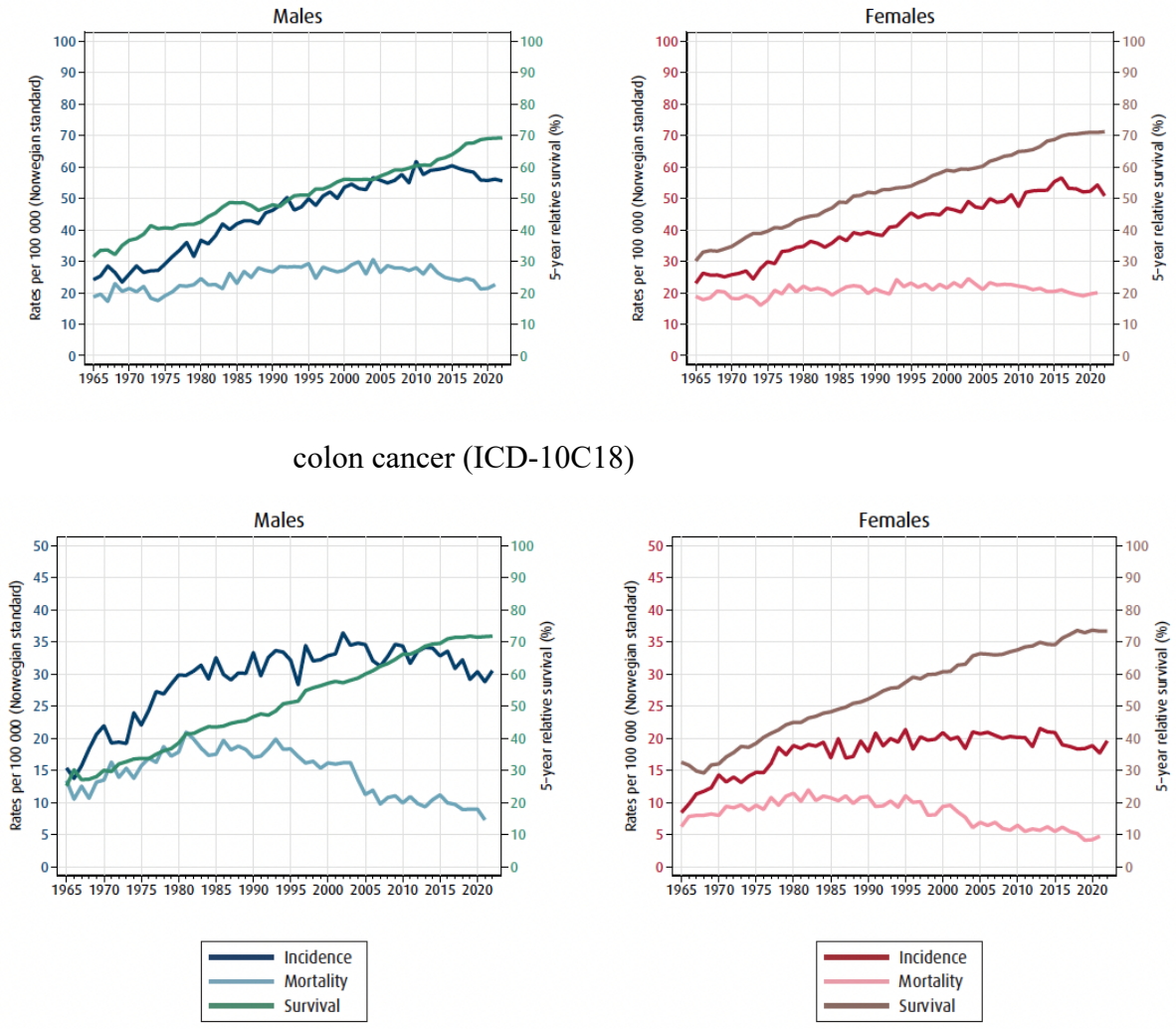
2 Background

2.1 Epidemiology of colorectal cancer

Colorectal cancer is the third most frequently diagnosed cancer worldwide. Among men it is the 3rd most common cancer and among women it is 2nd most prevalent cancer (World Cancer Research Fund, n.d.). It is also the second most common cause of cancer related deaths in the world, despite the advancement in the screening and treatment facilities (World Health Organization, n.d.).[3]

Colorectal cancer (CRC), classified by ICD-10 codes as C18 for colon cancer and as CD 19-20 for rectal cancer, shows substantial variability in both incidence and mortality rates worldwide. Although nearly 55% of CRC incidences occur in the developed and industrialised countries, the highest CRC-related mortality rates are observed in the less developed countries (Navarro et al., 2017). However, developing countries undergoing economic transitions are also witnessing a steady rise in CRC incidence due to the adoption of western lifestyle, increasing life-expectancy and dietary habits.
The risk of developing CRC increases markedly after the age of 50, and males are more likely to have lesions at an early age with 1.5-fold greater risk of having CRC than females across all age groups and countries (Grahn et al., 2008).

Norway has one of the highest incidence rates for CRC among all the countries. In the last 35 years, Norway has experienced a 3.5-fold increase in the annual number of new CRC cases, which is much higher than the neighbouring Nordic countries and limited knowledge is available about the reasons behind this trend (Malila et al., 2003) (Svensson et al.,2002). Figure 1 represents the trends in age and sex-adjusted incidence rates, mortality, and survival for the last 5 decades.



colon cancer (ICD-10C18)

Rectal cancer (ICD-10 C 19–20)

Figure 1 Trends in age- and sex-adjusted incidence rates, mortality, and survival in Norway from 1965 to 2020 for colon and rectum cancer. *Source: Cancer in Norway 2022*

2.2 Colorectal Cancer pathogenesis

Colorectal cancer is a malignancy that derives from the colon or rectum. Although the cancer can be referred to as colon cancer or rectal cancer depending on the site of arising, usually both cancers are grouped together due to their many common characteristics.

While normal cells typically undergo orderly growth and development, genetic mutations of somatic cells can lead to the formation of visible protrusions known as polyps (Ewing et al, 2014). Polyps can develop anywhere in the GI tract but are most frequently found in the colorectal region. Although polyps are mostly benign, they can slowly progress to malignant ones over time and the probability of polyps turning into malignant ones depends on the types of the polyps. Polyps can be classified into two classes depending on their likelihood of turning into cancerous lesions: non-neoplastic and neoplastic. While non-neoplastic polyps never turn into cancer, neoplastic polyps have the potential to develop into cancer over time. Neoplastic polyps can be subcategorized into adenomatous and serrated polyps, with adenomatous polyps being the most frequent subtype, constituting about 70% of all adenomas (UMHS, n.d.). The chance of developing cancer from adenomas increases as the adenomas grow larger and invasive cancer that arises from this type of adenomas is named adenocarcinoma, while the pathway of development of cancer from adenoma is known as adenoma-carcinoma sequence. Although most of the cancer arises following adenoma-carcinoma sequence, very rarely cancer can directly develop from normal colonic mucosa without any adenoma component, which is known as “de novo pathway” (Castleman et al., 1962).

Colorectal cancer typically originates in the innermost lining of the colon and progresses upwards as it develops. As the tumour cells multiply, they can infiltrate the blood vessels and lymphatic vessels, spreading to nearby lymph nodes or distant areas of the body through the bloodstream or lymphatic system. The degree of spread, known as metastasis, determines the stage of the cancer. This information is crucial in determining treatment approaches and estimating the patient's chances of survival. Stages of colorectal cancers are described in table 1.

Table 1: Stages of colorectal cancer.

Stage 0	The cancer is in its earliest stage, still in the innermost layer.
Stage 1	The cancer has invaded the innermost layer and moved into the outermost layer, but has not spread through the wall of the colon.
Stage 2	The cancer has invaded the wall of the colon but has not spread to the nearby lymph nodes.
Stage 3	The cancer has spread to nearby lymph nodes but has not spread to the distant organs.
Stage 4	The cancer has spread to distant organs.

TNM staging developed by American Joint Committee on Cancer (AJCC) and the International Union Against Cancer (UICC), is another frequently used method for staging of the cancer, where T describes the size and extent of the tumour, N describes spread of cancer to nearby lymph nodes and M describes metastasis to distant sites. The updated version of TNM staging is given in the following table:

Table 2: TNM staging of colorectal cancer. (*Source: Tong et al., 2018)*

T categories for colorectal cancer:	
Tx	Primary tumour cannot be assessed.
T0	No evidence of primary tumour.
Tis	Carcinoma *in situ*, limited to intraepithelial or invasive lamina propria.
T1	Tumour invading submucosa.
T2	Tumour invading the muscularis propria
T3	Tumour penetrates the muscularis propria and arrives at colorectal fat tissue.

T4	Tumour directly invades other organs or structures.
T4a:	Tumour penetrating visceral peritoneum.
T4b:	Tumour directly invades or is adherent to other organs or structures.
N categories for colorectal cancer:	
Nx	Regional lymph nodes cannot be assessed.
N0	No lymph node metastasis and no tumour deposits.
N1	Metastases in 1-3 lymph nodes.
N1c	Although there was no regional lymph node metastasis, tumours deposits were in submucosal, mesangial, or peritoneum-covered para-colorectal tissue.
N2	Metastasis in 4 or more regional lymph nodes.
N2a	Metastasis in 4–6 regional lymph nodes.
N2b	Metastasis to more than or equal to 7 lymph nodes.
M categories for colorectal cancer	
M0	No distant metastasis.
M1	There is distant lymph node metastasis.
M1a	Metastasis is confined to one organ or site .
M1b	Metastasis extend to more than one organ or site.

M1c	Metastasis to peritoneum with or without metastasis of other organs.

However, Cancer Registry Norway uses the terms Local, Regional, Distant and Unknown in its main database to describe the extent of the cancer. (Table 3)

Table 3: Cancer staging followed by Cancer Registry Norway. ***Source: Cancer Registry Norway (2022)*** **.**

Stages	Description
Local	Tumour confined to the primary organ.
Regional	Tumour invaded neighbouring tissues outside of the primary site or metastasized to nearby lymph nodes.
Distant	Tumour has metastasized to other organs or distant lymph nodes.
Unknown	Primary origin of tumour is unknown and sufficient information is unavailable to define the stage.

2.3. Treatment

The treatment of colorectal cancer usually involves a combination of surgery, chemotherapy, and radiation therapy. The specific treatment plan for an individual patient depends on several factors including the size, location, extent of the cancer, patient's overall health and preferences, and other individualised factors.

In Norway, treatment protocol of colorectal cancer is closely followed by guidelines written and revised by the Norwegian Health Directorate. According to the Norwegian guideline, treatment of colorectal cancer can be divided by the following type and extent of the cancer (Norwegian Health Directorate, n.d.):

Colon cancer

The primary treatment of colon cancer in the absence of any metastasis involves the surgical resection of the affected segments of the colon or colectomy, ensuring a 5-10 cm free margin. However, in case of adenocarcinoma, right sided hemicolectomy is the preferred treatment. When the cancer is metastasized to nearby lymph nodes in a later stage of cancer, removal of affected lymph nodes during surgery is recommended. In instances where there is distant metastasis to the liver, liver resection is suggested with the excision of the affected tumour and colon. However, for stage IV patients, palliative treatment is preferred instead of any surgical resection.

For treating advanced stages of colon cancer, postoperative or adjuvant chemotherapy is standard treatment to reduce the risk of recurrence or eradicate any remaining cancer cells. Initiating adjuvant chemotherapy within the recommended time frame of 4-6 weeks following surgery is advisable. Besides, chemotherapy is the preferred option for treating stage IV patients, however radiation therapy can also be employed to alleviate symptoms. In Table 4 the treatment alternatives for different stages of colon cancers are presented.

Table 4: Treatment of different stages of colorectal cancer. (*Source:* *Norwegian Health Directorate, n.d.)*

Stages of colon cancer	Surgical treatment	Post-operative treatment
0	Colectomy	-
I	Colectomy	-
II	Colectomy	Chemotherapy (in high-risk stage II)
III	Colectomy with removal of affected lymph nodes	Chemotherapy; Combination therapy
IV	Palliative therapy	Chemotherapy, Radiation therapy

Rectal Cancer

Primary treatment of rectal cancer includes total meso-rectal excision that involves the entire removal of intestine containing tumour along with the surrounding lymphatic tissues.

However, T1 tumours that don't have any pathological features can be treated with endoscopic submucosal resection (TEM). Low anterior reaction (LAR), abdominoperineal resection (APR) or rectal amputation are other available surgical methods for treating later stage rectal cancer.

Preoperative radiotherapy is commonly recommended for patients with potential lymph node metastases on the pelvic wall or local recurrence of rectal cancer. This therapy is also considered for patients who are intolerant of combination therapy or are older than 75 years with significant comorbidities or reduced functional capacities. On the other hand, chemoradiotherapy is recommended for rectal cancer cases involving at least one adjacent organ where the prognosis of resection is uncertain. The stage-wise treatment alternatives for rectal cancer are represented in Table 5.

Table 5: Treatment of rectal cancer. (*Source:* *Norwegian Health Directorate)*

Stages of colon cancer	Pre-operative treatment	Surgical treatment	Post-operative treatment
0	-	TME	-
I	-	TME	-
II	Radiation therapy	TME,LAR, APR	Chemotherapy
III	Radiation therapy, Combination therapy	TME,LAR, APR	Chemotherapy; Combination therapy
IV	Combination therapy	TME,LAR, APR	Chemotherapy, Radiation therapy, immunotherapy

2.4 Screening

Cancer screening refers to the process of cancer detection that targets testing apparently healthy individuals who do not have any signs or symptoms of the disease**.** The objective of the cancer screening program is to reduce cancer incidence and mortality through early detection of precancerous lesions and cancers, prior to the onset of symptoms. In the context of colorectal cancer, which is highly preventable by detecting precancerous adenomas, screening plays a pivotal role in prevention of cancers.

Cancer screening is based on 2 different concepts: prevention screening and early detection screening. The main objective of preventive screening is reducing future cancer incidences by detecting benign cancer precursors (such as adenomas). Conversely, early detection screening is intended to identify invasive cancer at an early stage. Typically, cancer screening is a multi-step process including administering the initial test, giving additional tests or procedures for individuals who receive positive findings to confirm the probable diagnosis, and treating the detected disease or precursors. Besides, people with negative screening results frequently need to be rescreened at regular intervals to maintain the effects of screening.

Screening may show four different test outcomes, which are included in Table 6.

Table 6: Different outcomes of screening

True positive	Individual actually has the disease and is diagnosed as positive in the test.
False positive	Individual is diagnosed as positive in the test, but actually does not have the disease.
True Negative	Individual is diagnosed as negative, while the individual does not have the disease,
False Negative	Individual actually has the disease but is diagnosed as negative in the test.

The least desirable outcomes of screening are false positive and false negative tests, which can lead to overdiagnosis or undertreatment of the disease as well as economic impact and psychological distress.

The diagnostic performance of a screening test is evaluated by diagnostic accuracy measures which assess the ability of the screening test to properly detect the presence or absence of a certain illness or disease. These measures provide insights into the effectiveness of the screening tests in terms of sensitivity, specificity, PPV, NPV and accuracy.

Sensitivity

Sensitivity can be defined as the ability of a diagnostic test to correctly identify individuals who truly have the disease. It is determined by the following equation:

Sensitivity = True Positive/ (True Positives +False Negatives)

A high sensitivity suggests that the test detects the condition cancer and has a low rate of false negatives.

Specificity

Specificity is the ability of a diagnostic test to accurately identify individuals who do not have the disease. It is calculated as:

Specificity = True negatives/ (True Negatives + False positives)

A high specificity means that the test is more effective at excluding the disease in healthy persons and has a low risk of false positives.

Positive Predictive value (PPV)

PPV indicates the proportion of individuals with positive tests who truly have the disease. It is determined by dividing the number of true positives by the sum of true positives and false positives.

PPV= True Positives/ (True Positives + False Positives)

Negative Predictive value (PPV)

NPV refers to the proportion of individuals with negative tests who do not have the disease. It is calculated as the number of true negatives divided by the total number of true negatives and false negatives.

NPV = True Negatives/ (True Negative + False Negative)

Accuracy

Accuracy refers to the overall ability of a test to correctly identify individuals as positive or negative for a specific condition. It is calculated as the proportion of correct identifications relative to the total number of individuals tested.

2.4.1 Overdiagnosis

In a screening procedure, overdiagnosis occurs when a lesion such as polyp or cancer is detected in an individual that would not show symptoms or cause death in the remaining lifetime of that person. Overdiagnosis is a major concern because it will significantly increase the incidence of early-stage cancer or pre-cancer without affecting the incidence of late-stage cancer or cancer-related death (Carter et al., 2017). In cancer screening programmes, slow growing and nonfatal cancers are the main source of overdiagnosis, as there is no definite way to distinguish them from the aggressive and lethal ones. So, both types of cancers will go through the same treatment and surveillance, that will lead to unnecessary expense, as well as complications and emotional distress instead of bringing any positive outcome. Regarding colorectal cancer, overdiagnosis of colorectal cancer has more serious implications than overdiagnosis of polyps, because cancer therapy is more extensive and hazardous than polyp treatment.

2.5 Colorectal cancer screening

Many countries have already started implementing colorectal cancer screening to prevent CRC and reduce the CRC incidence and mortality. Although there are several screening methods available, such as colonoscopy, flexible sigmoidoscopy (FS), faecal occult blood test

(FOBT), faecal immunochemical test (FIT) and CT colonography, the best screening tests for use in public health is not decided yet. Currently most commonly applied screening methods are FIT and colonoscopy, while FIT is used for early detection, colonoscopy is recommended for early detection and preventing CRC incidences. Some acceptable and commonly used screening tests other than colonoscopy includes:

Faecal immunochemical test (FIT)

FIT is a stool-based test which detects hidden blood in the stool, considered as an early sign of colorectal cancer. It particularly uses antibodies to detect any presence of invisible haemoglobin protein found in the red blood cells within the stool samples. FIT is a non-invasive and user-friendly screening method that does not require any dietary restrictions, making it more readily accepted than invasive procedures like colonoscopy or sigmoidoscopy. However, it only detects blood from the lower intestine and has lower sensitivity than colonoscopy and sigmoidoscopy for precancerous conditions. A positive result in the test requires follow-up with a colonoscopy.

Guaiac faecal occult blood test (gFOBT)

The gFOBT is another stool-based test that uses a chemical to detect the presence of haem, a component of haemoglobin in the red blood cells. As haem protein is also present in some foods like poultry or red meats, dietary restriction is required before taking the test. Although this test is cheaper, it is associated with lower sensitivity for detecting high-risk adenomas and CRCs. If any abnormality is observed in the test, colonoscopy is recommended for further evaluation.

Flexible sigmoidoscopy (FS)

Flexible sigmoidoscopy is an invasive procedure that examines the lower part of the intestine (sigmoid) and rectum. A flexible sigmoidoscope is inserted through the rectum towards the sigmoid colon along with air pumped into the colon that allows for visualisation and detection of polyps and adenoma. It also allows removal of any abnormal growth from rectum and sigmoid for further analysis. It is less invasive compared to colonoscopy and

requires no sedation of the patients. However, as this test does not provide access to the entire colon, it is often regarded as less effective compared to colonoscopy (Ko et al., 2019). In case of a positive result, further evaluation by colonoscopy is necessary.

CT colonography

CT colonography or virtual colonoscopy uses computed tomography imaging to produce a series of detailed images of colon and rectum. CT colonography is non-invasive and does not require sedation, however thorough bowel preparation is necessary to employ this screening test. Moreover, removal of suspected polyps is not possible and in case of abnormality colonoscopy is needed for further evaluation.

The current recommendation regarding starting age for colorectal screening and preferred screening methods differ across the countries. While European Union Council and the United States task team advocate initiating population screening at the age of 50 (Bishehsari et al., 2014) , the American Cancer Society recommends it at the age of 45. Only two countries, Japan and Austria recommend initiating screening at age 40 for the persons with average risk (Ebell et al, 2018). Colonoscopy as a screening method is used in the USA, Switzerland, Austria, and Germany, while in Canada colonoscopy is not recommended (Ebell et al., 2018). Norway has recently introduced faecal immunochemical tests (FIT) with gradual enrolment of colonoscopy.

Recommendation of screening strategies in different countries are described in Table 7.

Table 7: Recommendation for screening in different countries (*Source: OECD,2022 and Ebell et al., 2018)*

Country	Screening method	Starting age	Stopping age	Frequency
USA	Colonoscopy or FS+FIT	50 years	74 years	Colonoscopy- every 10 years. FS or CT colonography- every 5 years, FS - every 10 years plus FIT every year;
UK	FIT	60 years	74 years	Bi-annual

Germany	FIT/gFOBT	55 years	75+ years	FOBT - once a year from 50-54 years, then FOBT biannual. Colonoscopy - between 55-65 and another after 10 years of first colonoscopy
Austria	gFOBT/ FIT Colonoscopy	40	75 years	FIT - biennial Colonoscopy-every 10 years
Norway	FIT	50 years	74 years	Bi-annual
Netherlands	FIT	55 years	75 years	Bi-annual
Switzerland	FIT/gFOBT	50 years	70 years	FOBT-biennial Colonoscopy-10 years
Canada	FIT/gFOBT or FS	60 years	74 years	FOBT/FIT every 2 years, FS - every 10 years
Denmark	FIT	50 years	74 years	FIT- every other year for people aged 50-74, followed by colonoscopy .
Japan	FIT	40 years	75+ years	Biennial

Colonoscopy

Colonoscopy is a diagnostic tool as well as screening procedure, in which a long, thin, and flexible tube with a small camera inside (colonoscope) is inserted through the rectum and advanced to the other end of the large intestine. The colonoscope incorporates a small camera that remains connected to a computer. This setup enables the real time transmissions of high-quality images taken from the lining of the colon, enabling the endoscopists to directly visualise the entire colon. Additionally, it permits the storage and printing of the selected coloured images if required during this procedure. Although the main objective of

colonoscopy is the detection of polyps and CRC, taking tissue samples or removal of polyps and precancerous lesions are often possible in the same procedure.

Colonoscopy is considered as the gold standard of colorectal cancer screening and associated with significant reduction of CRC incidence and mortality (Pan et al., 2015). However, Colonoscopy is an endoscopist-dependent invasive procedure, which requires bowel preparation, air sufflation, anaesthesia and pain medications (Kronborg et al., 2007). There are associated risks of bleeding, colon perforation and very rarely death. Moreover, the procedure may not be well accepted by many patients due to associated discomfort, cost of participating and inconvenience.

Adenoma detection rate (ADR) is considered a quality indicator for colonoscopy. ADR is inversely related to the risk of interval cancer and CRC related mortality, while every 1% increase in the ADR is associated with 3% decrease in the risk of developing CRC and 5% decrease in the risk of fatal CRC incidents (Corley et al., 2014). While a minimum acceptable overall ADR is considered as 25%, there is a significant variation in ADR among different endoscopists, ranging from 7.35% to 52.5% (Kaminski et al., 2017), and this significant variation in ADR creates a challenge to the efficacy of the colonoscopy screening in preventing interval CRC.

Another important concern regarding standard colonoscopy is its inability to detect smaller adenomas and a variable miss rate in adenoma detection among endoscopists. Even experienced endoscopists may experience a significant miss rate that can lead to 52% to 57% of the post-colonoscopy CRC cases or interval cancers (Robertson et al, 2014). Although the causes of missed adenomas are still unclear, earlier investigations suggested that polyps that are smaller in size, multiple in number, flat-appearing, or located in the left colon are more likely to be missed during colonoscopy (Leufkens et al., 2012).

The diagnostic accuracy of a screening is mostly determined by the sensitivity and specificity of the test. Although standard colonoscopy is widely accepted due to its high sensitivity and specificity, the sensitivity of colonoscopy is influenced by the expertise of the endoscopists, leading to a considerable heterogeneity in the sensitivity of colonoscopy in detecting adenomas (ranging from 73% to 93% for adenomas 6 mm or larger), across published studies

(Lin et al., 2016). Furthermore, the sensitivity for detecting smaller adenomas is notably lower than that for larger adenomas, which contribute to the development of interval cancer.

To address these challenges faced by colonoscopy, artificial intelligence has been introduced that is considered more promising in adenoma detection and reducing polyp miss rate.

Artificial Intelligence assisted colonoscopy

Artificial intelligence (AI) can be defined as a field within computer science dedicated to the development of intelligent machines that possess the ability to perform tasks that typically require human-level intelligence (Shalev-Shwartz & Ben-David, 2014). AI-assisted colonoscopy is a medical application of artificial intelligence that aims to enhance the accuracy and efficiency of colonoscopies. It uses machine learning that allows mathematical techniques to create an algorithm based on provided data (such as images or videos) to predict a similar pattern or a specific task in unknown data (van der Sommen et al., 2020). Machine learning helps to analyse the images or videos captured by the camera of the colonoscope and identify the areas of concern for the physicians to investigate further. In traditional machine learning, also known as hand-crafted machine learning, a researcher manually inputs clinically relevant polyp characteristics. However, deep learning, a subtype of machine learning, has been adopted recently in colonoscopy which utilises a convolutional neural network (CNN) that automatically extracts specific features from data without any human intervention following adequate training with a very high number of learning samples (Spadaccini et al, 2023). Deep learning has shown higher performance in diagnosing colon cancer than conventional colonoscopy and previous hand-crafted machine learning methods (Kavitha et al., 2022).
Two most common uses of AI in colonoscopy include Computer-aided detection (CADe) and computer-aided diagnosis or distinction (CADx) . While CADe identifies precancerous lesions during colonoscopy by using machine learning algorithms, CADx aims to detect lesions by performing optical biopsies, averting the need for any histopathological evaluation (Roshan et al., 2022).

AI assisted colonoscopy has shown impressive diagnostic accuracy in the detection and classification of polyps compared to conventional colonoscopy. Recent studies have reported

higher sensitivity and ADR of AI assisted colonoscopy in detecting polyps compared to the expert and non-expert endoscopists. However, there is a significant heterogeneity of sensitivity and specificity values of CADe and CADx technologies among the published studies (Wang et al., 2021). Additionally, earlier studies often reported lower specificity for AI assisted colonoscopy, potentially leading to increased costs associated with a higher number of false-positive cases

3. Theoretical Framework

3.1 Economic Evaluation

Economic evaluation is an analysis that involves the comparison of alternative options in terms of the costs and consequences (Drummond et al., 2005). The aim of economic evaluation is to assist decision makers in making decisions about resource allocation by providing the information about the value for money of healthcare interventions. There are several types of economic evaluation frameworks available, however most commonly used frameworks are cost-benefit analysis, cost-effectiveness analysis. and cost-utility analysis. The preferred approach is mostly determined by the available information and the way of measuring outcomes.

Cost-benefit analysis (CBA) measures costs and effects of alternative healthcare interventions in monetary terms, allowing for direct comparison of their relative costs and benefits. In CBA, both costs and effects are quantified in the same unit, which provides more explicit and transparent decisions. Theoretically, cost-benefit analysis is based on the welfarist approach, and an intervention is only considered worthwhile if the benefits exceed the costs, or the net monetary benefit is positive.

Cost-effectiveness analysis, on the other hand, measures the costs of a healthcare intervention in relation to its outcome, typically in terms of the natural units, such as life of years gained, or death prevented. Incremental cost-effectiveness ratio (ICER) is used to express the result of cost-effectiveness analysis, and it is calculated by following equation:

$$\text{ICER} = \frac{Cost\ (screening) - Cost\ (no\ screening)}{Effect\ (screening) - Effect\ (no\ screening)}$$

If a new intervention, such as screening, shows higher effectiveness and lower cost than standard of care (for instance no screening), it is considered a dominant strategy, while if the new intervention has higher costs and lower effectiveness, it is indicated as a dominated strategy. Cost-effectiveness analysis is mostly used in situations where a decision-maker,

operating with a given budget, is considering a limited range of options within a given field (Drummond et al., 2005). However, it is challenging to compare different programmes using CEA, as it does not utilise a general outcome measure. This problem can be addressed by comparing health programmes with similar outcomes.

Cost-utility analysis is a variant of cost-effectiveness analysis, measures the costs and benefits of an intervention in terms of utilities. The measure used for this type of analysis is quality-adjusted life years (QALYs) which reflects both quantity and quality of life. Cost-utility analysis thus helps to understand to what extent an intervention helps to extend life years or improve the quality of life. QALY is calculated by multiplying the years lived in a given health state with a value representing the health-related quality of life (HRQoL), that represents an individual's perceived physical and mental health.

AS QALY is applicable to all types of diseases and interventions, CUA enables the comparison across several diseases and interventions. A cost-utility ratio (ICUR) is calculated using following formula:

$$\text{ICUR} = \frac{Cost\ (screening) - Cost\ (no\ screening)}{Utility\ (screening) - Utility\ (no\ screening)}$$

However, CUA often is not considered as the most appropriate choice in economic evaluation, because it does not consider main health benefits and measuring QALYs is more difficult as it depends on individual’s perceptions,

In both CEA and CUA analysis , ICER or ICUR is compared to a cost-effectiveness threshold, often referred to as willingness-to-pay (WTP) threshold, which represents the maximum amount of money society wants to pay for gaining an additional unit of health outcome. If the ICER falls below the WTP threshold, the new intervention is considered as cost-effective. In Norway, the WTP threshold weighted with the severity of the disease.

ICER or ICUR can also be expressed in terms of net monetary benefit (NMB), where NMB can be defined as:

NMB = Cost-effectiveness threshold × Incremental effect- Incremental cost.

The ICER can be represented graphically within a cost-effectiveness plane, which contains four distinct quadrants. In the CE plane, vertical y axis signifies the incremental costs of the new alternative, while horizontal x axis represents the incremental effects of the new alternative. If the ICER is located in the north-west quadrant, it means the new intervention has higher costs and lower effects than the current intervention, thus the new intervention is less favourable and dominated by the existing intervention. On the other hand, if the ICER lands in the south-east quadrant, it indicates a new alternative is cheaper and more effective, dominating the current one.

The remaining two quadrants suggest a more complex judgement has to be made between the two alternatives, as the north-east quadrant indicates the new intervention is more effective and costlier, while the southwest quadrant signifies the new intervention is less effective and cheaper than the current one. Figure 2 represents the cost-effectiveness plane with different quadrants.

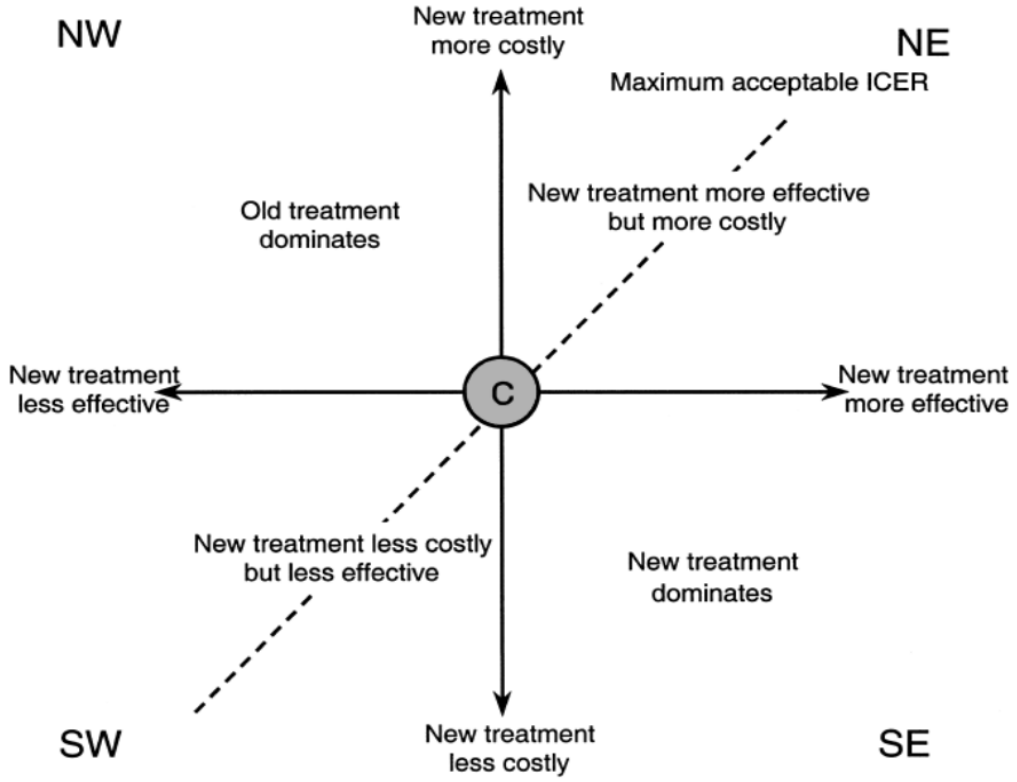


Figure 2: Cost-effectiveness plane showing different quadrants and interpretations. Source: Briggs et al(1998).

This study will measure and present health outcomes in terms of both the life year gained and QALYs gained, in accordance with the Norwegian recommendation (EuNetHTA, 2015).

In the presence of multiple strategies, the strategies can be presented in the efficiency frontier to find the optimal strategy. Efficiency frontier is a graphical representation where strategies are plotted according to their costs and strategies. After excluding extremely dominated and weakly dominated strategies, the remaining strategies represents cost-efficiency frontier. Each strategy on the frontier is considered cost-efficient, however, only one strategy can be identified as cost-effective (Aas et al, 2019).

3.2 Decision analytical modelling

Decision analytical modelling is a framework for economic evaluation that allows healthcare decision makers to compare the potential costs and effects of different available interventions. Economic evaluations should be conducted aligned with randomised controlled trials to allow the researchers using individual patient level data to measure cost-effectiveness, however a single randomised trial is often unable to provide enough evidence on all relevant outputs (Petrou et al., 2011). In the absence of such evidence, decision analytic modelling is the alternative framework. The main advantage of decision analytic modelling is its ability to incorporate data from multiple sources in a single model and predict the effects and costs of available alternative strategies based on the inputs that allows decision makers to make informed decisions. Moreover, it allows for the variability and uncertainty associated with each decision.

Screening is a complex system that includes several alternative strategies and requires evaluation of health outcomes and costs for a lifelong time horizon. Moreover, screening necessitates incorporation of relevant evidence from multiple literatures, clinical trials and register data, which make decision analytic modelling the preferred method for evaluating screening strategies.

There are several types of decision analytic models available, including state transition model or Markov model and decision tree model, and the choice of model depends on the research problem it is going to address.

Decision tree is the simplest form of decision analytical modelling, where alternative strategies are represented by a series of pathways (Petrou et al., 2011). A decision tree consists of nodes, branches, and outcomes. While starting with a single node a decision tree branches into different possibilities and each of those results leads to other nodes, which further branch off into other possibilities.

Contrarily, a Markov model includes several mutually exclusive and collectively exhaustive health states with transition probabilities from one state to another. Markov model simulates individuals or a cohort of individuals through these health states over a large number of cycles, and by attaching the estimates of costs and health outcomes to the states of the model,

the long-term costs and outcomes associated with an intervention can be measured. Although in reality transitions can occur at any time, in Markov model all state transitions occur simultaneously at the end of each cycle, which may result in over or underestimation of costs and effects. To deal with the inaccuracy of estimation, half-cycle correction can be applied, which assumes transitions occur, on average, halfway through each cycle.

In this thesis, a decision tree was used to allocate the cohort according to the screening results (true positive, false negative, false positive and true negative), which was followed by the Markov model that was used to represent all possible sequences of events over the lifetime and to simulate natural history.

The outcomes of a decision analytical model are influenced by uncertainties; hence it is necessary to address uncertainties in order to provide confidence in the decision maker´s decision about cost-effectiveness. Uncertainty can be mainly divided into two types: parameter uncertainty and structural uncertainty. Parameter uncertainty arises from the uncertainty related to the estimation of the parameters of interest and can be assessed by performing deterministic sensitivity analysis (DSA) and probabilistic analysis (PA). In a DSA, parameter values are manually varied to assess the model's sensitivity to individual parameters or groups of parameters, while in PA all the variables are varied simultaneously to investigate the effect of joint uncertainty in the variables. In PA, each of the variables in the analysis has a range and distribution associated with it, and a repeated Monte Carlo simulation is performed to choose the values from specified distribution and range. After performing repeatedly, simulations produce a distribution of the desired result, which can be used to calculate the probability of the strategy being cost-effective for a given WTP threshold and construct a cost-effectiveness acceptability curve (CEAC). Besides, a cost-effectiveness acceptability frontier (CEAF) can be drawn from the result, which represents the uncertainty surrounding the optimal strategy being cost-effective in different thresholds.

3.3 Survival analysis

Survival analysis is a statistical method that involves the estimation of survival time, which can be defined as the expected duration of time until an event of interest (e.g., death) occurs. While decision analytic modelling requires a long-time horizon, the studies usually cover a limited observation period. Not all the individuals experience the event of interest within this

limited time frame, resulting in an unknown survival time, known as right censoring. On the other hand, left censoring occurs when the event is observed, however the exact time of start (such as diagnosis) is unknown. Failing to account for both right and left censoring in the analysis can introduce bias in the results. Survival analysis is used in this context, which explicitly considers censoring, enabling the estimation of survival time beyond the study period in the presence of censoring.

Survival data are usually illustrated by survival and hazard functions.
Survival probability or survivor function S(t) can be defined as the probability that an individual would survive longer than a specific time t. For different values of t, survivor function changes, which provide important information about the survival status of the study population. The survival function can be presented as:

$$S(t) = Pr\,(T>t) = 1-F(t)$$

In this equation, F(t) represents the probability that the survival time is less than t.

Contrarily, the hazard probability h(t) shows the instantaneous rate of the event (e.g., death) for an individual who has already survived to time t (Clark et al, 2003). Hazard probability can be expressed as:

$$h(t) = lim_{\Delta t \to 0} \frac{P(T > t)}{\Delta t}$$

In other words, hazard probability represents the likelihood of an event taking place within a short time interval between t and t + Δt, given that the individual has survived until time 't'.

3.3.2 Time dependency

In some situations, hazard can change in value over the observation time or certain trends might affect the probability of the event of interest over time. This phenomenon is called time dependency.
Parametric survival functions are preferable in this context, and these functions assume that the baseline risk follows a given distribution in contrast to nonparametric and semiparametric functions. There are various parametric models available, including Exponential, Weibull, Gompertz, log-logistic, Generalised Gamma and log-normal models and each model has its individual characteristics that make the models more suitable for particular data sets. The

choice of the suitable model can be determined by using the framework proposed by Latimer (2011) that includes following methods:

Visual inspection

The assessment of parametric survival models in relation to the observed data often involves the visual inspection of how closely these models fit to the Kaplan-Meier curve. However, in presence of heavy censoring, a parametric model can closely match the curve in one segment, but not in the other, which may inappropriately indicate inadequacy of the model (Latimer, 2011). Furthermore, a well-fitting model can closely follow the K-M curve but still have an unrealistic tail. Hence, caution is required to use this method in order to assess the suitability of the parametric models.

Log-cumulative hazard plots

The shape of hazard function can also be used to assess the suitability of a distribution. Log-cumulative hazard plots can be constructed to assess the behaviour of hazard function over time in the observed data. By assessing whether the function is constant, monotonic, or non-monotonic, a suitable parametric model can be chosen. Different parametric models can capture different hazard patterns. While Weibull and Gompertz models are suitable for capturing monotonic hazards, exponential modes accommodate constant and non-zero hazards. Contrarily, log-normal, and log-logistic models allow for non-monotonic hazards with extended tails. Proportional hazard can also be assessed to choose the appropriate distribution.

Akaike information criterion (AIC) and the Bayesian information criterion (BIC) tests

AIC and BIC are statistical measures which are based on the principle of finding the trade-off between model complexity and goodness of fit. The AIC value for a model is calculated using the following formula:

AIC= -2*log-likelihood + 2*number of parameters

where log-likelihood measures how well the model fits the data, the number of parameters represent the complexity of the model.

On the other hand, BIC is based on the Bayesian principle which imposes stronger penalties for the number of parameters than AIC. BIC is calculated by following formula:

BIC= -2*log-likelihood + number of parameters *log (sample size)

However, in both cases, lower AIC or BIC number suggests the better fit of the model.

The parametric models considered by this study were exponential, Weibull, Gompertz, lognormal and log-logistic distributions. While all the parametric distributions were tested in this analysis, choice of the distribution was assessed by visual inspection method and the results of AIC and BIC tests.

4. Methods

4.1.1 Setting

The study was performed in Norwegian settings by using Norwegian costs, CRC related mortalities, in compliance with Norwegian guidelines.

4.1.2 Population

The population in this study included a hypothetical cohort of 100 000 men and women with average risk of colorectal cancer, aged 50, 55 and 60 at first invitation.

4.1.3 Interventions

The interventions of interest in this analysis were AI-assisted colonoscopy (CADe) and standard colonoscopy to diagnose polyps and CRCs in the population. AI assisted colonoscopy is still a new technology, compared to colonoscopy, while there is a lack of cost-effectiveness studies of AI assisted colonoscopy.

4.1.4 Comparator

The main comparator of this study was no screening strategy. The study measured and compared the health-related outcomes of AI assisted colonoscopy and standard colonoscopy strategies with no screening in terms of both the life year gained and QALY gained, in accordance with the Norwegian recommendation (EuNetHTA,2015).

4.1.5 Time horizon

In this thesis, the lifetime horizon (100 years or dead) was used to capture the life-time effect and downstream costs of colorectal cancer patients, however nearly 99% of individuals were dead by age 100.

4.1.6 Perspective

This study was conducted based on a societal perspective, which comprises all relevant societal costs and benefits, regardless of who bears the costs or receives the benefits. In Norway, the recommended perspective is an extended health care perspective. In extended

perspective, travel costs associated with travelling to health care interventions that are paid by the health care sector should be included. As screening implies inviting asymptomatic individuals to an examination, costs related to production loss is highly relevant even though not included in the recommended perspective.

4.1.7 Health outcomes

The main health outcome indicators considered in this study was quality-adjusted life years (QALYs). The other considered outcomes were life years gained (LYs), cancer and cancer-related death averted by the screening strategies.

4.1.8 Costs

The study included direct and indirect medical and non-medical costs. Direct medical costs consisted of lifelong cancer treatment costs, screening costs, while indirect medical costs included the end-of-life cost, which represented the costs of the last 6 months of the individuals before dying. Direct non-medical costs included cost of travel and cost of invitation, while indirect non-medical costs included productivity loss due to screening procedures. All the costs were adjusted for the annual price inflation using the consumer price index (2.60% per year).

4.1.9 Discounting

Following the Norwegian guidelines for economic evaluations, both costs and effects were discounted at 4% rate.

4.2 Model Structure

A Markov model was constructed to simulate the natural history of colorectal cancer and to estimate the incremental costs and effects of the strategies. The model contained following health states: No polyp, low risk adenoma (LRA), high risk adenoma (HRA), preclinical Local cancer (PC-LC), preclinical regional cancer (PC-RC), preclinical distant cancer (PC-DC), diagnosed local cancer (D-LC), diagnosed regional cancer (D-RC), diagnosed distant cancer (D-DC) and death (death due to cancer and other causes). The individuals can stay only in a single health state at once, so health states are mutually exclusive and collectively exhaustive.

The model considered 3 main analyses: screening starting at 50 years, screening starting at 55 years and screening starting at 60 years. The main analyses included the following strategies: no screening at age 50, 55 and 60 years, 10-year interval standard colonoscopy and AI assisted colonoscopy starting at 55 years and 60 years and single lifetime screening at age 50 years and 60 years. For comparing the outcomes of screening strategies, the simulation was performed separately, while the simulation of screening models was performed in the settings of sensitivity and specificity. Figure 3 below illustrates the possible health states and transitions among the health states.

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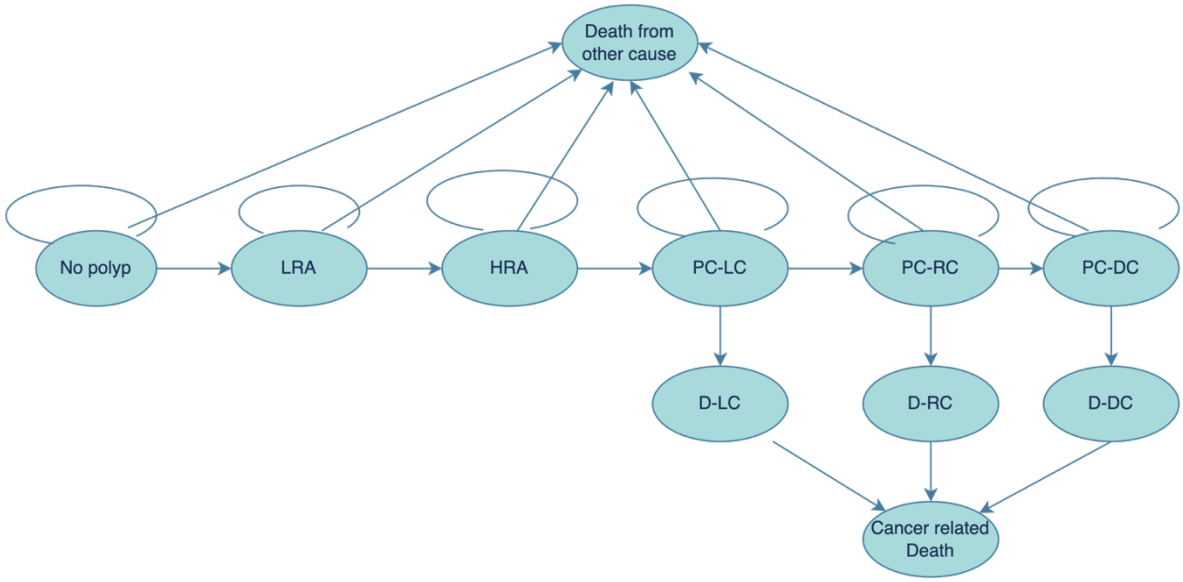

Figure 3: Markov model showing transition between health states, where D-LC, D-RC and D-DC are tunnel states

4.2.1 Natural History of CRC

At the beginning of the simulation a hypothetical cohort of 100 000 was distributed among the possible health states, according to the prevalence of no polyp, LRA, HRA and preclinical cancers at that age. The cycle length in the model was considered one year, and the model moved the cohort up to age 100 years or until death due to cancer or other causes.
In order to capture the effects of screening starting at age 50, 55 and 60 years, the natural history model started with 100,000 apparently healthy individuals of that age, and tried to compare outcomes with the screening arm of the relevant group.

Transitions between health states were determined by the transition probabilities. After one cycle individuals stayed in the same health state or progressed to another health state. As an example, individuals in *no polyp* state stayed in *no polyp* state or moved to the *low-risk adenoma (LRA)* state or die in the next cycle. In *LRA* state, an individual could either stay in *LRA,* progressed to *high-risk adenoma (HRA)* or died. In the following cycles individuals gradually moved to preclinical cancers (*PC-LC, PC-RC, and PC-DC*), and diagnosed CRC according to stage (local D-LC, regional D-RC, and distant D-DC), and death either all cause or cancer specific.

Death state (due to cancer and death due to other causes) was an absorbing state, which means after entering this state individuals never moved to another state. In the study, it was assumed that moving to death state was possible from each state. For capturing the probability of dying from precancerous states and preclinical states, the age-specific mortality probabilities for both genders were applied. A survival analysis was performed to obtain the time-dependent transition probabilities of dying from local, regional, and distant cancers.

4.2.2 Screening model

In the standard colonoscopy screening and AI assisted colonoscopy screening arms, 100 000 participants underwent the first screening either at age 50, age 55 or age 60 years and the cohort was distributed according to the prevalence and screening results. While individuals with negative results remained in "*No polyp"* state, those who were detected positive with low-risk or high-risk adenomas moved to "*LRA"* or "*HRA"* detected state and assumed to receive a polypectomy. Individuals detected as false positive and true negative were reassigned to the no polyp state at the following cycle.

Following the current recommendation (Winawer et al., 2006), individuals detected with low-risk adenoma were scheduled for surveillance screening every 5 years, continuing until the results were negative. On the other hand, those diagnosed with high-risk adenomas were recommended for screenings every 3 years until they received negative results. However, if they remained positive after the second surveillance screening, it was assumed they would return for a third surveillance in the 4^{th} year instead of 3^{rd} year, aligning with others due for their next population screening. If no polyp was detected at the surveillance colonoscopy, the

individual returned to the "*No polyp*" state, otherwise underwent the surveillance screening again following the recommendation. In the absence of any adenoma or cancer, the following screening was projected to be held 10 years after the last screening test, continuing until the age of 75, for the 10-year interval screening strategies. While for single screening strategies at 50 and 60 years, there were no available population-based screening, except surveillance screening for LRA and HRA detected individuals up to age of 75 years.

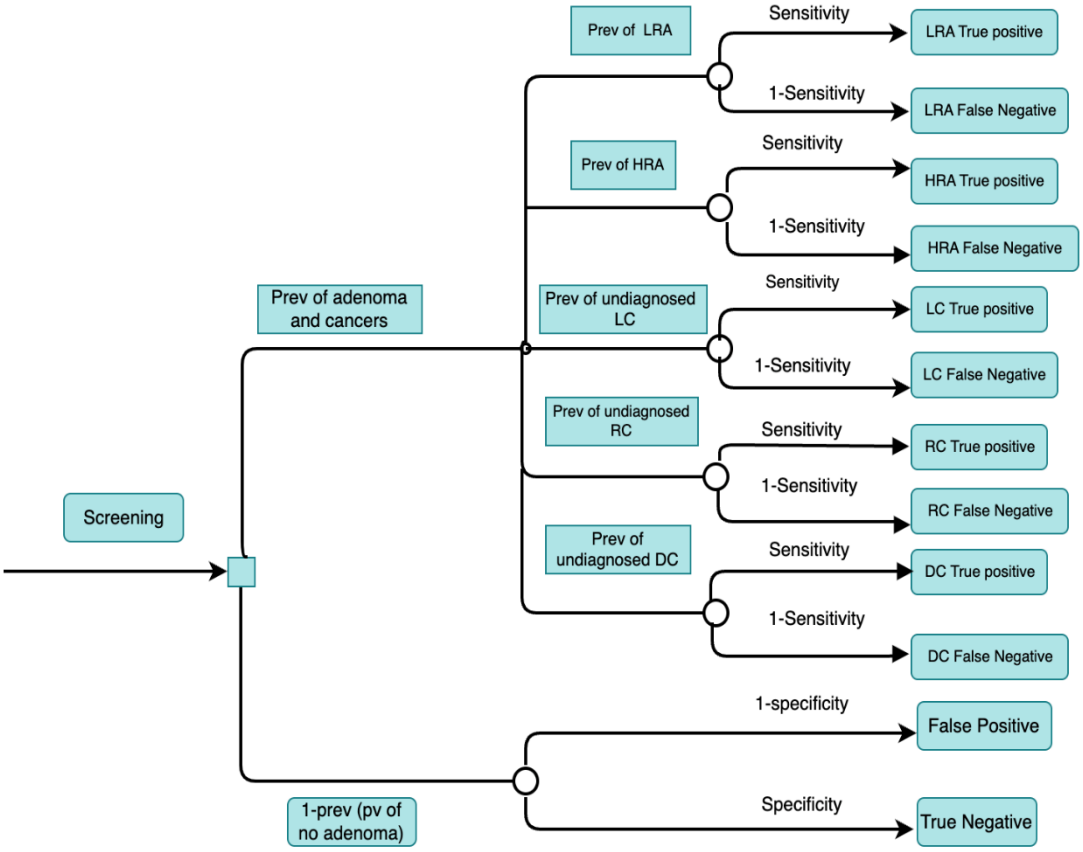

Figure 4: Decision tree showing the possible outcomes of screening.

In this study, it was assumed that all participants with preclinical cancers would be diagnosed in the screening, so they were transitioned to their corresponding diagnosed cancer states - local, regional, or distant. However, individuals with CRC who remained undetected due to the unavailability of scheduled screening tests in the interval between the onset of cancer and developing symptoms, were assumed to show symptoms at the simulated scheduled time.

In the model, it was presupposed that all individuals with a cancer diagnosis would undergo 100% cancer treatments. Individuals diagnosed with local, regional, or distant cancers were assumed to pass through the *'tunnel state'* of cancers starting from the year of diagnosis to the tenth year of diagnosis, during which time-dependent CRC-related mortality probabilities were applied to them. Nevertheless, for individuals who managed to survive beyond 10 years from the time of initial cancer diagnosis, age-dependent mortality probabilities were imposed.

4.3 Data Inputs

For obtaining values of the input parameters, a literature search was performed by using PubMed, Google scholar and Cochrane library. The inclusion criteria were as follows: studies reporting cost-effectiveness of AI-assisted colonoscopy and standard colonoscopy, studies containing diagnostic performances of colonoscopy with and without AI in detection and classification of polyps and CRCs, studies presenting prevalence of adenomas and cancers and transitional probabilities, studies showing post-polypectomy recurrence rate. Non-English publications, case reports and meeting abstracts were excluded from further considerations.
A CRC dataset obtained from Cancer Registry, Norway was used to obtain the CRC related mortalities up to 10 years of diagnosis for local, regional, and distant cancers.

4.3.1 Baseline probabilities

The age-dependent transition probabilities from "no polyp" to "LRA" state, were derived from Whyte et al. (2011), while other transitional probabilities among health states were derived from the cost-effectiveness analysis conducted by Frazier et al., (2000) and Areia et al. (2022). The prevalence of low-risk and high-risk polyps at age 50 years, were derived from Areia et al. (2022) and the aforementioned study used the available data on several endoscopic examinations from Vatn & Stalsberg (1982), Ladabaum & Song (2005). Prevalence of asymptomatic local, regional, and distant cancer in Norway were derived from Aas (2008). However, in the case of natural history of age 55 and 60 years, the prevalence of adenomas and cancers was obtained from the *natural history* model of 50 years. The recurrence rate of low-risk and high-risk polyps in post-polypectomy patients were derived from a meta-analysis conducted by Shi et al (2015).

Recurrence rate for low-risk adenomas was 60% at 5 years, and for high-risk adenomas recurrence rate were 12% at 3 years and 14% at 4 years respectively. Recurrence rates were converted into yearly probabilities to incorporate into the model by using following equation:

$$P = 1-\exp(-rt)$$

Where r is the recurrence rate, and t represents time period.

Following table represents the details of baseline probabilities used in this study.

Table 8: Baseline probabilities used in the study.

Description	Value	Distribution	Source
Prevalence of no polyps at 50 years	0.8485	Dirichlet	Calibrated and adjusted according to other prevalence
Prevalence of low-risk adenoma at 50 years	0.115	Dirichlet	Areia et al. (2022), Vatn & Stalsberg (1982), Ladabaum & Song (2005)
Prevalence of high-risk adenoma at 50 years	0.035	Dirichlet	Areia et al. (2022), Vatn & Stalsberg (1982), Ladabaum & Song (2005)
Prevalence of pre-clinical local cancer at 50 years	0.00080	Dirichlet	Aas (2008)
Prevalence of pre-clinical regional cancer at 50 years	0.00070	Dirichlet	Aas (2008)
Prevalence of pre-clinical distant cancer at 50 years	0.00004	Dirichlet	Aas (2008)
Prevalence of no polyps at 55 years	0.8310	Dirichlet	Obtained from natural history (50 years) model prevalence.
Prevalence of low-risk adenoma at 55 years	0.1255	Dirichlet	Obtained from natural history (50 years) model prevalence.

Description	Value	Distribution	Source
Prevalence of high-risk adenoma at 55 years	0.0380	Dirichlet	Obtained from natural history (50 years) model prevalence.
Prevalence of pre-clinical local cancer at 55 years	0.0036	Dirichlet	Obtained from natural history (50 years) model prevalence.
Prevalence of pre-clinical regional cancer at 55 years	0.0015	Dirichlet	Obtained from natural history (50 years) model prevalence.
Prevalence of pre-clinical distant cancer at 55 years	0.00040	Dirichlet	Obtained from natural history (50 years) model prevalence.
Prevalence of no polyps at 60 years	0.8131	Dirichlet	Obtained from natural history (50 years) model prevalence..
Prevalence of no polyps at 60 years	0.1395	Dirichlet	Obtained from natural history (50 years) model prevalence.
Prevalence of low-risk adenoma at 60 years	0.0412	Dirichlet	Obtained from natural history (50 years) model prevalence.
Prevalence of pre-clinical local cancer at 60 years	0.0040	Dirichlet	Obtained from natural history (50 years) model prevalence.
Prevalence of pre-clinical regional cancer at 60 years	0.0017	Dirichlet	Obtained from natural history (50 years) model prevalence.
Prevalence of pre-clinical distant cancer at 60 years	0.0005	Dirichlet	Obtained from natural history (50 years) model prevalence.
Transitional probabilities of no polyps to low-risk adenoma			
Age 50-59	0.0053	Beta	Whyte et al., (2011)
Age 60-69	0.011	Beta	Whyte et al., (2011)
Age 70-79	0.0156	Beta	Whyte et al., (2011)

Description	Value	Distribution	Source
Age 80-89	0.0019	Beta	Whyte et al., (2011)
Age 90 and above	0.0046	Beta	Whyte et al., (2011)
Transitional probability of low risk to high-risk adenoma	0.022	Dirichlet	Frazier et al., (2000), Coretti et al.,
Transitional probability of high-risk adenoma to local cancer	0.05	Dirichlet	Frazier et al., (2000)
Transitional probability of local cancer to regional cancer	0.310	Dirichlet	Areia et al (2022), Vatn & Stalsberg (1982), Ladabaum & Song (2005),Williams et al (1982), Rickert et al (1979), Hasan et al (2008)
Transitional probability of regional to distant cancer	0.280	Dirichlet	Areia et al (2022), Vatn & Stalsberg (1982), Ladabaum & Song (2005),Williams et al (1982), Rickert et al (1979), Hasan et al (2008)
Transitional probability of being diagnosed from local cancer	0.19	Dirichlet	Areia et al (2022), Vatn & Stalsberg (1982), Ladabaum & Song (2005),Williams et al (1982), Rickert et al (1979), Hasan et al (2008)
Transitional probability of being diagnosed from regional cancer	0.43	Dirichlet	Areia et al (2022), Vatn & Stalsberg (1982), Ladabaum & Song (2005),Williams et al (1982), Rickert et al (1979), Hasan et al (2008)

Description	Value	Distribution	Source
Transitional probability of being diagnosed from distant cancer	1	-	Assumption
Probability of post polypectomy relapse of low-risk adenoma at 5 years	0.45	Beta	Shi et al (2015)
Probability of post polypectomy relapse of high-risk adenoma at 3rd year	0.11	Beta	Shi et al (2015)
Probability of post polypectomy relapse of high-risk adenoma at 4th years	0.13	Beta	Shi et al (2015)
Probability of occurring major bleeding during colonoscopy	0.00008	Beta	Areia et al., (2022), Ko CW (2010), Committee & Fisher DA (2011), Reumkens et al., (2016) Lin et al., (2016)
Probability of occurring perforation during colonoscopy	0.00004	Beta	Areia et al., (2022), Reumkens et al, 2016, (49), Lin et al, 2016 Lin et al, 2016 (50), Lo et al, 2015 Korman et al, 2003

4.3.1.1 Data inputs on diagnostic performance

The inputs on diagnostic performance of screening (sensitivity, and specificity) were derived from Frazier et al. (2000), Areia et al (2022), Kudo et al (2020) and Yamada et al (2019). Variables related to diagnostic test performances are presented in Table 8.

Table 8: The inputs on diagnostic performance of screening strategies.

DESCRIPTION	VALUES	DISTRIBUTION	SOURCE
Sensitivity of the standard colonoscopy for detecting low-risk adenoma	0.85	Beta	Frazier et al., (2000)
Sensitivity of standard colonoscopy for detecting high-risk adenomas	0.95	Beta	Frazier et al.,(2000)
Specificity of the standard colonoscopy for detecting low-risk and high-risk adenoma	0.9	Beta	Areia et al., (2022), Repici et al.,(2020)
Sensitivity of the AI-assisted colonoscopy for detecting low-risk and high-risk adenoma	0.969	Beta	Kudo et al. (2020), Yamada et al., (2019)
Specificity of the AI-assisted colonoscopy for detecting low-risk and high-risk adenoma	0.85	Beta	Areia et al., (2022), Repici et al.,(2020)
Sensitivity of the standard colonoscopy for detecting cancer	1	Beta	Assumption
Sensitivity of AI assisted colonoscopy for detecting cancer	1	Beta	Assumption

4.3.1.2 Age-specific mortality probability:

Age-specific background mortality probability was derived from Statistics Norway (2022). The age-specific mortality probability is given in the Appendix: Table 2.

4.3.2 Cancer related all-cause mortality probabilities

For obtaining the annual mortality probabilities for cancer patients, a dataset derived from Norwegian Cancer Registry was used, which included a total of 66 074 patients diagnosed with CRC between 2000 and 2016 in Norway. A survival analysis was performed to obtain the time dependent cancer mortalities for local, regional, and distant cancers. The survival analysis was performed by using STATA 17/MP. The detailed characteristics of the patients by age, gender and stage is provided in Appendix Table 1.

4.3.2.1 Choice of distribution

Visual Inspection

In the analysis, visual fitness was checked for exponential, Weibull, log-normal, log-logistic and Gompertz distributions. Figure 3 shows the extrapolated survival function of colorectal cancer patients and comparison with different distributions regarding survival function.

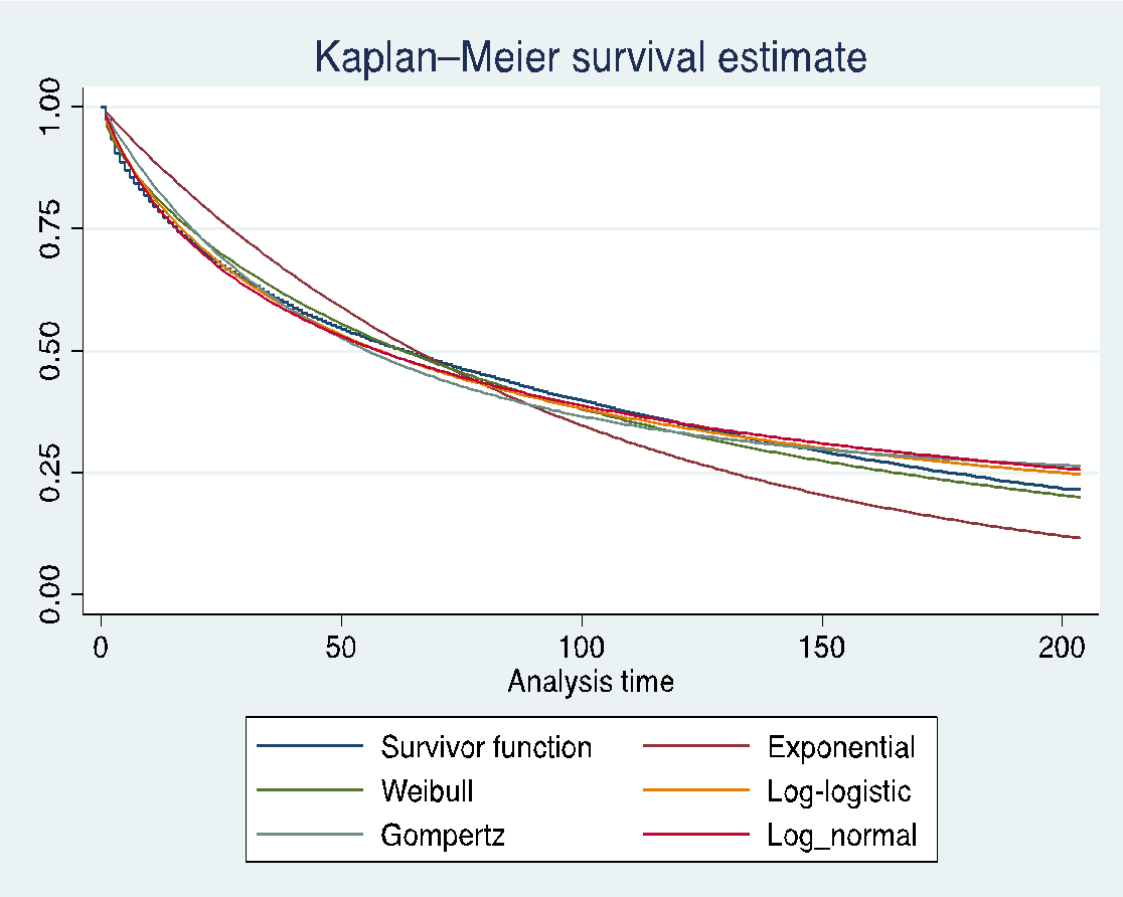

Figure 5: Comparison of KM survival curves and different distributions.

In general, log-normal, log-logistic and Gompertzian distribution showed heavier tails than Weibull and exponential ones, however the Weibull distribution appeared to fit the data well since the Weibull curve was very close to the survivor function curve.

AIC and BIC test

An assessment of the parametric distributions was performed by using AIC and BIC statistics. Table 9 represents the AIC and BIC values for different distributions.

Table 9: AIC and BIC values for considered distributions.

Distribution	AIC	BIC
Exponential	155174	155201
Weibull	153404	153440
Log-logistic	152177	152213
Log-normal	153010	153046
Gompertz	153559	153595

Although log-logistic and log-normal distributions achieved the lowest AIC and BIC values, those were excluded from further considerations, as these distributions are typically preferred when the hazard function exhibits a rising trend followed by a decline, which is not relevant to the current analysis. Hence, among the remaining distributions, Weibull showed the lowest AIC and BIC values, which indicated a better fit than others.

Standard survival analyses are based on hazard rates, while Markov models apply transition probabilities, so the stagewise mortality rates derived from parametric function were converted into probabilities before incorporating into the Markov model. The annual time dependent mortality transition probability was calculated by using the following equation:

$$\text{CRC related mortality probability} = 1 - \frac{survival\ function\ at\ the\ end\ of\ a\ Markov\ cycle}{survival\ function\ at\ the\ beginning\ of\ the\ cycle}$$

The obtained transition probabilities were then incorporated into the Markov model in order to derive the number of local, regional, and distant cancer related deaths in each cycle. Cancer related mortality probability for each stage of cancer is attached in the Appendix Table 3.1-3.3.

4.3.3 Utilities

In this study, utility values for different health states were derived from literature search. The utility of health states without diagnosed cancer was assumed 1, and utility of death was assumed as 0. Utility values for local, regional, and distant cancers were obtained from the cost-effectiveness study of Ladabaum et al., (2018), which used the QALY estimates for cancer survivors from Ramsey et al., (2000). In their study, Ramsey et al. (2000) included HUI (Health Utilities Index), SF-36 questionnaire and Center for Epidemiological Studies Depression Scale for measuring the QoL of long-term cancer patient survivors. The utilities of each health state were multiplied by the time an individual spent in each state and the results were summed over the individual's lifetime to obtain the Quality Adjusted Life Years (QALYs). The utility values used in the model are described in Table 10.

Table 10: Utility values for different health states.

DESCRIPTIONS	VALUE	DISTRIBUTION	SOURCE
QALY estimates for without cancer stage	1	Beta	Assumption
QALY estimates for local colorectal cancer.	0.9 (SD .06)	Beta	Ramsey et al., (2000), Ladabaum et al., (2018).
QALY estimates for regional colorectal cancer.	0.8 (SD .22)	Beta	Ramsey et al., (2000), Ladabaum et al., (2018).
QALY estimates for distant colorectal cancer	0.76 (SD .11)	Beta	Ramsey et al., (2000), Ladabaum et al., (2018).

QALY estimates for death	0	Beta	Assumption

4.3.4 Costs

4.3.4.1 Direct medical costs

Direct medical costs are directly related to the costs of medical service, such as treatment costs, screening costs. In this study, direct medical costs were considered cancer treatment costs, screening costs and costs of treating adverse effects related to colonoscopy procedures.

4.3.4.1.1 Screening costs

The colonoscopy screening costs were derived from Health Directorate Norway. The DRG system was used to calculate the colonoscopy screening costs, where the cost is determined by multiplication of the DRG weight and corresponding DRG unit price. The obtained cost for colonoscopy was NOK 3394 or Euro 307. On the other hand, expert opinion was used to determine the cost of using AI. According to expert opinion, the cost was NOK 15,000 assuming 120 colonoscopies were performed in a month. So, per colonoscopy cost of AI was determined NOK 125 or EURO 11. Hence, the total costs of AI assisted colonoscopy were calculated by combining the cost of colonoscopy and costs of using AI.

Table 11: Cost of screening procedures. Cost per procedure. Numbers in Euro.

DESCRIPTION	UNIT COSTS IN 2023	SOURCE
Cost of conventional colonoscopy	€ 307	Health Directorate Norway (2022)
Cost of using AI	€ 11	Expert opinion
Cost of AI assisted colonoscopy	€ 318	Combined costs of colonoscopy and using AI

4.3.4.1.2 Cancer treatment costs

The costs of life-time cancer treatment for local, regional, and distal cancer were derived from the study published by Joranger et al (2015). However, the aforementioned study considered cancer stages based on TNM staging, so costs in that study were available for stage I, II, III and IV . Therefore, in this thesis the costs of local, regional, and distant cancer were assumed to be similar to the costs of stage I cancer, average costs of stage II and III, and stage IV cancer respectively. Lifetime cost of cancer treatment included cost of examination, primary treatment, surgery, adjuvant/neoadjuvant chemotherapy, palliative chemotherapy, cost of recurrence and follow-up costs. As comorbidities were not related to screening, costs of treating comorbidities were not included in the cancer treatment costs.
The lifetime cancer treatment costs were added once in the first year of diagnosis of cancer, as the majority of cancer related expenditure occurs in the first year.

Table 12 : Cancer treatment costs per individual for different cancer stages.

Description	Unit costs in 2023	Value in 2017	Source
Lifetime costs of treating patients with local cancer	€ 31,874	€26,630	Joranger et al. (2015)
Lifetime costs of treating patients with regional cancer	€ 56,811	€47,465	Joranger et al., (2015)
Lifetime costs of treating patients with metastatic cancer	€ 83,652	€69,890	Joranger et al., (2015)

**In the study by Joranger et al (2015), the expected lifetime costs of treating cancers were € 38130 and € 56,800 for stage II and stage III respectively; while in this thesis, cost of regional cancer was assumed as the average cost of treating stage II and III: (€ 38130 + €56800)/2 or €47465 in 2016.

4.3.4.1.3 Adverse event management costs

In this study, the considered adverse event management costs were the cost of treating major haemorrhage and the cost of treating colon perforation resulting from colonoscopy procedure. The cost of hospitalisation for treating haemorrhage was € 790, as reported by Lonne et al., (2015), while the cost of treating colon perforation was € 3440, sourced from the Vervaart et al., (2018), that used the data from Norwegian Directorate of Health (2016). To account for price inflation, both costs were adjusted using the consumer price index, which reflects an annual increase of 2.60%.

Table 13: Cost of treating adverse events. One off cost per event. Numbers in Euro.

Description	Costs in 2023	Source
Cost of treating major haemorrhage	€ 945	Lonne et al., 2015
Cost of treating perforation	€ 4048	Norwegian Directorate of Health (2016)

4.3.4.3 Indirect medical costs

In this study, indirect medical costs included the cost for the last 6 months before death of the individuals. The end-of-life costs included primary care and home and community-based care (including nursing homes), all numbers derived from Bjørnelv et al., (2020) and a forthcoming paper. According to the studies, the home care and primary care cost for the last 6 months of a non-cancer patient were NOK 226,667 and NOK 9,167 respectively, thus the total end of life cost was NOK 236,434 or € 32,155 in 2013 (considering NOK 1= € 0.136 in 2013). While for a cancer patient, home care and primary care cost were comparatively lower, NOK 155,360 and NOK 11,553 respectively, which resulted in a total cost of NOK 166913 or € 22700 for the last 6 months of a cancer patient in 2013. After adjusting for the price inflation (by using CPI 2.6% per year) the obtained end of life costs for individuals with cancer and non-cancer were € 27,362.00 and € 38,760.00 respectively. Table 14 represents the end-of-life costs for cancer and non-cancer individuals.

Table 14: Cost of end of life for individuals with and without cancer.

Description	Unit costs in 2023	Source
Total cost of the last 6 months of a non-cancer person	€ 38,760	Bjørnelv et al (2020)
Total cost of the last 6 months of cancer patients	€ 27,362	Bjørnelv et al (2020)

4.3.4.4 Non-medical Costs

In economic evaluation, non-medical costs consist of direct and indirect costs resulting from any intervention. Direct non-medical costs include those costs which directly result from the intervention, however not directly related to the medical services, such as costs of travel, costs of invitation etc. In this study, considered direct non-medical costs were travel costs and cost of invitation in the screening programme. Travel cost included the total cost of round trip to the medical centre per screening, while cost of invitations to screening included the costs of reminder, stamps, envelopes, and letters. Round travel costs to the medical centre for screening and cost of invitation including reminder were derived from Aas (2015) and were adjusted for the price inflation.

On the other hand, indirect costs include the costs which are related to the loss of productivity due to any disease or intervention. This study considered the productivity loss due to absence from work for the screening procedures. The duration of absence from work due to the colonoscopy procedure was considered as 5 hours, estimated by Aas (2015). The estimated proportion of working people was 0.82 for 50-54 years,0.81 for 55-59 years and 0.62 for 60-64 years (Aas, 2004,2005). The proportion of working people from 65-67 years was assumed to be the same as 60-64 years. Productivity loss was calculated by multiplying the proportion of people working in the respective age with hourly wage in Norway and duration of the screening procedure. According to Statistics Norway, the monthly average wage in Norway is NOK 53,150 NOK and Norwegians work for 37.5 hours weekly, which results in an hourly

wage of 354 NOK or € 35.4. After adjusting it with 1.4 for social costs, the total productivity loss due to standard colonoscopy resulted in €248. According to the study by Ahmad et al (2022), the duration of AI assisted colonoscopy may take up to 0.9 minutes more than standard colonoscopy due to increased procedure and withdrawal time, which made the total duration for AI assisted colonoscopy 5.15 hours. As a result, the productivity loss due to AI assisted colonoscopy was calculated as € 255, after adjusting for social costs.

Table 15: Non-medical costs associated with CRC screenings.

Description	Unit costs in 2023	Source
Cost of invitation and reminder for colonoscopy procedure	€ 29	Aas (2015)
Cost of travel (round trip per visit) to medical centre	€ 41	Aas (2015)
Cost of productivity loss due to standard colonoscopy procedure per individual	€ 248	Aas (2015)
Cost of productivity loss during AI assisted colonoscopy procedure per individual	€ 255	Aas (2015), Ahmad et al (2022)

4.4 Sensitivity Analysis:

Sensitivity analyses were performed to explore the uncertainties surrounding the model parameters. Deterministic sensitivity analysis was performed to evaluate the influence of important parameters. Additionally, a probabilistic analysis was conducted to capture the joint parameter uncertainty, by using a Monte Carlo simulation for 1000 iterations which uses random sampling from parameter distributions. In this analysis, prevalence and polynomial probabilities followed Dirichlet distribution. As costs are highly skewed, gamma distribution

was used for modelling costs, while for utilities, recurrence probabilities and other variables beta distribution was chosen. The standard error of each parameter either derived from available literature or assumed to be 20%. The results of the probabilistic analysis were displayed through scatterplots. Additionally, cost-effectiveness acceptability curves were constructed based on the results, which showed the probability of AI-assisted colonoscopy being cost-effective compared to standard colonoscopy and no screening for screening starting at 50 years, 55 years, 60 years, once in lifetime at 50 years and 60 years for various thresholds from €0 to €50000.

4.4.1 Scenario analysis

100% compliance in screening is not always achievable in real life, so the study included a scenario analysis considering 70% compliance instead of 100%, in addition to baseline analysis.

5. Results

5.1 Base-case analysis

The base-case analyses considered implementation of screening at age 50 years, 55 years, and 60 years with 100% participation.

5.1.1 Screening starting at 50 years

Screening every 10 years

In the base case analysis considering screening of age-group 50 years with 100% participation, the estimated number of colorectal cancer cases was 8,371 and the number of colorectal cancer-related deaths was 7,486 per 100,000 individuals over a time horizon of 50-100 years for *no screening* strategy. Estimated discounted costs were € 12,819 per individual, estimated discounted QALYs were 18.405 and estimated discounted mean Life Years were 18.45 per individual.

Standard colonoscopy strategy reduced the CRC incidences from 8,371 to 1,325, and CRC related deaths from 7,846 to 1,137. Although this strategy resulted in additional costs of $1,281 per individual due to inclusion of colonoscopy costs, costs of treating adverse events and productivity losses, the estimated discounted costs €12,415 per individual was € 404 lower than no screening strategy due to reduced cancer treatment costs and end-of-life costs. Estimated discounted QALYs for this strategy were 18.602 and estimated discounted mean Life Years were 18.609 per individual.

Compared to standard colonoscopy, AI assisted colonoscopy further reduced the CRC cases from 1,325 to 1,049, and CRC related deaths from 1,137 to 882. Although this strategy included higher screening costs and productivity losses compared to standard colonoscopy, this was offset by reduced cancer treatment cost and end-of-life costs. Total estimated discounted costs for AI assisted colonoscopy screening was €12,376, which was € 39 less than standard colonoscopy and € 443 less than no screening strategy. The estimated discounted QALYs were 18.609 and discounted mean life years were 18.614, both were

higher than standard colonoscopy and no screening strategy. Table 16 represents the results of baseline analysis considering screening starting at 50 years in detail.

Table 16: Results of base-case analysis of screening at 50 years.

	No screening	Standard colonoscopy	AI assisted colonoscopy
CRC cases per 100000 persons	8,371	1,325	1,079
Incidence reduction (%)	-	7,046 (84%)	7,322 (87.5%)
Stagewise number of CRC cases per 100000 persons (% of all cases)			
Local	3,300 (39.4%)	647 (48.9%)	511 (48.7%)
Regional	3,119 (37.3%)	467 (35.2%)	374 (35.7%)
Distant	1,951 (23.3%)	211 (15.9%)	164 (15.6%)
Screen-detected adenomas per 100,000 persons (including surveillance)			
Low risk adenoma	-	35,024	38,940
High risk adenoma	-	5,552	5,142
Lifetime colonoscopies per 100,000 persons (including 3 population-based screening and all surveillance colonoscopy)		316,122	317,658
Total number of false positives (including 3 population-based and all surveillance screenings)	-	26,855 (8.5%)	40,758 (12.8%)

	No screening	Standard colonoscopy	AI assisted colonoscopy
Interval cancer cases (within available screenings)	-	138	76
CRC deaths per 100000 persons	7,860	1,137	882
Mortality reduction,%	-	6,723 (85.5%)	6,978 (88.7%)
Costs per person (discounted)	€ 12,819	€ 12,415	€ 12,376
Incremental costs per person (vs no screening)	-	€ 404	€ 443
QALYs per person (discounted)	18.405	18.602	18.609
Incremental QALYs per person (vs no screening)	-	0.197	0.204
Mean LYs per person (discounted)	18.447	18.609	18.614
Incremental LYs gained per person	-	0.162	0.167
Incremental cost/QALY gained (vs no screening)	-	€ 2,050	€ 2,171
Incremental cost/LYs gained (vs no screening)	-	€2,495	€2,644

Of the three mentioned strategies, it is evident that the costliest and least effective strategy was *no screening*, while AI assisted colonoscopy was the least costly and most effective one with the incremental cost being € 2,171 per QALY and € 2,644 per LYs gained. On the other

hand, standard colonoscopy was slightly more costly and less effective than AI assisted colonoscopy, with an ICER being €2,050 per QALY and €2,495 per LYs gained.

Once in life screening at 50 years

Considering a single population-based screening event at age 50 years, the analysis showed standard colonoscopy averted about 56% cancer incidence and 57% cancer mortality. AI-assisted colonoscopy showed considerably better performance with 63% CRC incidence and 65% mortality reduction. However, compared to screening starting at 50 years, incidence and mortality reduction were significantly lower. Notably, the occurrence of interval CRC incidences for standard and AI assisted colonoscopy were 500 and 321 respectively, which were substantially higher than strategies considering screening starting at 50 years. Standard colonoscopy saved € 70 per individual with incremental 0.171 QALYs and 0.143 LYs gained, compared to no screening strategy. Contrarily, AI assisted colonoscopy saved € 163 per individual, with 0.183 QALYs and 0.153 LYs gained, which indicates more cost-effectiveness compared to standard colonoscopy and no screening.

Table 17: Outcomes of analysis assuming screening once in lifetime at 50 years.

	No screening	Standard colonoscopy	AI assisted colonoscopy
CRC cases per 100,000 persons	8,371	3,671	3,125
Incidence reduction (%)	-	4,700 (56.1%)	5,246 (62.7%)
Stagewise number of CRC cases per 100000 persons(% of all cases)			
Local	3,300 (39.4%)	1,626 (44.3%)	1,386 (42.4%)
Regional	3,119 (37.3%)	1,324 (36.1%)	1,129 (36.1%)

	No screening	Standard colonoscopy	AI assisted colonoscopy
Distant	1,951 (23.3%)	721 (15.6%)	610 (19.5%)
Screen-detected adenomas per 100 000 persons (including surveillance)			
Low risk adenoma	-	15,628	19,380
High risk adenoma	-	3,711	3,794
Lifetime colonoscopies per 100,000 persons (including surveillance)		118,998	122,671
Total number of false positives (including population-based and surveillance screenings)	-	9,654 (8.1%)	14,788 (12.1%)
Interval cancer cases (within available screenings)	-	500	321
CRC deaths per 100000 persons	7,860	3,394	2,775
Mortality reduction,%	-	4,466 (56.8%)	5,086 (64.7%)
Costs per person (discounted)	€ 12,819	€ 12,749	€ 12,656
Incremental costs per person (vs no screening)	-	€ 70	€ 163
QALYs per person (discounted)	18.405	18.576	18.588

	No screening	Standard colonoscopy	AI assisted colonoscopy
Incremental QALYs per person (vs no screening)	-	0.171	0.183
Mean LYs per person (discounted)	18.447	18.59	18.60
Incremental LYs gained per person	-	0.143	0.153
Incremental cost/QALY gained (vs no screening)	-	€ 409	€ 886
Incremental cost/LYs gained (vs no screening)	-	€467	€1,060

5.1.2 Screening starting at 55 years

Initiating CRC screening at the age of 55 years, instead of 50 years showed similar outcomes. Under the no screening strategy, the estimated incidences of CRC and associated deaths for no screening were 7,921 and 7,405 respectively. These figures were significantly higher than the corresponding values for the standard colonoscopy strategy, which were 1,424 and 1,300 respectively. AI assisted colonoscopy strategy exhibited even lower estimated CRC incidences and deaths, with figures of 1,212 and 1,069 respectively.
Nevertheless, it is important to note that all the screening strategies showed lower CRC incidence reduction and mortality reduction compared to 10-year interval screening initiating at 50 years.

In comparison to no screening strategy, incremental cost per QALY gained for standard colonoscopy and AI assisted colonoscopy were estimated as € 2,379 and € 2,507 respectively, while incremental LYs gained per person were estimated as € 2,960 and € 3,124. Table 18 shows the results of screening starting at 55 years in detail.

Table 18 : Results of screening starting at 55 years.

	No screening	Standard colonoscopy	AI assisted colonoscopy
CRC cases per 100000 persons	7,921	1,464	1,212
Incidence reduction, %	-	6,457 (81.5%)	6,709 (84.6%)
Stagewise number of CRC cases per 100000 persons(% of all cases)			
Local	3,087 (39.0%)	829 (56.6%)	699 (57.7%)
Regional	2,955 (37.3%)	449 (30.7%)	366 (30.2%)
Distant	1,879 (13.7%)	186 (12.7%)	146 (12.1%)
Lifetime colonoscopies per 100000 persons (including surveillance)	-	300,990	302,569
Total number of false positives (including population-based and surveillance screening)	-	25,067 (8.3%)	38,122 (12.6%)
Screen-detected adenomas per 100000 persons (including surveillance)			
Low risk adenoma	-	36,701	40,643
High risk adenoma	-	6,026	5,587
Interval cancer cases within screening	-	149	80
CRC deaths per 100000 persons	7,405	1,300	1,069
Mortality reduction, (%)	-	6705 (79%)	6,870 (81%)

	No screening	Standard colonoscopy	AI assisted colonoscopy
Costs per person (discounted)	€ 14,973	€ 14,578	€ 14,542
Incremental costs per person (vs no screening)	-	€ 395	€ 432
QALYs per person (discounted)	17.034	17.200	17.206
Incremental QALYs per person (vs no screening)	-	0.166	0.172
Mean LYs per person (discounted)	17.077	17.211	17.216
Incremental LYs gained per person	-	0.134	0.138
Incremental cost/QALY gained (vs no screening)	-	€ 2,379	€ 2,507
Incremental cost/LYs gained (vs no screening)	-	€ 2,960	€ 3,124

5.1.3 Screening starting at 60 years

5.1.3.1 Screening every 10 years

Assuming screening initiation at 60 years represented AI assisted colonoscopy outperformed both standard colonoscopy and no screening strategies, with incremental costs € 3,723 per QALY gained and incremental costs € 4,818 per life year gained compared to no screening. Conversely, for standard colonoscopy the estimated incremental costs per QALY and LY gained was € 3,534 and € 4,4624 respectively, which was also cost-effective compared with no screening.

However, the number of incidence and death related to CRCs were observed to be higher in the case of colonoscopy, both with and without AI, when compared to the scenarios where 10-year interval screening implemented at 50 and 55 years. Consequently, the reduction in incidence and mortality was comparatively lower, suggesting a decreased effectiveness of the screening strategies in mitigating CRC cases and mortality when screening initiation were delayed until the age of 60. Furthermore, the estimated costs per individual were found to be considerably higher for standard and AI assisted colonoscopy, while the estimated QALYs and LYs were lower than those associated with screening initiation at 50 years and 55 years. The outcomes of screening starting at 60 years are presented in table 19.

Table 19: Results of analysis assuming screening starting at 60 years.

	No screening	Standard colonoscopy	AI assisted colonoscopy
CRC cases per 100000 persons	7,111	1,732	1,471
Incidence reduction, %	-	5,379 (75.6%)	5,640 (79.3%)
Stagewise number of CRC cases per 100000 persons(% of all cases)			
Local	2,770 (39.0%)	921 (53.2%)	797 (54.2%)
Regional	2,651 (37.2%)	554 (32.0%)	883 (31.6%)
Distant	1,691 (23.8%)	257 (14.8%)	216 (14.2%)
Total Screening	-	217,829	219,564
Total number of false positives (including population-based and surveillance screenings	-	17,580 (8.0%)	26,740 (12.2%)
Screen-detected adenomas per 100000 persons (including surveillance)			
Low risk adenoma	-	30,050	33,971

	No screening	Standard colonoscopy	AI assisted colonoscopy
High risk adenoma	-	5,597	5,346
Interval cancer cases within screening	-	108	61
CRC deaths per 100000 persons	6,589	1,533	1,471
Mortality reduction, (%)	-	5,056 (76.7%)	5118(77.7%)
Costs per person (discounted)	€ 17,200	€ 16,748	€ 16,706
Incremental costs per person (vs no screening)	-	€ 451	€ 493
QALYs per person (discounted)	15.50	15.623	15.628
Incremental QALYs per person (vs no screening)	-	0.128	0.132
Mean LYs per person (discounted)	15.54	15.636	15.639
Incremental LYs gained per person	-	0.099	0.102
Incremental cost/QALY gained (vs no screening)	-	€ 3,534	€ 3,732
Incremental cost/LYs gained (vs no screening)	-	€ 4,562	€ 4,818

5.1.3.2 Screening once in lifetime at 60 years

Assuming a single population-based screening at 60 years, colonoscopy with and without AI showed less favourable outcomes than screening starting at 60 years. Performance of standard colonoscopy and AI assisted colonoscopy in reducing CRC incidence decreased to

16.3% and 14.2% compared to those strategies starting at 60 years. Moreover, performance on reducing mortalities also decreased 16.8% for standard colonoscopy and about 10% for AI assisted colonoscopy.

Total cost for standard colonoscopy and AI assisted colonoscopy were € 16,960 and € 16,882 respectively, which were € 239 and € 318 less than no screening strategy. However, the total cost of standard and AI assisted colonoscopy increased compared to both strategies starting at 60 years.

Implementation of standard colonoscopy resulted in 0.117 QALYs and 0.093 LYs gained, while AI assisted colonoscopy yielded 0.124 QALYs gain and 0.098 LYs gained per individual. The outcomes of the implementing screening at 60 for once in lifetime are presented in Table 20.

Table 20: Outcomes of single population-based screening starting at 60 years.

	No screening	Standard colonoscopy	AI assisted colonoscopy
CRC cases per 100000 persons	7,111	2,897	2,481
Incidence reduction, %	-	4,214(59.3%)	4,630 (65.1%)
Stagewise number of CRC cases per 100000 persons(% of all cases)			
Local	2,770 (39.0%)	1345 (53.2%)	1177 (54.2%)
Regional	2,651 (37.2%)	1004 (32.0%)	850 (31.6%)
Distant	1,691 (23.8%)	549 (14.8%)	454 (14.2%)
Lifetime colonoscopies per 100000 persons (including surveillance)	-	121,451	125,118
Total number of false positives (including population-based and surveillance screenings)	-	9457 (7.8%)	14493 (11.6%)

	No screening	Standard colonoscopy	AI assisted colonoscopy
Screen-detected adenomas per 100000 persons (including surveillance)			
Low risk adenoma	-	18,425	22,562
High risk adenoma	-	4,365	4,463
Interval cancer cases within screening	-	108	61
CRC deaths per 100000 persons	6,589	2,575	2,129
Mortality reduction, (%)	-	4,014 (60.9%)	4460 (67.7%)
Costs per person (discounted)	€ 17,200	€ 16,960	€ 16,882
Incremental costs per person (vs no screening)	-	€ 239	€ 318
QALYs per person (discounted)	15.496	15.613	15.620
Incremental QALYs per person (vs no screening)	-	0.117	0.124
Mean LYs per person (discounted)	15.537	15.59	15.60
Incremental LYs gained per person	-	0.093	0.098
Incremental cost/QALY gained (vs no screening)	-	€ 2,038	€ 2,548
Incremental cost/LYs gained (vs no screening)	-	€ 2,569	€ 3,231

5.2 Ranking of the strategies

All the considered strategies were ranked based on their implementation age and plotted in the efficiency frontier to find the optimal screening strategy.

5.2.1 Screening starting at 50 years

The considered strategies for screening initiating at 50 years were "no screening", "10 yearly population-based AI assisted colonoscopy and standard colonoscopy" and "single population-based AI assisted and standard colonoscopy". Among all the mentioned strategies at 50 years, no screening showed the lowest gain at highest cost, making it the strongly dominated one. Among the remaining strategies, AI assisted colonoscopy showed highest QALYs gained at lowest cost, indicating it is the optimal cost-effective strategy. The ranking of all strategies starting at 50 years is included in Appendix table 5.

Figure 6 shows the efficiency frontier of all the considered strategies at the age 50 years, where AI-assisted colonoscopy is the lowest right one, indicating greater cost-effectiveness compared to other strategies due to highest QALY gained at lowest cost. The strategies which are more upward and left to the AI-assisted colonoscopy screening at 10-year interval, are dominated due to being more costly with less QALY gained.

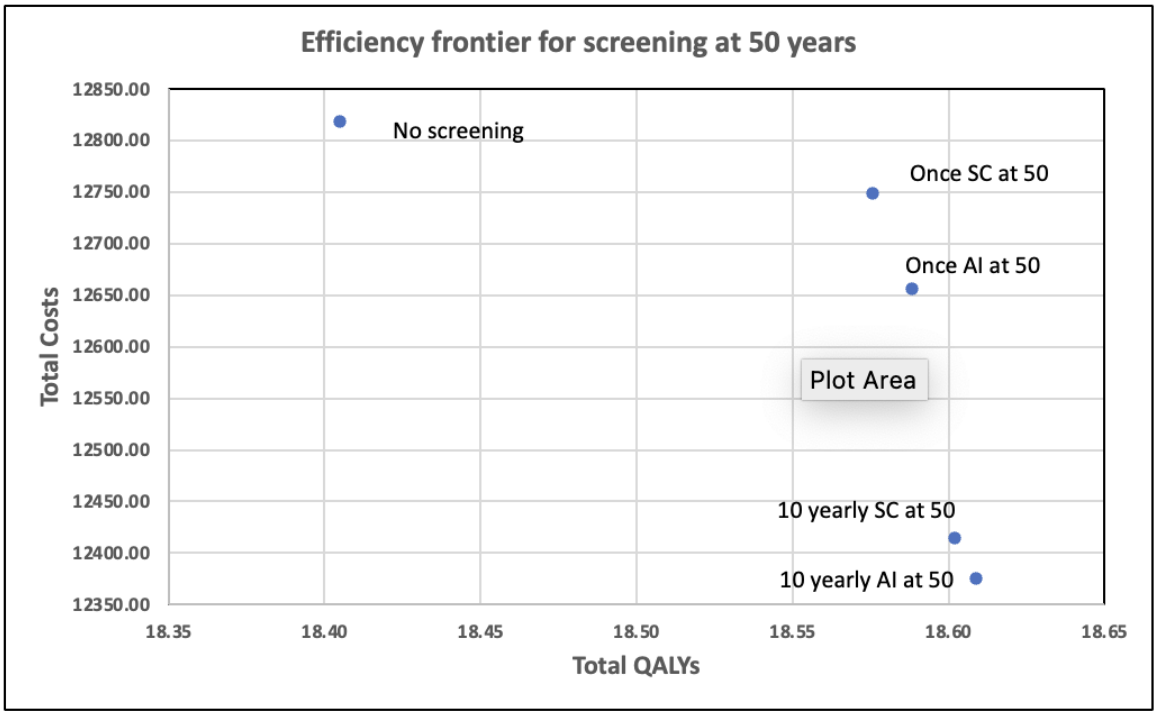

Figure 6: Efficiency frontier showing strategies starting at 50 years.

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5.2.2 Screening starting at 55 years

For screening starting at 55 years, the considered strategies were *no screening*, *10 yearly AI assisted colonoscopy* and *10 yearly standard colonoscopy*. The strategies were plotted in the graph according to their total costs and health gains. The efficiency frontier for age-group 55 years is presented in Figure 7.

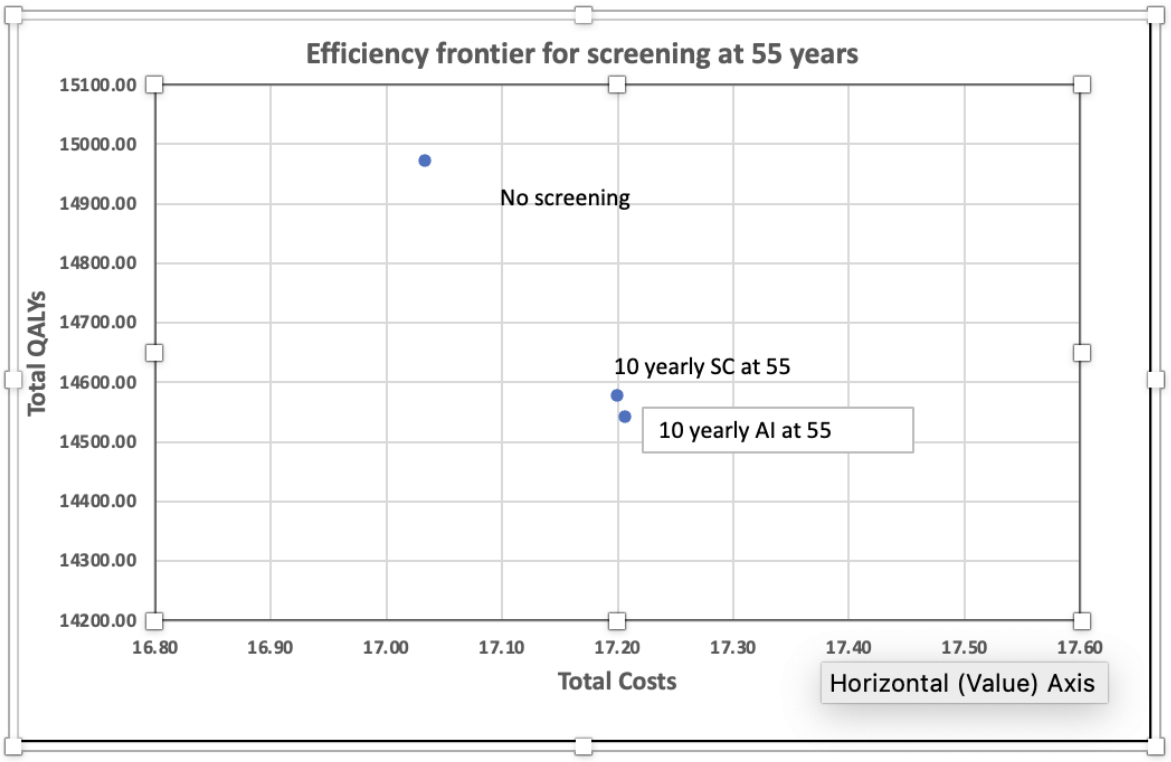


Figure 7: Efficiency frontier for screening starting at 55 years.

Among the three considered strategies at 55 years, the efficiency frontier in Figure 7 shows that *no screening* strategy is strongly dominated, standard colonoscopy every 10 years is weakly dominated, and AI-assisted colonoscopy every 10 years is the dominant strategy.

5.2.3 Screening starting at 60 years

Assuming screening starting at 60 years, the considered strategies were no screening at 60 years, AI-assisted colonoscopy, and standard colonoscopy every 10 years, once in lifetime AI-assisted colonoscopy and standard colonoscopy. All the strategies were plotted on the efficiency frontier according to their cost and effects and presented in Figure 8.

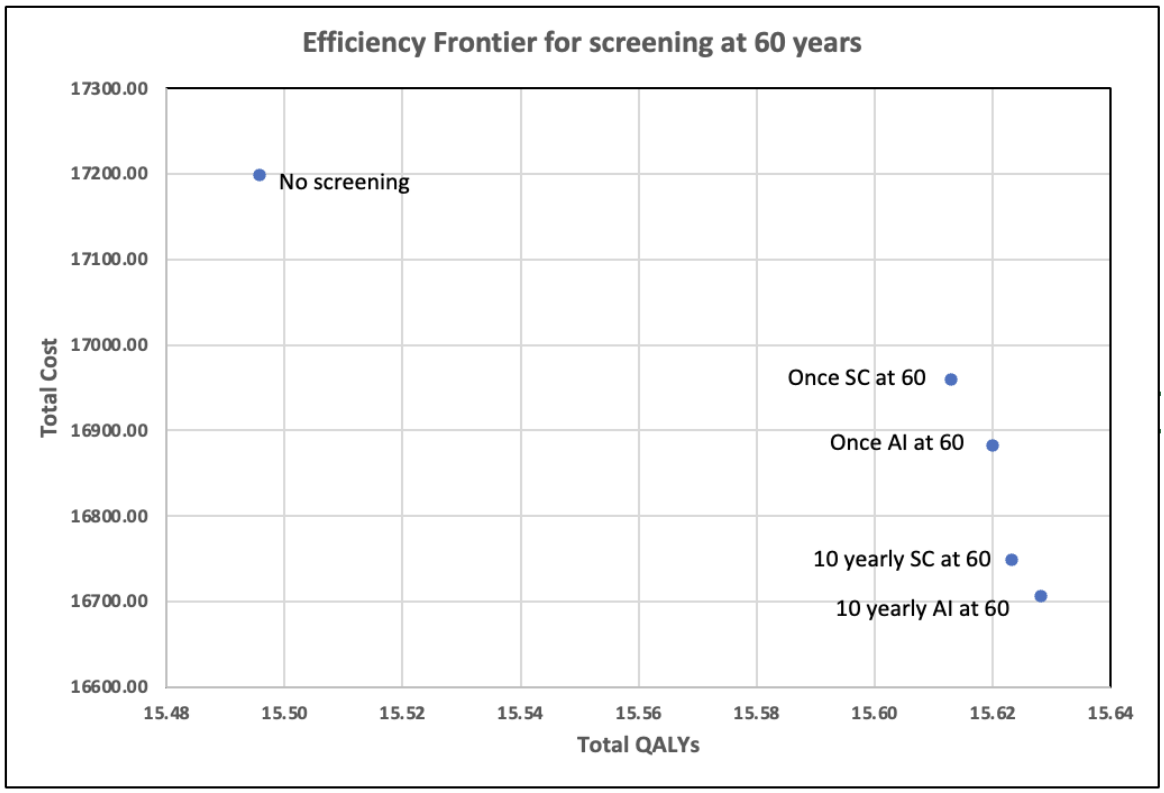


Figure 8: Efficiency frontier of screening implemented at 60 years.

From Figure 8, it is evident that AI assisted colonoscopy is the optimal strategy for screening implemented at 60 years, due to lower cost and higher utility, while no screening strategy is strongly dominated due to highest cost compared to lowest health gain. The rankings of the strategies according to their overall cost and QALY gained is presented in Appendix: Table 7.

The assessment of the cost-effective strategies across different implementation times indicates that the implementation of AI-assisted colonoscopy at the age of 50 years provides the greatest utility at the lowest costs, establishing it as the most optimal cost-effective strategy.

5.3 Scenario analysis

Assuming participation rate or test compliance as 70% for both population-based screening and surveillance screening, the obtained results for screening starting at 50 years showed that AI-assisted colonoscopy outperformed standard colonoscopy and no screening strategy. However, the reduction in CRC incidence and mortality rate for colonoscopy with AI and

without AI were notably lower than all the other strategies considering screening starting at 50 years, 55 years, and 60 years or once in lifetime screening with 100% participation. Compared to *no screening* strategy at age 50 years, total costs for standard colonoscopy were € 59 higher with 0.102 incremental QALYs and 0.085 incremental LYs gained per individual. For AI assisted colonoscopy, the total cost was € 34 higher compared to no screening, however the incremental QALYs and incremental LYs gained were 0.107 and .089 respectively.

Table 21: Outcomes of screening at 50 years with 70% participation rate.

	No screening	Standard colonoscopy	AI assisted colonoscopy
CRC cases per 100000 persons	8,371	5,329	5,172
Incidence reduction, %	-	3,042 (36.3%)	3,199 (38%)
Stagewise number of CRC cases per 100000 persons, (% of all cases)			
Local	3,300 (39.4%)	2174 (40.8%)	2101 (40.6 %)
Regional	3,119 (37.3%)	1972 (37.0%)	1918 (37.1%)
Distant	1,951 (23.3%)	1183(22.2%)	1153(22.3%)
Screen-detected adenomas per 100000 persons (including surveillance)			
Low risk adenoma	-	15,992	17,809
High risk adenoma	-	3,209	3,071

	No screening	Standard colonoscopy	AI assisted colonoscopy
Lifetime colonoscopies per 100000 persons (including surveillance)	-	221,616	222,155
Total number of false positives (including population-based and surveillance screenings)	-	13,628 (6.2%)	20,059 (9.0%)
CRC deaths per 100000 persons	7,860	4,924	4,775
Mortality reduction,%	-	6,723 (85.5%)	6,978 (88.7%)
Costs per person (discounted)	€ 12,819	€ 12,878	€ 12,853
Incremental costs per person (vs no screening)	-	€ 59	€ 34
QALYs per person (discounted)	18.405	18.507	18.512
Incremental QALYs per person (vs no screening)	-	0.102	0.107
Mean LYs per person (discounted)	18.447	18.532	18.536
Incremental LYs gained per person	-	0.085	0.089
Incremental cost/QALY gained (vs no screening)	-	€ 581	€ 321

	No screening	Standard colonoscopy	AI assisted colonoscopy
Incremental cost/LYs gained (vs no screening)	-	€ 695	€385

5.4 Deterministic Sensitivity Analysis

A one-way deterministic sensitivity was performed to observe the influence of parameter change on the ICERs. Among all the considered parameters, ICERs of strategies were more sensitive to the sensitivity of AI assisted colonoscopy and standard colonoscopy. AI assisted colonoscopy was not cost-effective anymore compared with standard colonoscopy, if sensitivity of AI assisted colonoscopy decreases 10% or sensitivity of standard colonoscopy increases 10%. However, ICERs were indifferent to change of colonoscopy cost. The result of the one-way sensitivity analysis is presented in Appendix Table 8-10.

5.5 Probabilistic Analysis

The outcomes of PA for different strategies were plotted on a cost-effectiveness plane for group wise comparison among screening starting at 50 years, 55 years, and 60 years. Additionally, cost-effectiveness acceptability curves were constructed based on the results of PA, to compare the probabilities of strategies being cost-effective in different threshold levels.

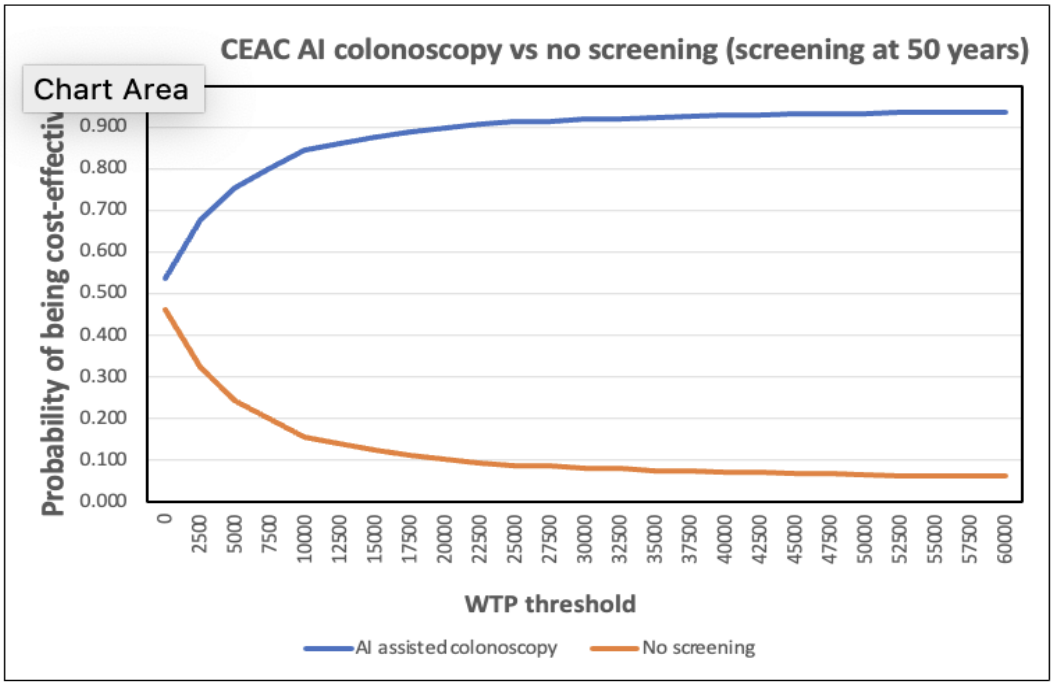
5.5.1 Screening initiation at 50 years

Every 10-year population-based screening

After plotting the outcomes of PA in a cost-effectiveness plane, most of the iterations for AI-assisted colonoscopy screening at 50 years were in the south-east quadrant, indicating it is more effective and less costly compared with *no screening* strategy. Standard colonoscopy also showed similar results; however, some iterations of ICERs were present in the north-east and north-west quadrant indicating in some cases it costs more for higher QALYs gained and

it may result in higher cost and lower effects compared with "no screening". (Appendix: Figure 3)

In comparison to no screening, AI assisted colonoscopy showed cost-effectiveness in 91% cases at a WTP threshold of € 25000 per QALY gained, while standard colonoscopy showed cost-effectiveness in 72% cases.



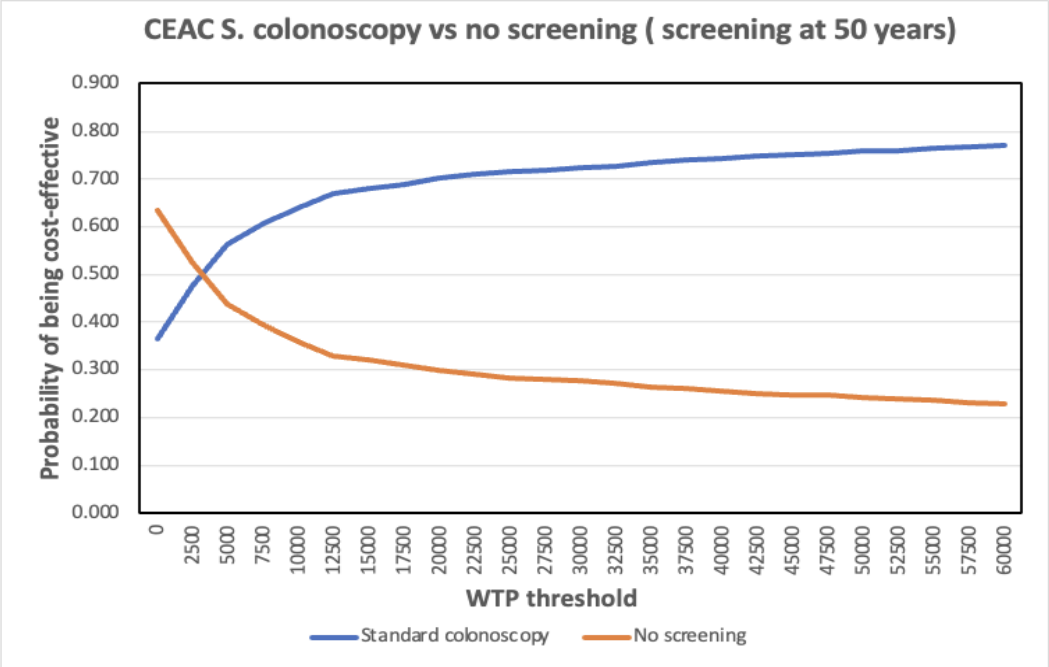


Figure 9: Cost-effectiveness acceptability curve of AI assisted colonoscopy and standard compared with no screening for screening starting at 50 years.

The direct comparison between colonoscopy with and without AI showed that, the probabilistic ICER of AI assisted colonoscopy was € 7874 compared to standard colonoscopy. After plotting the ICERs in the cost-effectiveness plane, the analysis indicated that around 70% simulations were in south-east quadrant (Appendix: Figure 4).
The findings of CEAC (Figure 10) also indicates that AI assisted colonoscopy was constantly cost-effective in the 68% simulations compared to standard colonoscopy at different WTP thresholds.

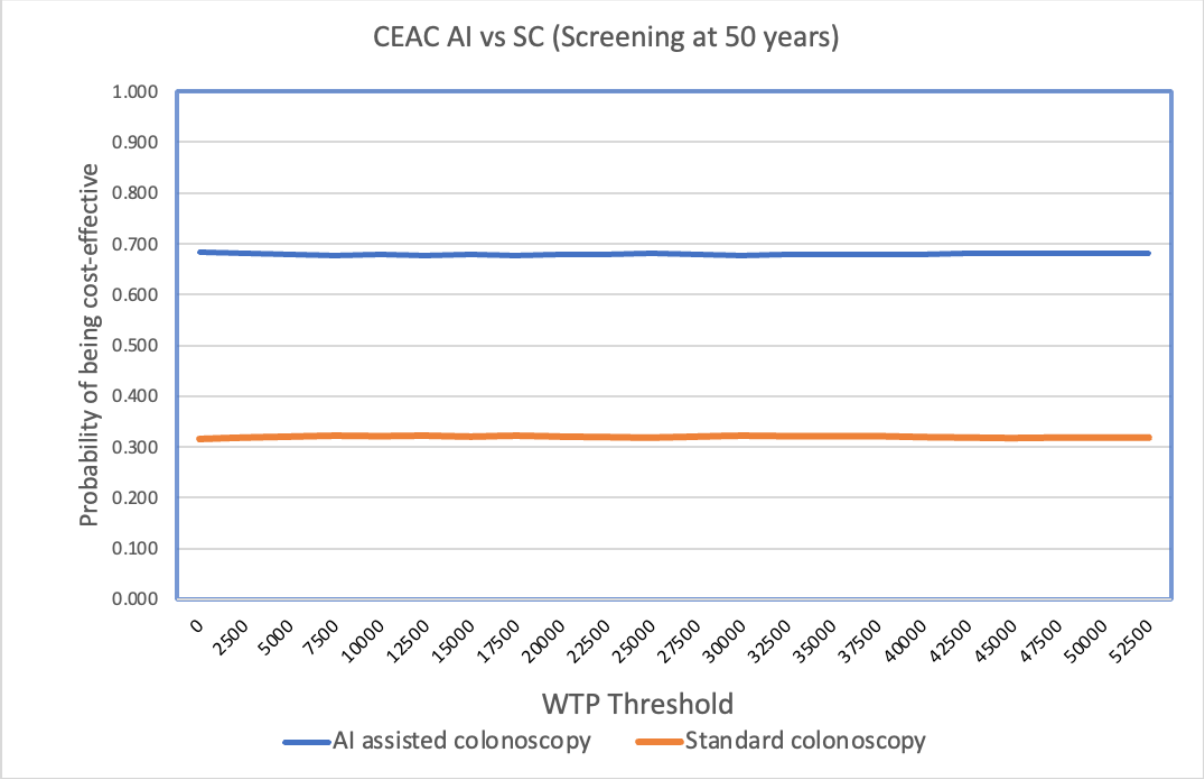
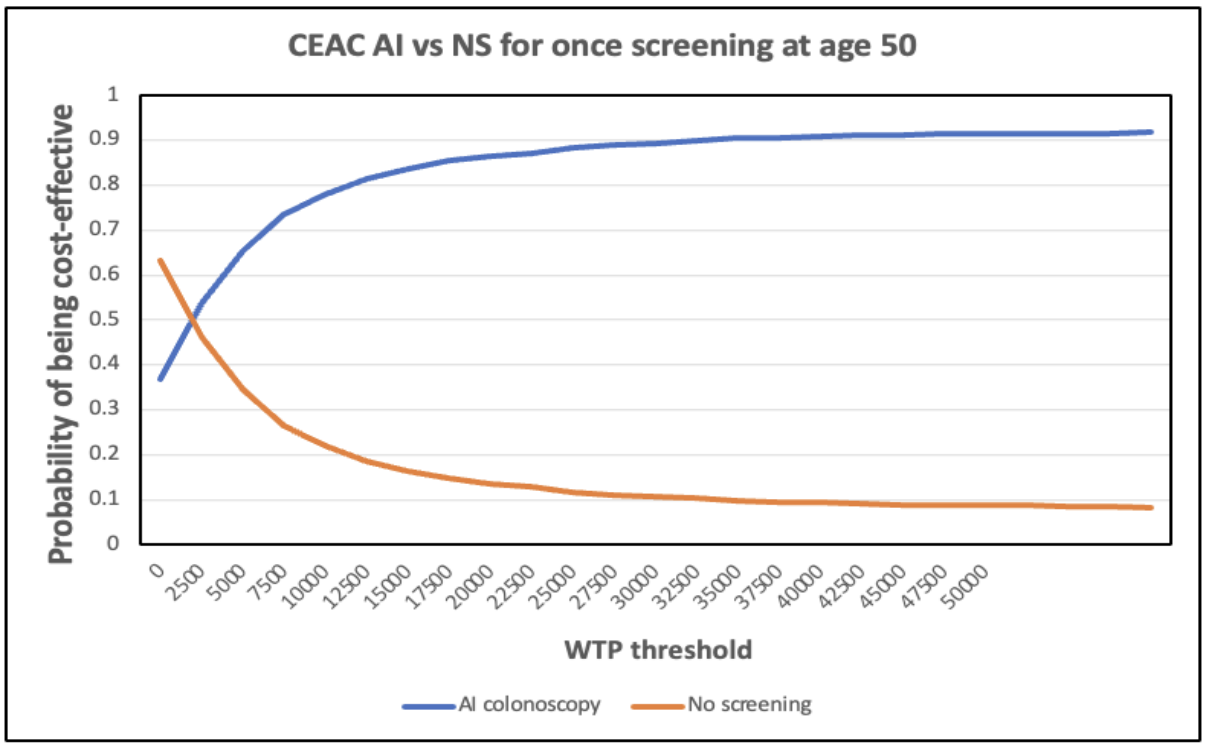


Figure 10: CEAC of AI assisted colonoscopy and standard colonoscopy.

Screening once at 50 years

Considering once in a lifetime screening at 50 years, the probability of cost-effectiveness of AI assisted colonoscopy was 88% at WTP threshold € 25000 per QALY gained, while for standard colonoscopy the probability was 66% in comparison with no screening. From PA it

is evident that screening once in lifetime decreased the magnitude of the probability of screening strategies being cost-effective.



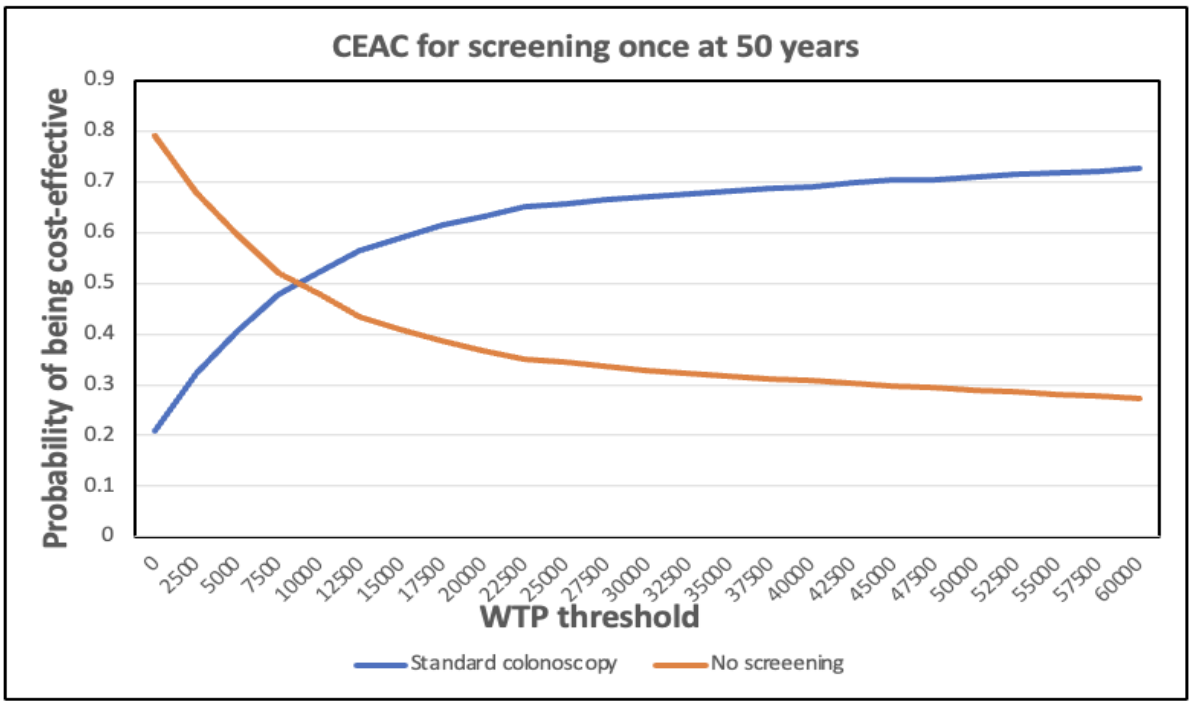


Figure 10: CEAC of AI assisted colonoscopy and standard colonoscopy compared with no screening for screening once in lifetime at 50 years.

The direct comparison between AI assisted and standard colonoscopy for once in lifetime screening at 50 years suggested, AI assisted colonoscopy was consistently cost-effective in 73% simulations in different thresholds from € 0 to € 25000.

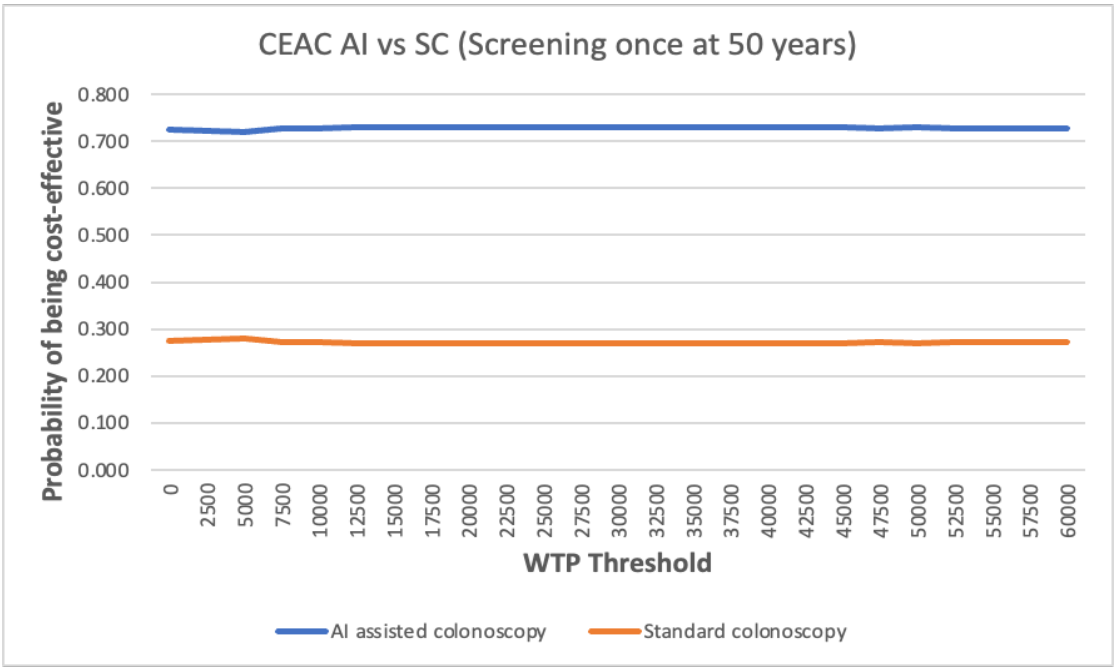


Figure 11: Cost-effectiveness acceptability curve of direct comparison between AI assisted and standard colonoscopy.

5.5.2 Screening starting at age 55 years

Considering screening starting at 55 years, the obtained PA outcomes were plotted in the cost-effectiveness plane, which revealed 87% of the iterations of AI-assisted colonoscopy were in the south-east quadrant, whereas for standard colonoscopy the respective figure was 68% compared with no screening.

From Figure 13, it is evident that the probability of AI-assisted colonoscopy being cost-effective at WTP threshold of € 25,000 per QALY gained is 87%, which increased up to 91% at WTP threshold of € 60,000 per QALY gained. Conversely, standard colonoscopy was 68% cost-effective at WTP threshold of € 25,000 and increased up to 73% at € 60,000.

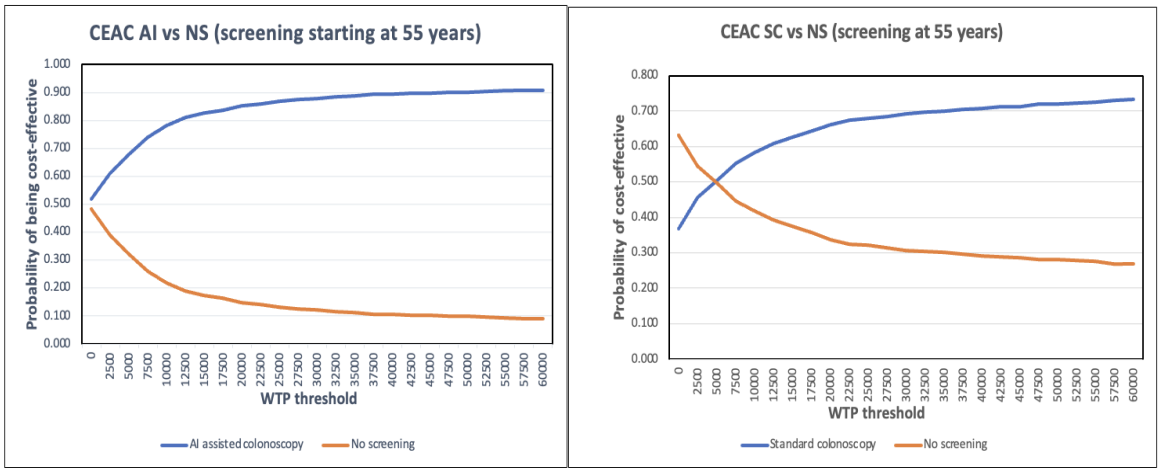


Figure 12: CEAC of colonoscopy with and without AI compared with no screening strategy for screening starting at 55 years.

Direct comparison between AI-assisted colonoscopy and standard colonoscopy in Figure 14 represents, AI assisted colonoscopy was cost-effective in 66% cases at WTP threshold of € 0, which slightly decreased to 62 % at WTP threshold of € 25,000 and further decreased to 61% at WTP threshold of € 50,000. While standard colonoscopy showed an increase in the probability of being cost-effective from 34% at WTP of € 0 to 39% at WTP threshold of € 50,000. (Figure 14)

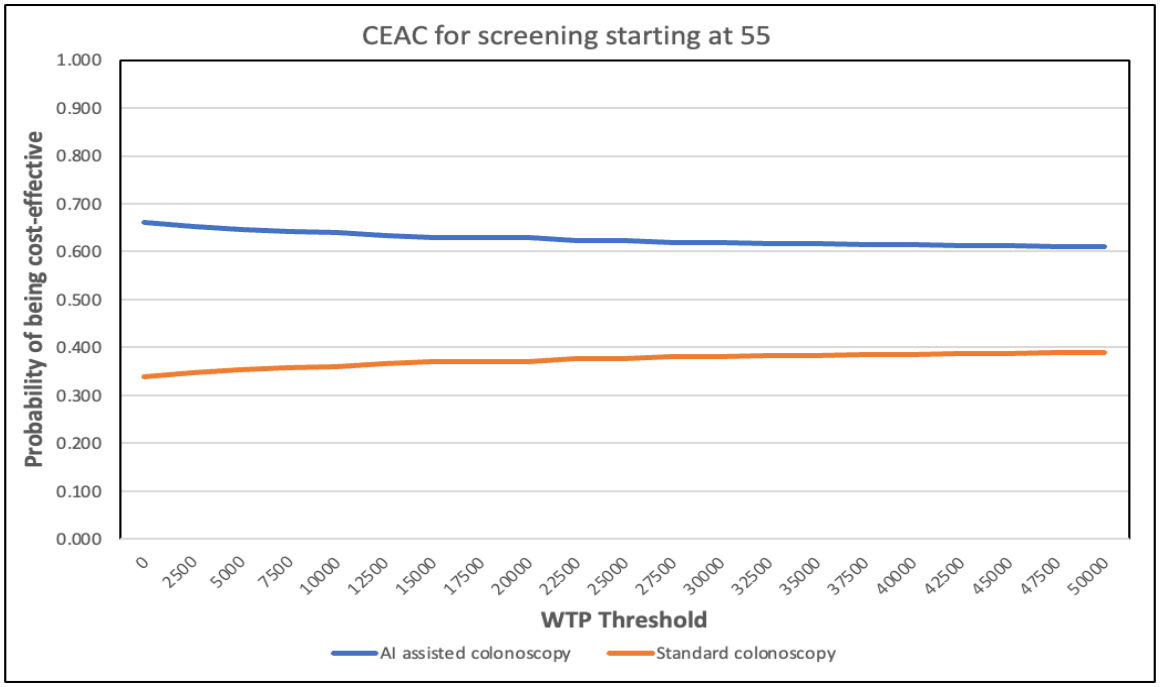


Figure 13: Cost-effectiveness acceptability curve showing direct comparison of AI assisted colonoscopy and standard colonoscopy.

5.5.3 Screening initiation at 60 years

5.5.3.1 Every 10-year screening

After plotting the outcomes of PA in the cost-effectiveness plane, it was observed that 87% of the ICER simulations of AI assisted colonoscopy were lying in the south-east quadrant, while for standard colonoscopy, 69% of simulations were in the south-east quadrant.

CEAC of AI assisted colonoscopy revealed that at no willingness to pay level, cost-effectiveness of AI assisted colonoscopy was 58%, which increased to 87% at WTP threshold of €25,000 per QALY gained and further increased to 90% at WTP threshold € 60,000 per QALY gained. However, standard colonoscopy was 41% cost-effective in no willingness to pay threshold, which gradually increased to approximately 69% at the recommended WTP threshold €25,000 and further increased to 73% at WTP threshold of € 60,000 per QALY gained.

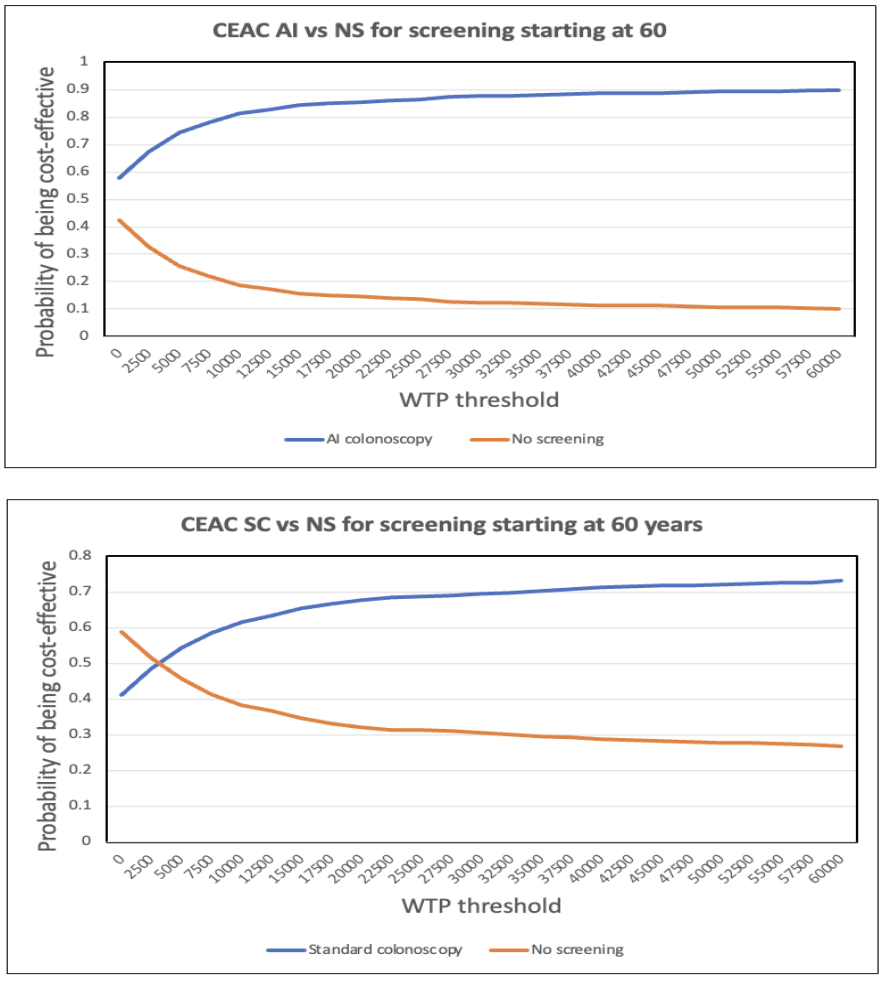


Figure 14: CEAC of colonoscopy with and without AI compared with no screening strategy at 60 years.

Direct comparison between AI assisted colonoscopy and standard colonoscopy showed, the probabilistic ICER of AI assisted colonoscopy was € 11371per QALY gained. Cost-effectiveness plane revealed nearly 63% of ICERs lie in the south-east quadrant, which indicates AI assisted colonoscopy gained higher QALYs in lower cost compared to standard colonoscopy.

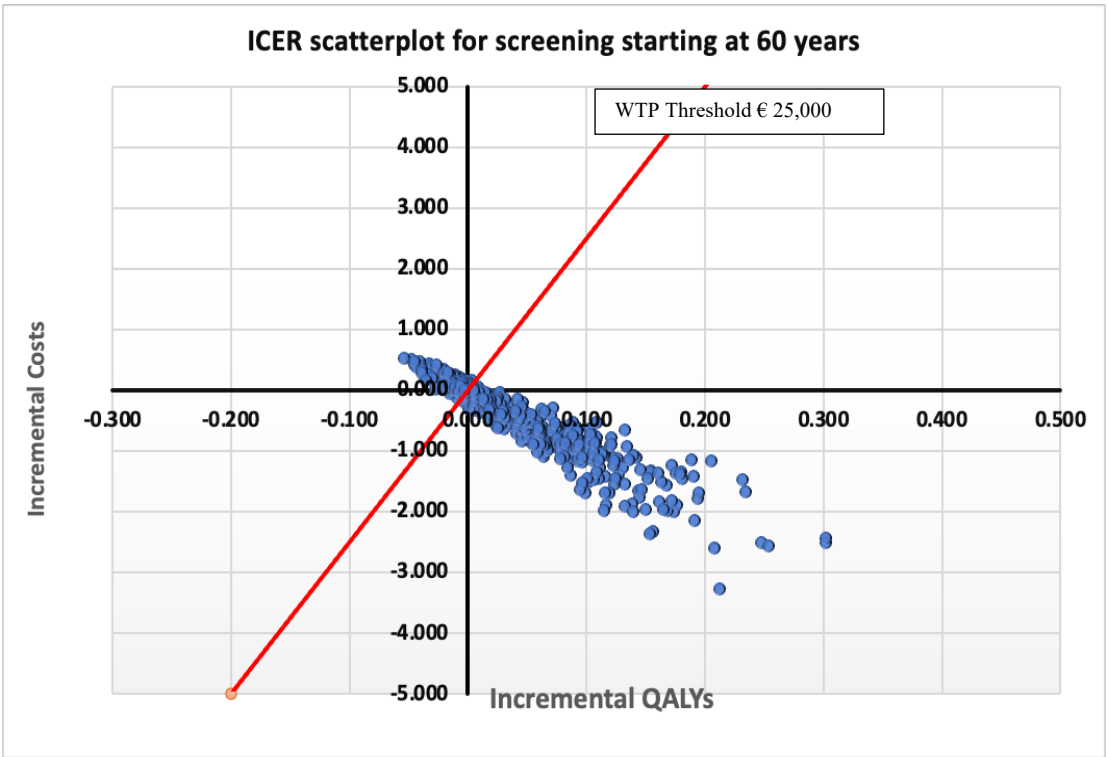


Figure 15: Cost-effectiveness plane of AI assisted colonoscopy compared to standard colonoscopy.

The CEAC (Figure 17) represents that, in 63% cases AI assisted colonoscopy was cost-effective compared to standard colonoscopy at WTP threshold of € 25,000.

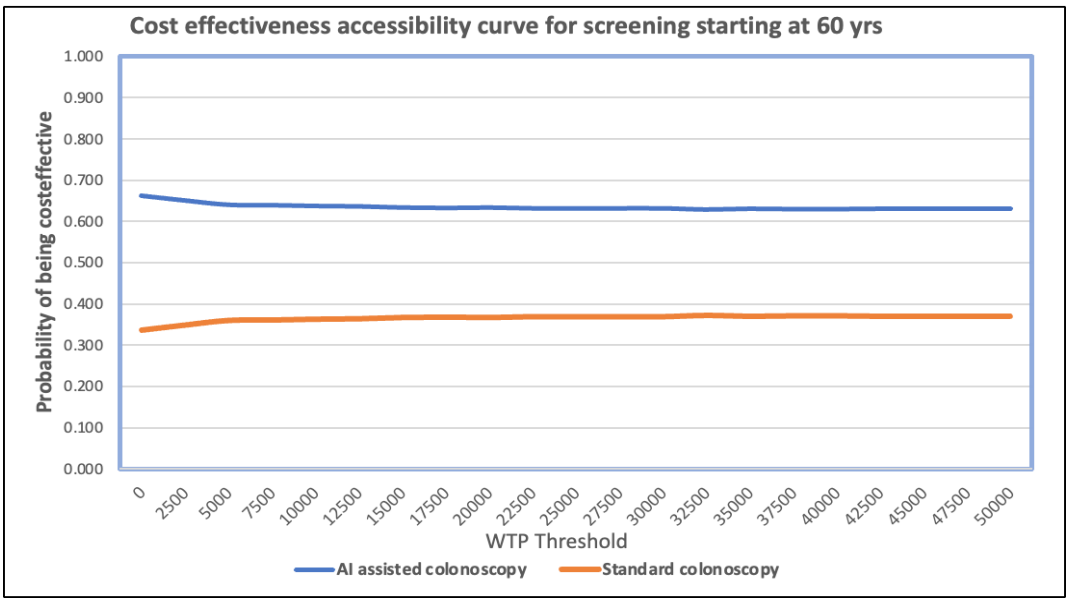


Figure 16: Cost-effectiveness acceptability curve of AI assisted colonoscopy and standard colonoscopy.

5.5.3.2 Screening once in lifetime at 60 years:

Assuming single population-based screening at 60 years, PSA outcomes showed that compared with no screening, 83% of ICER simulations were in the south-eastern and north-east quadrant for AI assisted colonoscopy, whereas for standard colonoscopy it was 64%. CEAC in Figure 18 indicates that the probability of AI assisted colonoscopy was about 4% lower than no screening at WTP level of € 0, however the probability gradually increased and turned into 85% at WTP threshold of € 25,000. However, standard colonoscopy was only 31% cost-effective initially, which increased up to 64% at WTP threshold of € 25,000.

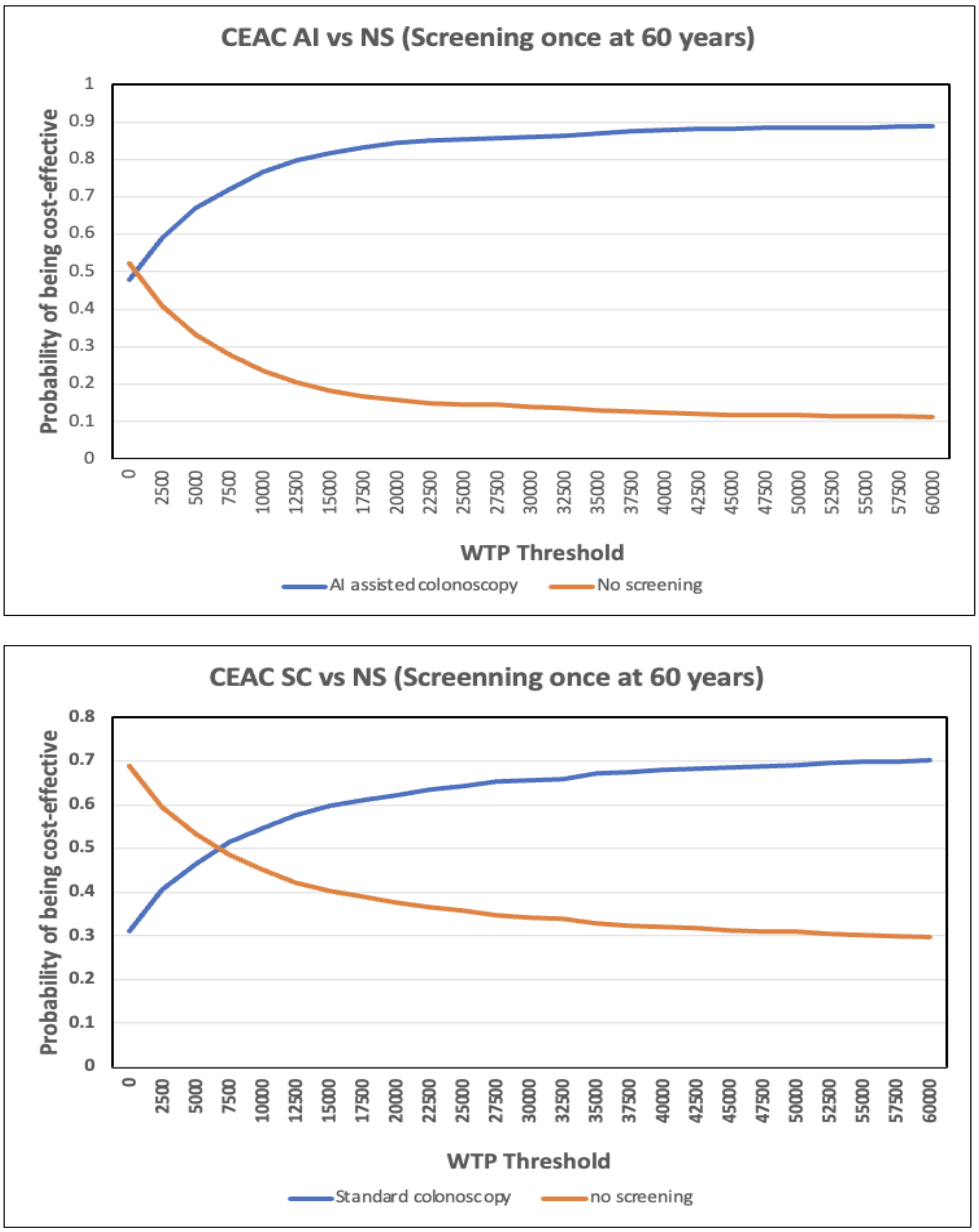


Figure 17: Cost-effectiveness acceptability curve of AI-assisted and standard colonoscopy compared to no screening for once in lifetime at 60 years.

Direct comparison between AI-assisted colonoscopy and standard colonoscopy (Figure 19) showed that nearly 67% of ICERs were in the south-east quadrant of the cost-effectiveness plane indicating AI assisted colonoscopy provides higher QALYs in lower costs compared to standard colonoscopy.

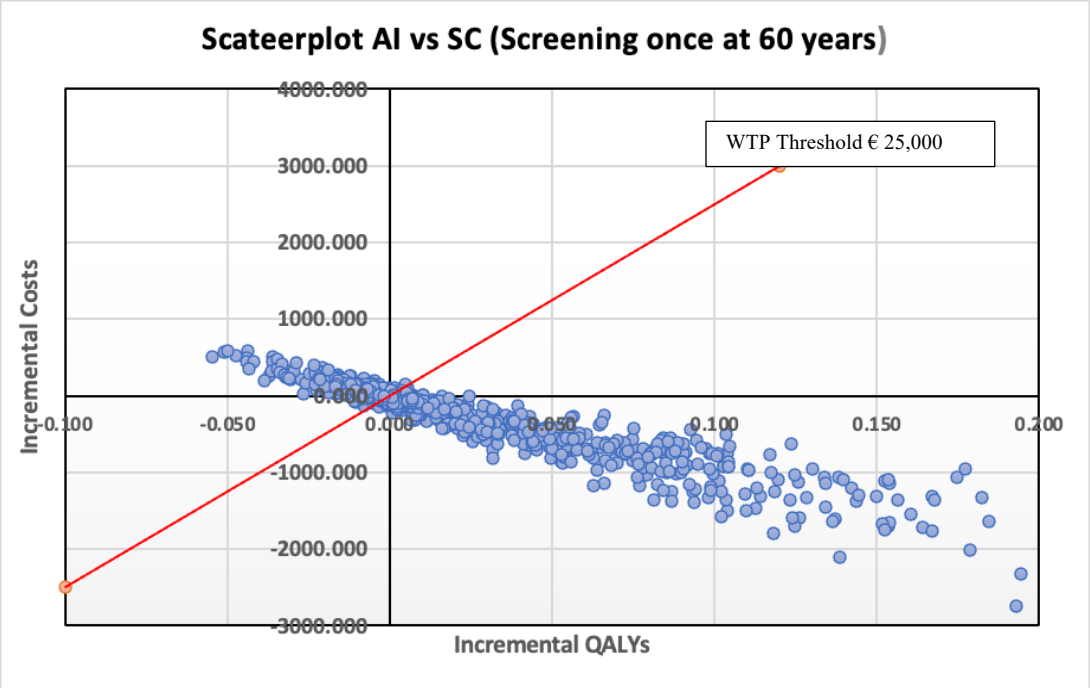


Figure 18: Cost-effectiveness plane of AI assisted colonoscopy compared to standard colonoscopy.

CEAC in Figure 20 indicates that initially AI assisted colonoscopy was 69% cost effective in the absence of willingness to pay, however it gradually decreased to nearly 67% at WTP threshold of € 25,000. Contrarily, the probability of being cost-effective was gradually increased for standard colonoscopy, nevertheless it remained 33% at WTP threshold of € 25,000.

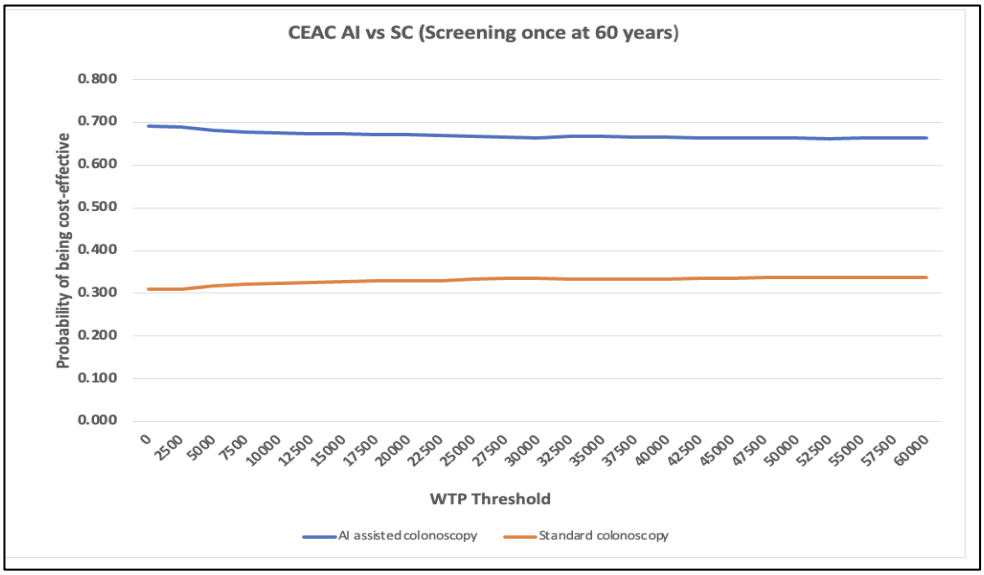


Figure 19 : CEAC of the comparison between AI assisted colonoscopy and standard colonoscopy for once at 60 years.

6. Discussion

6.1 Main Findings

The cost-effectiveness analysis demonstrated that implementation of AI-assisted colonoscopy was more cost-effective compared with conventional colonoscopy and no screening strategies, regardless of the starting age, participation rate, or screening frequency. AI-assisted colonoscopy demonstrated 3-6% more reduction in cancer incidence and 2-8% more reduction in mortality rate compared with conventional colonoscopy. Besides, despite incurring higher additional costs of implementing AI technology and productivity losses due to increased procedure time, AI-assisted colonoscopy yielded lower overall costs and higher gains in quality-adjusted life years (QALYs) and life years (LYs) in comparison, which can be attributed to the higher reductions in cancer incidence and mortality rates that resulted in lower cancer treatment and end-of-life costs per individual.

All the screening strategies were cost-effective compared to subsequent no screening strategies. However, among all the strategies, AI assisted colonoscopy screening at 50 years yielded lowest overall costs and highest QALYs and LYs gained per individual, which makes it the optimal cost-effective strategy. Although AI-assisted colonoscopy and conventional colonoscopy consistently exhibited greater cost-effectiveness than no screening across all strategies, as implementation age increased, both AI-assisted colonoscopy and standard colonoscopy demonstrated lower capacity of reduction in colorectal cancer incidence and mortality compared with no screening. This finding suggests that initiating screening at an earlier age holds the potential for greater reductions in cancer incidence and cancer-related mortality. However, with advancing age, the incremental costs of the screening strategies increased while the incremental effects decreased in comparison to no screening, resulting in higher incremental cost-effectiveness ratios (ICERs), despite lower effectiveness.

The analysis also showed participation rate can considerably influence the extent of cost-effectiveness of a screening strategy. With a 70% participation rate, cost-effectiveness of screening strategies reduced remarkably compared with 100% participation. It can be explained by the fact that with the reduction of the participation rate, total screening costs per individual increased and total QALYs decreased, which resulted in lower ICERs. However, AI-assisted screening was still more cost-effective than conventional colonoscopy and no

screening strategies, while both screening strategies were cost-effective compared with no screening strategy.

The analysis considered sensitivity and specificity as the measures of diagnostic accuracy instead of ADR, as sensitivity and specificity truly capture the extent of the effects of having false-positive cases. In an optimal screening test, the sensitivity and specificity values would ideally be as close to 100% as possible, indicating high accuracy in identifying individuals with the condition and excluding individuals without the condition. It is important to note that, despite being a more cost-effective strategy than standard colonoscopy, AI assisted colonoscopy was associated with higher false positive cases (3-4% higher compared with standard colonoscopy) which may lead to increased cost and resource utilisation, as well as anxiety and psychological distress in the detected individuals. However, despite the higher false positive rate, AI assisted colonoscopy still remained the dominant strategy regarding cost-effectiveness.

Another notable finding of the analysis was AI-assisted colonoscopy detected a higher number of LRA, but a lower number of HRA compared to conventional colonoscopy in majority of the cases. It can be attributed to the capability of AI-assisted colonoscopy to detect the diminutive polyps, which deterred most adenomas to turn into HRA, consequently to CRC incidences. Besides, AI-assisted colonoscopy resulted in lower interval cancers compared to standard colonoscopy, which is aligned with the findings of other recent international studies.

6.2 Validation of the model

The validation of the model was assessed by comparing the findings of the model with the data obtained from Cancer Registry Norway. The Registry data indicates that the cumulative risk of developing colorectal cancer for both males and females is on average, 6.4% (7.1% for males and 5.7% for females) until the age of 80. In contrast, the analysis using the model yielded CRC incidences of 5615 cases (cumulative risk 5.62%) between the ages 50 to 79, which is slightly lower than the figures reported by the registry.

It is important to note that cumulative risk in CRN includes the summation of age-specific rates of developing CRC over each year of age from age 1 to 79. Given this, the obtained

cumulative risk of 5.6% over 30 years from the model aligns well with the data from Registry.

6.3 Comparison with other cost-effectiveness studies

To the best of our knowledge, there is no available cost-effectiveness studies of screening including both AI-assisted colonoscopy and standard colonoscopy in Norway to compare, however the results of this study were consistent with other recent international studies regarding cost-effectiveness of CADe assisted colonoscopy. The cost-effectiveness study conducted by Areia et al (2020) showed that implementation of AI in colonoscopy resulted in higher QALYs gain at lower costs in US settings. The study used Markov model microsimulation in a hypothetical cohort of 100,000 individuals aged 50-100 years, and the principal measures of effectiveness were cancer incidence and mortality reduction. The study reported that AI assisted colonoscopy resulted in 4.8% incremental gain for CRC incidence reduction and 3.6% incremental gain in mortality reduction compared to colonoscopy without AI, which saved $ 57 per individual.

The cost-effectiveness study of Barkun et al (2023) showed, AI assisted colonoscopy was a dominant, cost-effective strategy over conventional colonoscopy in the Canadian health care setting. According to the study, implementation of CADe resulted in .019 incremental life year gained and .024 incremental QALYs gained compared to conventional colonoscopy, with projected $14 overall cost savings given that 1000 colonoscopies performed in a year.

However, the obtained cancer incidence and mortality reduction was slightly higher in this study compared to other published studies. This can be explained by the intensive surveillance of LRA diagnosed individuals at every 5 years, where most of the studies used surveillance colonoscopy for LRA at every 10 years, While the international guidelines recommend surveillance colonoscopy for LRA every 5-10 years, from the analysis it is evident that surveillance at 5-year interval has more potential to reduce interval cancer incidences than 10-year interval.

6.4 Study limitations

The conducted study has some methodological limitations.

Simulation model inherently incorporates some uncertainties due to several assumptions. To minimize these uncertainties, this study analysed the effects of screening for three different implementation ages. Moreover, a scenario analysis was performed assuming participation rate as 70% for reducing any uncertainties regarding different screening adherence rates. Furthermore, one-way sensitivity analysis and probabilistic analysis were performed to address parameter related uncertainties.

A limitation of this study includes considering colon cancer and rectal cancer together, while these two cancers are different regarding prognosis and treatment. However, the individual data for associated costs of colon and rectal cancer is rare to find, as they are considered together in most of the studies. Moreover, the unknown stage of cancer was not included in the model, as there is no sufficient information to define the stage.

Another limitation of the study was using relatively old data. The dataset used for deriving time-dependent mortality probability for different cancers, contained data from 2000-2016. Thus, there is a difference in CRC related mortality between the estimated one and current one, as CRC related mortality further decreased after 2016. Moreover, the data related to cancer treatment cost, cost of invitation, productivity cost and end-of-life cost are not recent either, however inflation adjustments were performed to address this problem.

Although the study considered productivity costs related to screening, it did not consider productivity losses resulting from cancer due to lack of data, which may result in underestimation of total costs of the strategies. However, including productivity loss for suffering from cancer may result in more cost-effectiveness of screening strategies compared to no screening.

This study did not include the effects of obtaining false-positive results on quality of life due to lack of related data. Increased false-positive results of a screening may result in disutility due to anxiety and unnecessary investigations, which was not incorporated in this study.

In this study, the natural history model considered all cancers originate from the adenomatous polyps, however recent evidence suggests that a small percentage of cancer may develop from non-polypoid precursors like flat adenomas. Including flat adenomas may further decrease the cost-effectiveness of colonoscopy screening compared to AI-assisted colonoscopy, nevertheless it will merely affect the ranking of the strategies.

Although men develop CRC at an early age and possess higher risk of developing cancer compared to women, this study did not consider any separate analysis for these two groups. Further research on sub-group analysis might explore the impact of different initiation ages for men and women.

7. Conclusion

From this analysis, it is evident that AI assisted colonoscopy is a dominant cost-effective strategy compared with standard colonoscopy and no screening strategy. Moreover, implementation of screening at early age is more beneficial than initiation at a later stage. Further research including de-novo cancer pathway, sub-group analysis, productivity losses for CRC related illness and considering disutility of having false-negative results are required to provide further confidence in policy makers decision.

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9. Appendix

Tables

Appendix Table 1: Characteristics of patients in the dataset.

Characteristics of the patients in the dataset diagnosed with colorectal cancer in the time period 2000-2016 by gender, age-groups, and diagnostic stage are presented in Table 1.

Table: Characteristics of patients in the dataset.

	Males		Females		Total
	N	%	N	%	
Age					
0-49	1,658	49.24	1709	50.76	3,367
50-59	3,841	53.94	3280	46.06	7,121
60-69	8,446	56.23	6574	43.77	15,020
70-79	10,756	52.87	9588	47.13	20,344
80-89	7,575	43.92	9673	56.08	17,248
90 and over	1,008	33.89	1966	66.11	2,974
Stage					
Local	6,525	50.17	6,481	48.83	13,006
Regional	16,358	49.88	16,438	50.12	32,796
Distant	7,734	52.14	7,099	47.86	14,833
Unknown	2,667	49.04	2,771	50.96	5,438

Appendix Table 2: Age-dependent mortality probability for both sex (Source : Cancer Registry Norway)

Age	Mortality probability
50	0.002
51	0.002
52	0.002
53	0.003
54	0.003
55	0.003
56	0.003
57	0.004
58	0.004
59	0.004
60	0.005
61	0.006
62	0.006
63	0.007

Age	Mortality probability
64	0.007
65	0.008
66	0.010
67	0.010
68	0.010
69	0.013
70	0.013
71	0.015
72	0.017
73	0.019
74	0.021
75	0.025
76	0.027
77	0.031
78	0.033
79	0.036

Age	Mortality probability
80	0.040
81	0.046
82	0.053
83	0.063
84	0.071
85	0.080
86	0.091
87	0.102
88	0.122
89	0.138
90	0.153
91	0.169
92	0.197
93	0.213
94	0.245
95	0.270
96	0.300

Age	Mortality probability
97	0.314
98	0.343
99	0.342
100	0.397

Appendix 3.1: Time-dependent mortality probability for local cancer

Description	Baseline value
Transition probability from local cancer to death in 1st year	0.074
Transition probability from local cancer to death in 2nd year	0.066
Transition probability from local cancer to death in 3rd year	0.063
Transition probability from local cancer to death in 4th year	0.061
Transition probability from local cancer to death in 5th year	0.060
Transition probability from local cancer to death in 6th year	0.059
Transition probability from local cancer to death in 7th year	0.058

Description	Baseline value
Transition probability from local cancer to death in 8th year	0.058
Transition probability from local cancer to death in 9th year	0.057
Transition probability from local cancer to death in 10th year	0.057

Appendix 3.2: Time-dependent mortality probability for regional cancer

Description	Baseline Value
Transition probability from regional cancer to death in 1st year	0.118
Transition probability from regional cancer to death in 2nd year	0.096
Transition probability from regional cancer to death in 3rd year	0.089
Transition probability from regional cancer to death in 4th year	0.085
Transition probability from regional cancer to death in 5th year	0.082
Transition probability from regional cancer to death in 6th year	0.080

Description	Baseline Value
Transition probability from regional cancer to death in 7th year	0.078
Transition probability from regional cancer to death in 8th year	0.076
Transition probability from regional cancer to death in 9th year	0.075
Transition probability from regional cancer to death in 10th year	0.074

Appendix 3.3: Time-dependent mortality probability for distant cancer

Description	Baseline value
Transition probability from distant cancer to death in 1st year	0.477
Transition probability from distant cancer to death in 2nd year	0.380
Transition probability from distant cancer to death in 3rd year	0.350
Transition probability from distant cancer to death in 4th year	0.331
Transition probability from distant cancer to death in 5th year	0.317
Transition probability from distant cancer to death in 6th year	0.307

Description	Baseline value
Transition probability from distant cancer to death in 7th year	0.299
Transition probability from distant cancer to death in 8th year	0.291
Transition probability from distant cancer to death in 9th year	0.285
Transition probability from distant cancer to death in 10th year	0.280

Appendix table 5: ranking of strategies implemented at 50 years compared to No screening

Strategies	Total Cost	Total QALYs	Increment. Cost	Increment. QALYs	ICERs	Ranking
10 yearly AI assisted colonoscopy	€ 12,376	18.61	€ 443	0.204	€ 2170	Dominant
10 yearly standard colonoscopy	€ 12,415	18.60	€ 404	0.197	€ 2050	Dominated (2)
Once AI at 50	€ 12,656	18.59	€ 163	0.183	€ 887	Dominated (3)
Once SC at 50	€ 12,749	18.58	€ 70	0.171	€ 409	Dominated (4)

No screening	€ 12,819	18.405	-	-	-	Strongly dominated

Appendix table 6: ranking of strategies implemented at 55 years compared to No screening

Strategies	Total Cost	Total QALYs	Incremen-tal Cost	Incremen-tal QALYs	ICERs	Ranking
10 yearly AI assisted colonoscopy	€ 14542	17.206	€ 432	0.172	€ 2507	Dominant
10 yearly standard colonoscopy	€ 14578	17.20	€ 395	0.166	€ 2379	Dominated
No screening	€ 14973	17.034	-	-	-	Strongly dominated

Appendix Table 7: Ranking of strategies implemented at 60 years compared to no screening

Strategies	Total Cost	Total QALYs	Incremental Cost	Incremental QALYs	ICERs	Rank
10 yearly AI assisted colonoscopy	€ 16706	15.628	€ 493	0.132	€ 3723	Dominant
10 yearly standard colonoscopy	€ 16748	15.623	€ 451	0.128	€ 3534	Weakly dominated

Once AI at 50	€ 16882	15.620	€ 317	0.124	€ 2548	Dominated
Once SC at 50	€ 16960	15.613	€ 239	0.117	€ 2038	Dominated
No screening	€ 17199	15.496	-	-	-	Strongly dominated

Appendix Table 8: One-way sensitivity analysis for screening strategies starting at 50 years compared to no screening at 50 years.

Strategies	Colonoscopy cost		Sensitivity AI		Sensitivity SC LRA		EOL cost cancer		Base-case ICER
	+20%	-20%	+10%	+10%	-10%	-10%	+10%	-10%	
Every 10-year AI	**€ 2171**	**€ 2171**	**€ 2268**	**€ 2788**	**€ 2171**	**€ 2171**	**2788**	**1553**	**€ 2171**
Every 10-year SC	**€ 2050**	**€ 2050**	**€ 2050**	**€ 2667**	**€ 2222**	**€ 1825**	**2667**	**1433**	**€ 2050**
Once AI	**€ 887**	**€ 887**	**€ 1129**	**€ 1435**	**€ 887**	**€ 887**	**1435**	**339**	**€ 887**
Once SC	**€ 409**	**€ 409**	**€ 409**	**€ 945**	**€ 991**	**€ 264**	**945**	**128**	**€ 409**

Appendix Table 9: One way sensitivity analysis for screening strategies starting at 55 years compared to no screening at 55 years.

Strategies	Colonoscopy cost		Sensitivity AI		Sensitivity SC LRA		EOL cost cancer		Base-case ICER
	+20%	-20%	+10%	-10%	+10%	-10%	+10%	-10%	

Every 10-year AI	€ 2507	€ 2507	€ 2619	€ 1415	€ 2507	€ 2507	€ 3242	€ 1772	€ 2507
Every 10-year SC	€ 2379	€ 2379	€ 2379	€ 2379	€ 2566	€ 2133	€ 3113	€ 1645	€ 2379

Appendix Table 10: One way sensitivity analysis for screening strategies starting at 60 years compared to no screening.

Strategies	Colonoscopy cost		Sensitivity AI		Sensitivity SC LRA		EOL cost cancer		Base-case ICER
	+20%	-20%	+10%	+10%	-10%	-10%	+10%	-10%	
Every 10-year AI	€ 3723	€ 3723	€ 3854	€ 2420	€ 2171	€ 2171	€ 4615	€ 2830	€ 3723
Every 10-year SC	€ 3534	€ 3534	€ 3534	€ 3534	€ 2222	€ 1825	€ 4421	€ 2646	€ 3534
Once AI	€ 2548	€ 2548	€ 2823	€ 195	€ 887	€ 887	€ 3370	€ 1725	€ 2548
Once SC	€ 2038	€ 2038	€ 2038	€ 2038	€ 991	€ 264	€ 2842	€ 1233	€ 2038

Figures

Figure 1

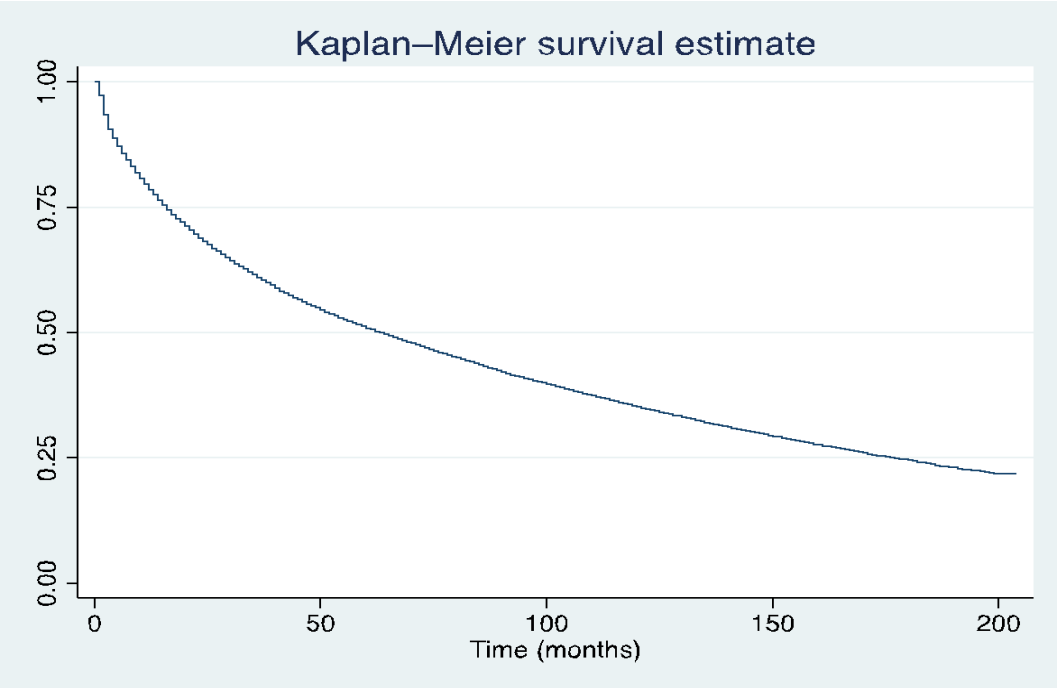
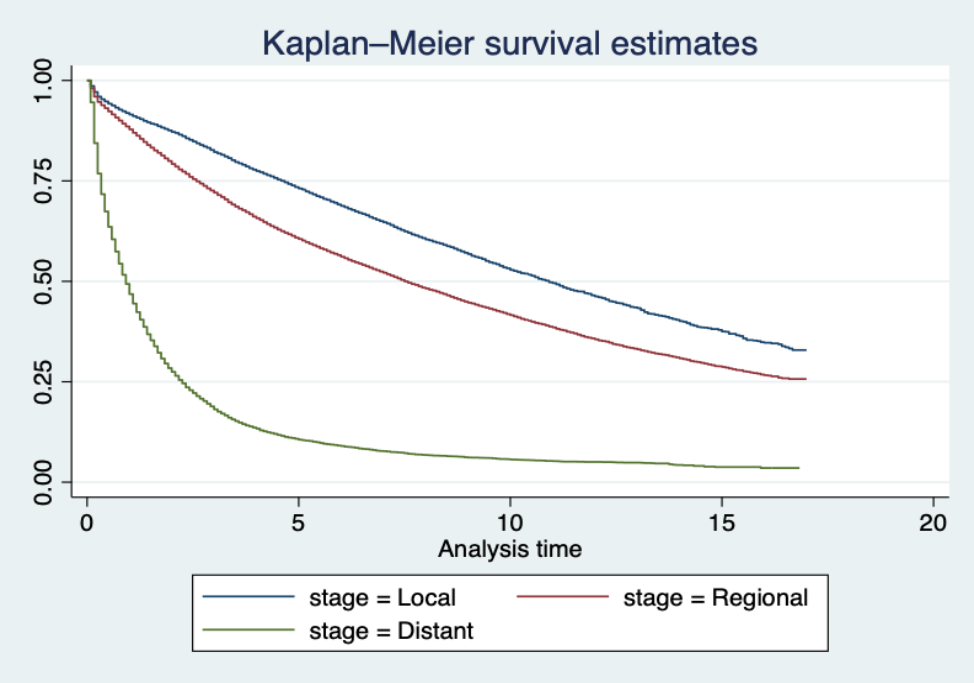


Figure 1: KM survival curve showing survival times up to 17 years.

Figure 2



Appendix Figure2: KM survival curve by stage

Figure 3

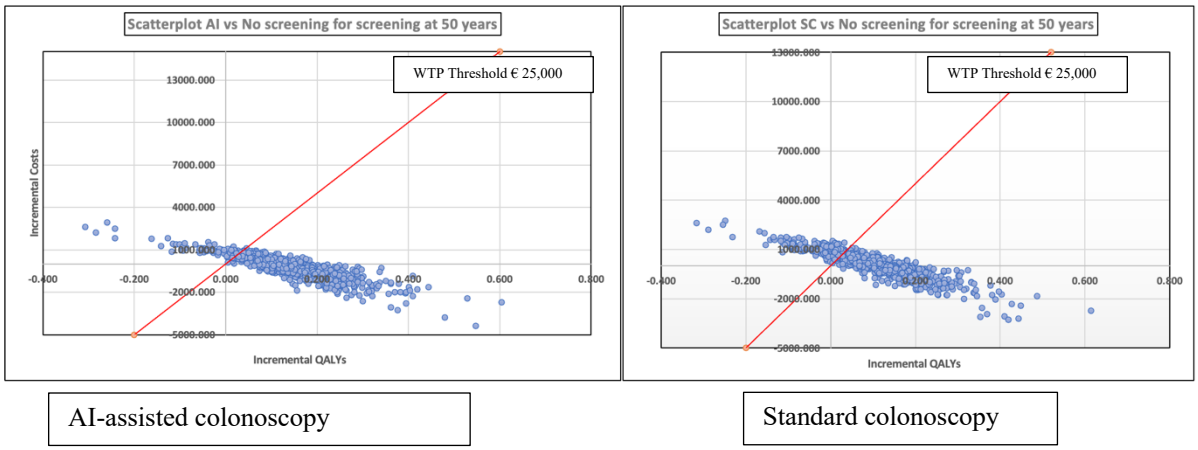


Figure 3 : Cost-effectiveness plane showing ICERs distributions of AI-assisted colonoscopy and standard colonoscopy compared with no screening at age 50 years.

Figure 4

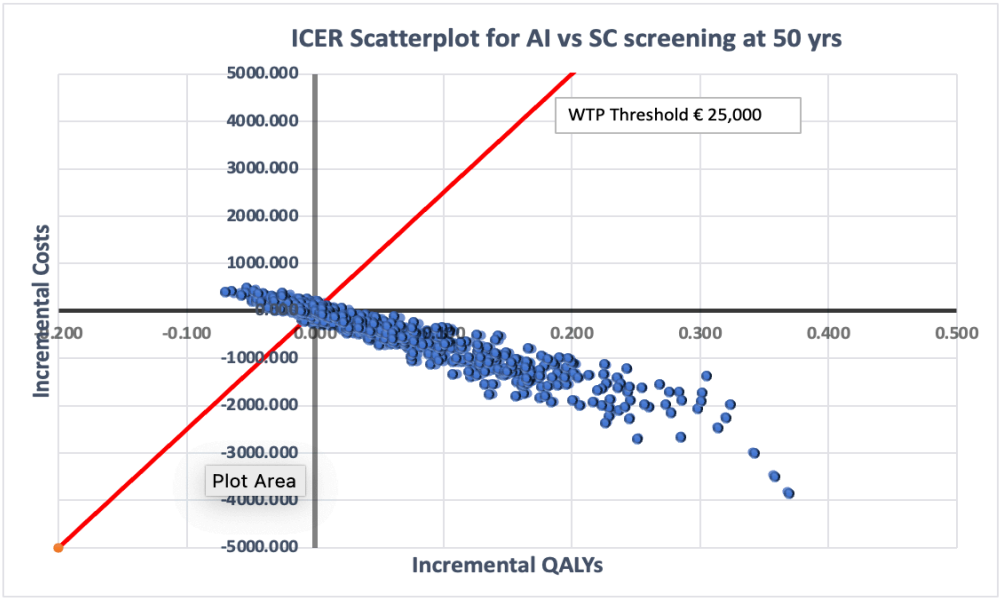


Figure 4: Cost-effectiveness plane showing direct comparison between AI assisted and standard colonoscopy for screening starting at 50 years.