Universitat de Girona
Facultat de Medicina

Final Degree Project

COLORECTAL CANCER SCREENING AMONG INDIVIDUALS AGED 40-49 YEARS

A randomised controlled field trial

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1. ABSTRACT

TITLE: Colorectal cancer screening among individuals aged 40-49 years

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BACKGROUND: Colorectal cancer (CRC) incidence and mortality have declined among older adults (age ≥ 50 years), principally due to the implementation of screening. In contrast, the incidence and mortality of CRC diagnosed before the age of 50, also known as early onset CRC (eoCRC), are increasing in several high-income countries across the globe, with the largest absolute increase among the 40–49 year-old group. Patients with eoCRC tend to present with a more-advanced stage and a less favourable prognosis. Although the American Cancer Society recommends screening from 45 years of age, this screening strategy is still not offered in Europe. Screening starting at the age of 40 may thus be a robust option to curb these worrisome trends.

OBJECTIVE: The main objective of this study is to assess If early screening using biennial faecal immunochemical test (FIT) strategy reduces eoCRC mortality at 5 years in 40–49-year-old men and women from the general population. Secondary objectives aim to evaluate screening results and complications, to assess eoCRC risk factors, and compare the quality of life between screened and unscreened patients with eoCRC.

DESIGN AND SETTING: This study was designed as a population-based, randomized, parallel, group, open field trial, aiming to compare screening vs not screening strategies. It will be a multicentric study conducted in the Primary Care Centres and 8 Hospitals of the Health Region of Girona.

METHODS: 20,236 participants will be enrolled using a consecutive sampling, the time of recruitment will be of 1 year. Participants will be randomised into two groups: 1) undergoing screening with biennial FIT followed by colonoscopy in case of a positive result, 2) not undergoing screening. The intervention will last for 4 years, and those patients diagnosed with CRC during the study will be followed for 5 years after the diagnosis. Major outcome variable will be CRC mortality at 5 years.

KEYWORDS: *age, colorectal cancer, early onset, screening, FIT, colonoscopy.*

2. ABBREVIATIONS

AJCC – American Joint Committee of Cancer

ASA PS - American Society of Anesthesiologists Physical Status

BHA – Basic Health Area

BMI – Body Mass Index

CA.19.9 – Carbohydrate antigen 19.9

CEA – Carcinoembryonic antigen

CEIC – Comitè d'Ètica d'Investigació Clínica

CIMP – CpG Island Methylator phenotype

CIN – Chromosomal Instability

CRC - Colorectal Cancer

CRF – Case Report Form

CRI – Central Registry of Insured

CT – Computed Tomography

CTC – Computed Tomography Colonography

eoCRC- Early Onset Colorectal Cancer

EORTC – European organization for Research and Treatment of Cancer

FIT- Faecal Immunochemical Test

FOBT – Faecal Occult Blood Tesst

gFOBT- guaiac-based Faecal Occult Blood Test

HDI - Human Development Index

HNPCC - Hereditary Non- Polyposis Colorectal cancer

HPs - Hyperplastic Polyps

HR – Health Region

IBD - Inflammatory Bowel Disease

IHC – Individual Health Card

MMR – Mismatch Repair

MRI – Magnetic Resonance Imaging

MSI – Microsatellite Instability

MSI-H – High-frequency Microsatellite Instability

NSAIDs – Non-Steroidal Anti-Inflammatory drugs

PCC – Primary Care Centre

PDPCCR – "Programa de Detecció Precoç de Càncer de Còlon i Recte"

PPV – Positive Predictive Value

QoL – Quality of Life

SEER – Surveillance Epidemiology and End Results

SPs - Serrated Polyps

SSPs - Sessile serrated polyps

TNM – Tumour, Node, Metastasis

TSA - Traditional Serrated Adenoma

WHO – World Health Organisation

3. INTRODUCTION

3.1. CONCEPTS AND DEFINITIONS

Colorectal cancer (CRC) is defined as the uncontrolled division of abnormal cells of the large intestine (including cecum, ascending, transverse and descending colon, sigma and rectum) arising from the mucosa and growing both into the lumen and bowel wall. Adenocarcinoma is the most frequent histological strain (90-95% of the cases) and will be the tumour we refer to when talking about CRC. The oncogenesis of colorectal tumors is a multifactorial process, consequence of the interaction of genetic, environmental, and behavioural factors involved in triggering a sequential accumulation of somatic mutations from a normal colonic stem cell (1,2).

The great majority of colorectal tumours are sporadic (70-80%) and only a small proportion of cases are secondary to hereditary forms (3-5%). Inherited CRC syndromes include Lynch Syndrome or hereditary nonpolyposis colorectal cancer (HNPCC) (2-5%), familial adenomatous polyposis (<1%), MYH-associated polyposis, serrated polyposis and hamartomatous polyposis syndromes (3). In addition, up to 20-25% of CRC cases reveal family history of CRC (one or more first degree relatives), suggesting the involvement of an unknown hereditary component, what is also named as familial CRC (4). About 1% of CRCs are secondary to inflammatory bowel disease (Ulcerative colitis and Crohn disease with colonic involvement (1).

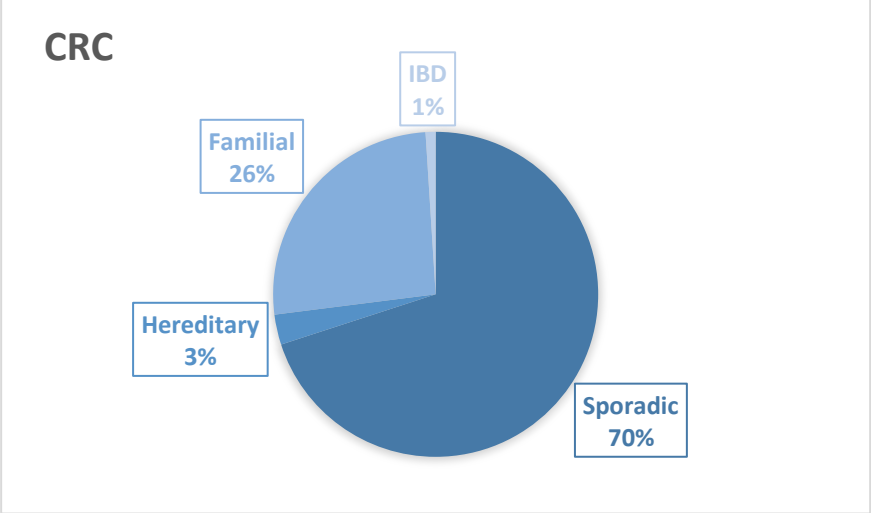


Figure 1- Colorectal cancer Distribution. The graph shows percentatges sporadic, familial, hereditary and IBD subtypes of CRC (1,3).

NOTE: **IBD (inflammatory bowel disease)*

CRC often affects elderly individuals. However, while the overall incidence rates have remained stable or even decreased, incidence and mortality of early onset colorectal cancer (eoCRC), defined as those cases of CRC diagnosed under 50 years of age, have been increasing worldwide. Although about 4% to 21% of eoCRC are related to HNPCC, the majority are sporadic (5).

3.2. EPIDEMIOLOGY

3.2.1. CRC STATISTICS WORLDWIDE

Colorectal cancer is the third most commonly diagnosed cancer and the second leading cause of cancer death worldwide for both sexes combined, with a total number of 1,880,725 new cases and 915,880 deaths in 2020 (6). Rates of CRC are higher in men than women for the majority of regions worldwide.

Incidence rates are closely linked to the territory, reaching rates up to 4 times higher in developed countries compared with underdeveloped countries, but revealing less variation when it comes to mortality rates mainly due to the worse prognosis found in the latter regions. The territories with higher rates of CRC show similarities in distribution, among which stand out European regions, Australia, New Zealand, North America, Hungary, and Norway. Significantly lower incidence rates of both colon and rectal cancer are found in regions like South Central Asia and Africa(4,6). Human development index (HDI) levels have been correlated with the incidence rates of CRC, and therefore CRC can be considered a socioeconomic marker. Classically, countries with higher HDI levels revealed higher rates of CRC incidence. This relation has been mainly attributed to the risk factors associated with western lifestyle habits, such as an excessive animal-source food intake, smoking, sedentarism, overweight, etc. In addition, incidence in “low-risk” and lower HDI countries has revealed an increasing trend reflecting a shift towards adopting similar unhealthy western lifestyle habits (6).

3.2.2. CRC STATISTICS IN SPAIN

CRC is the most frequently diagnosed cancer among Spanish population for both sexes, with 40,441 new cases in 2020 (14.3% in total), followed by prostate (34,613), breast

(34,088), lung (29,188) and bladder (18,512) (excluding non-melanoma skin cancer). Analyzing the incidence by sex, in 2020, CRC was the second most diagnosed tumor in men (24,619 new cases, 15% in total) only preceded by prostate, and the second leading cause of cancer in women (15,831 new cases, 13.3% in total) only preceded by breast cancer. Likewise, focusing on prevalence, CRC was the third most prevalent tumor among general Spanish population (118,922 5-year prevalent cases), behind prostate and breast cancer. For this reason, CRC must be considered a Public Health issue threatening our population (7,8).

CRC is the second leading cause of cancer death in Spain (8), for both men and women, and was responsible for 14,670 deaths in 2020 (7). The average survival rate in Spain is similar to other European countries with an estimated 5-year survival rate of approximately 50% (9). The prognosis of the disease depends on the stage at the time of diagnosis, ranging from 90% in the earliest stages to 15% in metastatic disease. Therefore, the trend towards a stability in terms of survival may not only be due to improved treatments, but in part to the advances in early diagnosis with screening techniques (10).

Marked differences of incidence and mortality can be found among Spanish territories; Catalonia is the second Autonomous Community with the highest incidence of CRC, with a total number of 2,070 new cases registered in 2017 (only considering population between 50 to 69 years), and it was only preceded by Andalucía that registered up to 2.252 new cases that same year for the same age population. Analysing the incidence in Catalan territories, in 2017 the province of Girona was in second place after the province of Tarragona, with 114 new cases of CRC per 100,000 individuals exceeding the national average incidence rate (112 new cases/100,000 individuals in 2017). In terms of mortality, Catalonia registered a total number of 624 deaths for CRC in 2017, being the second Autonomous Community with major mortality rates for CRC, only preceded by Andalucía. Mortality rates in the province of Girona were significantly better than the rest of the Catalan provinces and did not overpass the national average (>34 CRC deaths/100,000 individuals in 2017), with a ratio of 25 deaths per 100,000 individuals in 2017 (11). Mortality in Catalonia has declined globally since the implementation of

screening strategies, and Girona is the province with the most significant mortality decrease since the start of screening in 2013 (12), going from 41 deaths per 100,00 individuals in 2014 to 25 deaths per 100,000 in 2017 (Table 1). In conclusion, Girona presents high incidence for CRC overpassing the national average, but at the same time presents mortality rates significantly lower than the rest of Spanish territory. The territories experiencing this same phenomenon are the ones with higher coverage and participation in CRC screening programs. This reveals that screening strategies allow a correct (and early) detection of CRC new cases and that these do not necessarily end up in death, which would be the optimal and desirable scenario for every territory (11).

Table 1– Mortality evolution from 2014 to 2015 (population between 50 and 69 years old in the Catalan Provinces) (11)

	TOTAL DEATHS				DEATHS PER 100,000 INDIVIDUALS			
	2014	2015	2016	2017	2014	2015	2016	2017
Barcelona	485	512	458	465	38	39	35	35
Girona	71	47	46	47	**41**	**26**	**25**	**25**
Lleida	38	35	43	44	38	34	41	41
Tarragona	66	76	67	68	36	40	35	35

3.2.3. TRENDS AND EVOLUTION OF CRC

Over the last decades most “high-risk/ high-income” countries showed a decline in CRC incidence and mortality. Meanwhile, “low-risk” countries, revealed and increasing trend when it comes to incidence and mortality for CRC, probably due to the adoption of less healthy lifestyles (6,13).

The overall decline of CRC incidence and mortality in some high-risk countries involves particularly adults over 50 years. This decline is partly attributed to the improvements in treatments (12%), the raising awareness of healthier lifestyles and the changing patterns in risk factors (35%), but mostly to the uptake of CRC screening strategies (53%) (13).

3.2.4. AGE SPECIFIC INCIDENCE AND MORTALITY TRENDS

CRC incidence trends overall, reflect the majority of cases occurring among older age groups (>50 years). This fact can easily mask the worrisome increasing trends of early

onset colorectal cancer experienced in some high-income territories. Early onset colorectal cancer (eoCRC) is the term used to describe the cases of CRC affecting adults before the age of 50 years, which is widely considered the optimal age for initiating CRC screening for individuals at average risk. Since 1990, in the United States it has been observed that CRC incidence rates have been increasing in adults under the age of 50 years (Fig.2). This pattern is subjected to a so-called "birth cohort effect" because generations of individuals with a higher incidence of CRC carry this risk as they age. In fact, this effect has started to become more evident among the US population who are also experiencing a CRC increase in the ages 50-65 years, after decades of decline (Fig.2) (13–15).

Although a subset of eoCRC patients harbour highly penetrant germline mutations, most cases of eoCRC are sporadic (80%) (16). Up to 75.5% of the eoCRC cases affect individuals in the 40-49 age range, with the median age of diagnosis being 44 (17).

Mortality trends are also modified by age. In those age groups that fall within the screened population (>50 years), mortality has decreased sharply since the implementation of screening strategies (18). In contrast, the overall CRC mortality has generally increased for individuals under 50 years of age (Fig.2). These differences are mainly due to the delayed diagnosis in younger patients, as when mortality is stratified by stage, younger patients (<50 years) have better prognosis than older patients (19,20).

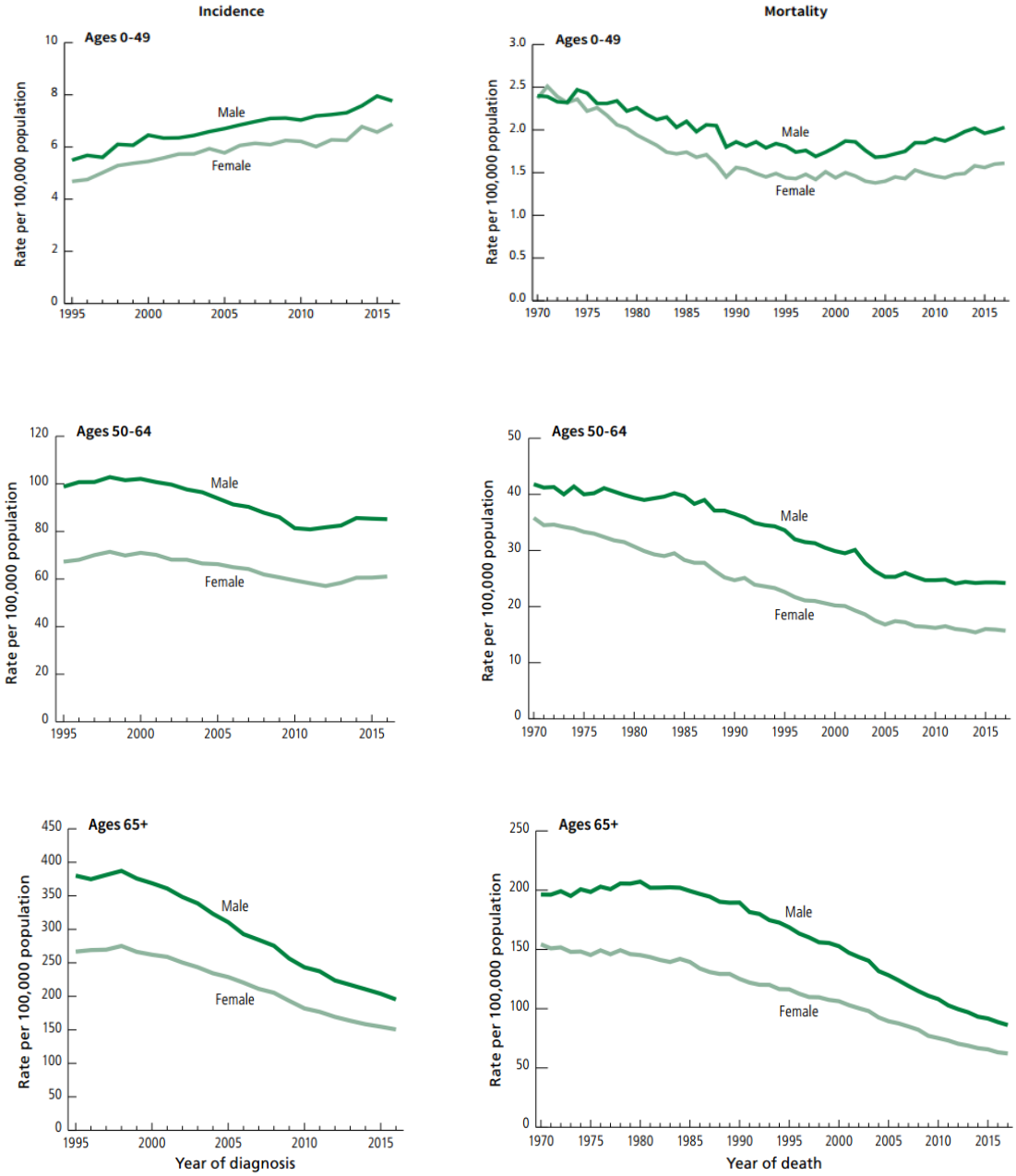


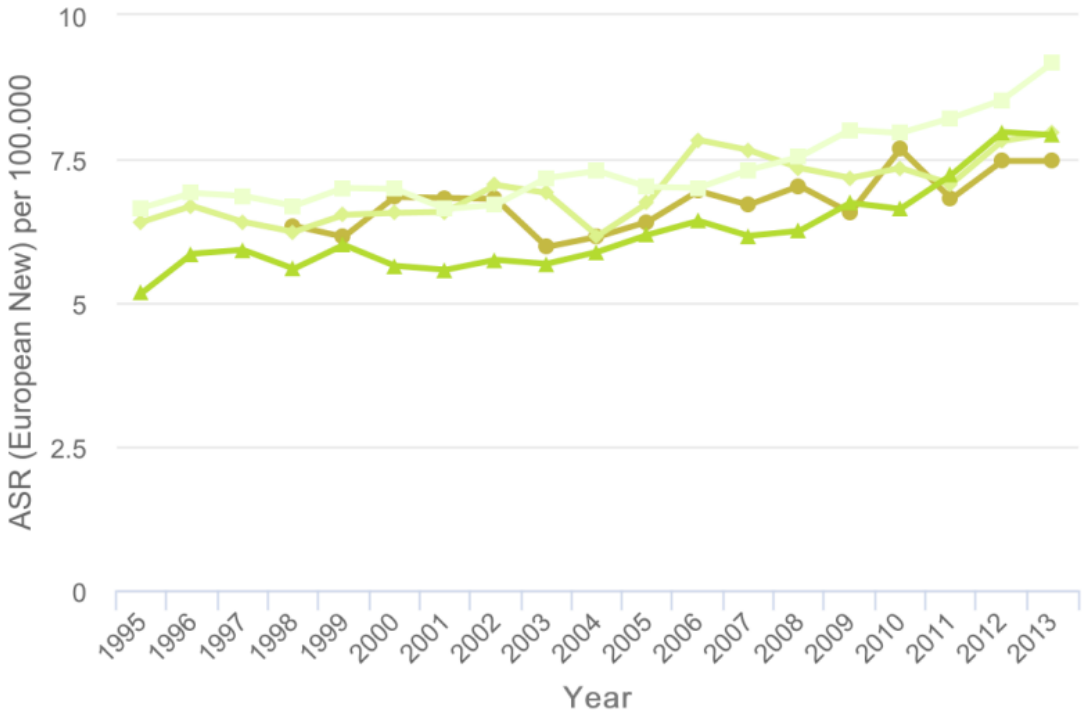
Figure 2- Trends in CRC Incidence (1995-2016) and Mortality (1970-2017) Rates by Age and Sex, in the US.

Source: The American Cancer Society - Facts and Figures 2020-2022 (14).

Note: Rates are age adjusted to the 2000 US standard population

The most recent data from the US population (2012-2016) indicate a 2.25% annual increase in CRC in patients under 50 years of age, which contrasts clearly with the 3.3% annual decrease observed in patients over 65 years of age (20). These trends are not only observed in the United States, but are also beginning to be seen in other developed

western alike regions (Australia, Canada, etc.) and European countries like the Netherlands, Finland, Sweden, Germany, UK, and Denmark (Fig.3) (6,21,22).



Indicator	Registry	Sex	Cancer	Age Group
Incidence	DE Berlin et al	Both sexes	Colon, rectum, and anus	10-49
Incidence	DK Denmark	Both sexes	Colon, rectum, and anus	10-49
Incidence	NL Netherlands	Both sexes	Colon, rectum, and anus	10-49
Incidence	UK England	Both sexes	Colon, rectum, and anus	10-49

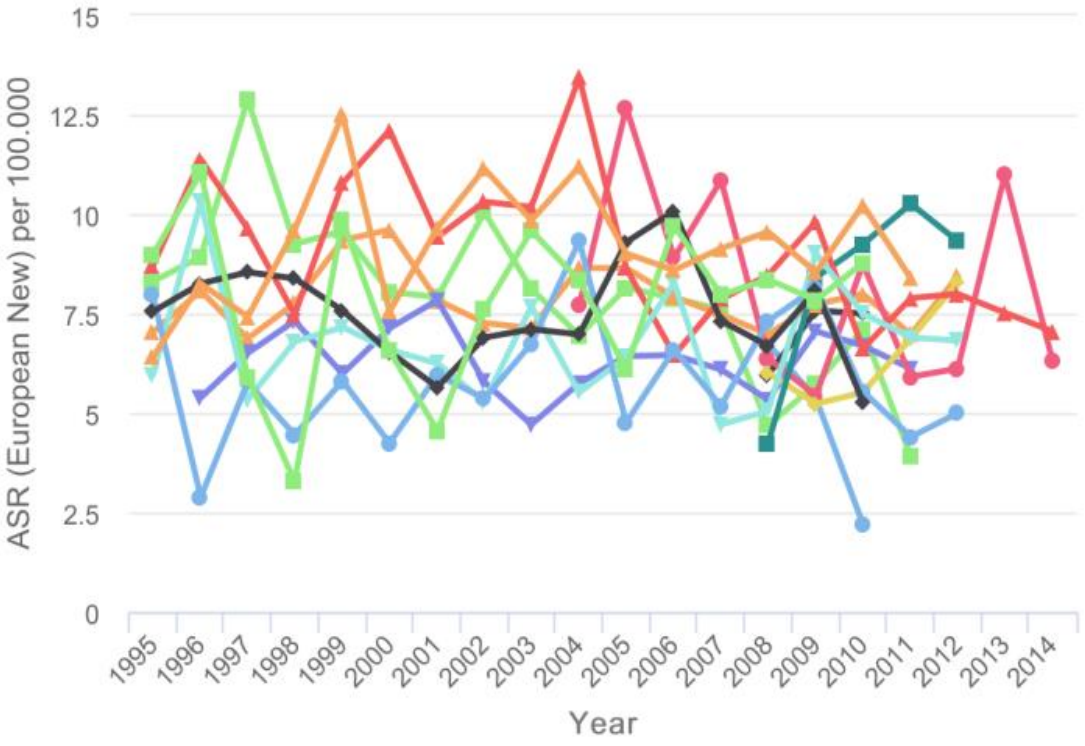
Figure 3 Trends in CRC* Incidence rates for both sexes, in 4 European Countries, among individuals aged 10-49 by period (1995-2013) ***.**

Source: European Cancer Information System (ECIS) from incidence and mortality historical data explorer

Note: Rates are age adjusted to the new European Standard Population.
**Anal cancer is also included in the represented data.*
*** Only Netherlands, Denmark and England had a unique global register at a national level, in contrast to Germany where the available information was disaggregated for cities or regions. To facilitate the interpretation of this figure it has been decided to represent Germany using Berlin's data available, the most representative territory in terms of population density.*
****Notice how the information available from the registers only reaches up to 2013.*

The data available from oncology registries in Spain do not show a significant trend towards an increase of CRC incidence among patients under 50 years of age (23). Prior to the assessment of CRC incidence trends, it should be noted that oncology registries in Spain are scarce, and information is only available for a few territories (Fig.4). The data from the Girona registry of cancer (24), despite being one of the most complete in

the country, does not provide information on the overall trend of eoCRC. In addition to this fact, we must emphasise that the latest available records correspond to years prior to 2014 and comparative data for recent years is lacking. All this prevents us from knowing for sure what direction eoCRC is taking in Spain (Fig4.).



Indicator	Registry	Sex	Cancer	Age Group	
Incidence	ES Albacete	Both sexes	Colon, rectum, and anus	10-49	
Incidence	ES Asturias	Both sexes	Colon, rectum, and anus	10-49	
Incidence	ES Balearic Islands	Both sexes	Colon, rectum, and anus	10-49	
Incidence	ES Basque Country	Both sexes	Colon, rectum, and anus	10-49	
Incidence	ES Canary Islands	Both sexes	Colon, rectum, and anus	10-49	
Incidence	ES CastellÃ³n	Both sexes	Colon, rectum, and anus	10-49	
Incidence	ES Ciudad Real	Both sexes	Colon, rectum, and anus	10-49	
Incidence	ES Cuenca	Both sexes	Colon, rectum, and anus	10-49	
Incidence	ES Girona	Both sexes	Colon, rectum, and anus	10-49	
Incidence	ES Granada	Both sexes	Colon, rectum, and anus	10-49	
Incidence	ES La Rioja	Both sexes	Colon, rectum, and anus	10-49	
Incidence	ES Murcia	Both sexes	Colon, rectum, and anus	10-49	
Incidence	ES Navarra	Both sexes	Colon, rectum, and anus	10-49	
Incidence	ES Tarragona	Both sexes	Colon, rectum, and anus	10-49	

Figure 4- Trends in CRC* incidence rates for both sexes in 14 Spanish registries among individuals aged 10-49 by period (1995-2014)

Source: European Cancer Information System (ECIS) from incidence and mortality historical data explorer (22).

Note: Rates are age adjusted to the new European Standard Population.

**Anal cancer is also included in the represented data.*

When assessing the trends in the rates of incidence stratified by age group in Girona and Tarragona, it can be seen that in both areas the group most affected by eoCRC is by far the one between 40 and 49 years of age. On the contrary, there are discrepancies in the trends, as in Tarragona there is an upward trend in the number of cases of eoCRC, while in Girona the phenomenon is the opposite (Fig.5). The same heterogeneity is observed among the rest of the Spanish communities (22).

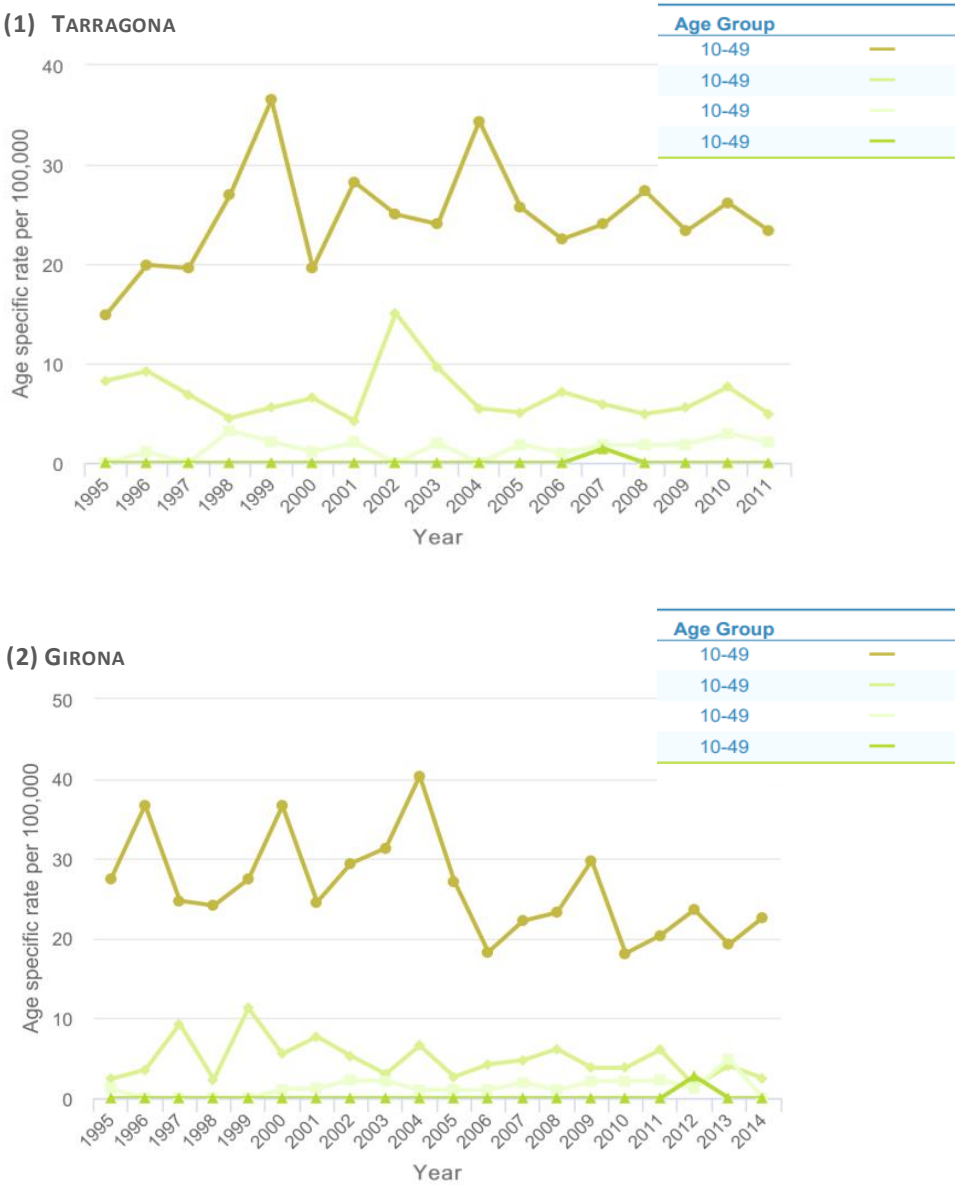


Figure 5- Trends in CRC* incidence rates for both sexes in Tarragona (1) and Girona (2) among individuals aged 10-49 stratified by 10 year age group.

Source: European Cancer Information System (ECIS) from incidence and mortality historical data explorer (22)

*Note: *Anal cancer is also included in the represented data.*

It is thought that the overall increasing trends of eoCRC may reflect the adoption of CRC risk factors from earlier ages, or the exposure to other factors that remain to be understood. However, the reason for this increase is still unknown, which makes primary prevention specific measures difficult to apply.

3.3. CARCINOGENESIS (AETIOPATHOGENESIS)

The majority of sporadic CRCs cases derive from a precursor lesion, specifically from some types of colorectal polyps. A polyp is a non-malignant growth that develops in the inner lining of the colon or rectum mucosal layer. These lesions are very common among the general population and can be found in 50% of average-risk individuals undergoing a colonoscopy. Initially polyps are benign, but with years they can potentially progress to invasive cancer (adenocarcinoma). Most polyps are completely asymptomatic, and usually only manifest with silent or minor bleeding. Only 10% of polyps are estimated to undergo this progression which usually occurs slowly over 10-15 years, offering an ample threshold wide to detect and remove them (1,25,26).

From a morphological point of view, polyps can be classified using *The Paris endoscopic classification for neoplastic lesions* (Fig.6) (ANNEX 1). This classification was designed in order to estimate the invasion of submucous layer. According to this classification colorectal lesions can be (25,27,28):

- **Polypoid:** its size is directly proportional to the risk of invasive adenocarcinoma. It is further divided in: Pedunculated (Ip), Sessile (Is).
- **Non-polypoid:** associated (regardless of size) with a major risk of invasive adenocarcinoma. It is further divided in: Flat elevated (IIa), Flat (IIb), Flat depressed (IIc), Excavated (III) .(25,28)

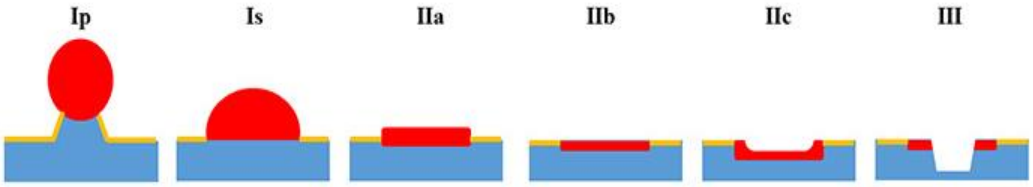


Figure 6– Summary of the morphological classification (25,28)

From a histological point of view, and according to their intrinsic risk of malignancy, polyps can be classified into the following groups (29):

- **Non-neoplastic polyps**, lacking malignant potential:
  - **Hyperplastic polyps (HPs),** nowadays classified as a subtype of serrated polyps with no potential for malignant progression. It is considered to be the most common polyp subtype, typically found in the sigma-rectum among older individuals (60-70 years).
  - **Inflammatory polyps**, also known as pseudopolyps, are the result of the regeneration process of inflammatory points. They are associated with inflammatory bowel disease (IBD), infectious or ischemic colitis and rectal ulcer syndrome.
  - **Hamartomatous polyps** are the result of the proliferation of mature mucosal cells. Solitary lesions are not related to malignant progression. Nonetheless, those associated with hamartomatous polyposis syndromes (Peutz-Jeghers syndrome, Cowden disease, Juvenile polyposis, etc) can potentially progress to malignant tumours.
- **Neoplastic polyps**, potential forerunners of colorectal cancer. These are the target lesions of screening programs.
  - **Serrated polyps (SPs):** so-called because of its saw-toothed appearance under the microscope. Based on biological characteristics, serrated polyps can be further subdivided into sessile serrated polyps (SSPs), traditional serrated adenomas (TSA), and HPs. The latter are usually millimetric lesions located in rectum-sigma, and they are not considered to have malignant potential (as long as they meet the characteristics mentioned). Like adenomas, SSPs, TSAs and only large HPs are associated with higher risk of CRC progression. Serrated polyps are considered to be responsible for 20-30% of CRC. The malignant pathway followed by serrated polyps is known as the “serrated pathway” (30,31).
  - **Adenomatous polyps (AP) (i.e, adenoma)** are the most frequent precancerous lesions among the average risk population, up to 80% of CRC come from adenomas. These lesions are the result of epithelial proliferation showing some grade of dysplasia. According to its histology, adenomas can be

classified as tubular (70%), villous (5-10%) and tubulo-villous (10-25%). As commented before, approximately 10+/-5 years are required for malignant transformation to adenocarcinoma, therefore, early endoscopic detection is an effective strategy to reduce the incidence of CRC. The malignant pathway followed by adenomas is the traditional carcinogenic pathway of chromosomal instability (CIN) (26,29).

Not all neoplastic polyps have the same risk of malignancy, the factors related to malignant transformation are shown in Table 2. The follow-up plan for resected polyps will be modified depending on the presence of these factors (25,32).

	CRC risk	Size	Number	Histological subtype	Dysplasia
ADENOMAS	Low	<10mm	≤4 adenomas	Tubular	Low grade
	High	≥10mm	>4 adenomas	Villous	High grade
SERRATED POLYPS	Low	<10mm	≤4 serrated	-	Low grade
	High	≥10mm	>4 serrated	-	High grade

Table 2 - Factors related to polyp malignant transformation. *Made by the author.*

3.3.1. CARCINOGENIC PATHWAYS

Sporadic CRC is the result of consecutive genetic events from a normal colonic stem cell. As mentioned before, although only a small proportion evolve to cancer, adenomatous polyps are considered to be the principal source of sporadic CRC (80%). The adenoma-carcinoma sequence has become the paradigm of CRC carcinogenesis and it is also known as chromosomal instability (CIN) (Fig.7), suppressor pathway or carcinogenic traditional pathway. Understanding this process and its timeline, has become one of the key pillars supporting the usefulness of screening strategies (26,30).

Adenoma's formation starts with a somatic mutation of APC suppressor gene that results in an aberrant dysplastic crypt focus on the glandular colon epithelium with malignant transformation potential. This process is the result of a slow gradual growth, in which other genetic alterations of oncogenes and tumour suppressor genes are added, such as: K-RAS and SMAD4-SMAD2 mutations, in charge of apoptosis prevention

and cell growth promoters, or p53 mutation, that typically appears on final stages of the process, and it is responsible for the final formation of carcinoma. The accumulation of these genetic mutations, in conformity with chromosomal instability, allows the transition from healthy intestinal lining towards the formation of a benign polyp, later passing to high-grade adenoma and finally transitioning to adenocarcinoma (26).

Alternatively, the microsatellite instability (MSI) pathway (Fig.7), despite being the paradigm of Lynch syndrome or HNPCC, has also been related to 15% of sporadic CRC. This pathway is the result of a DNA mismatch repair (MMR) deficiency that results in a strong mutator phenotype and high-frequency microsatellite instability (MSI-H). MSI-H is characterized by length alterations within simple repeated sequences, microsatellites. Lynch syndrome is primarily due to germline mutations in one of the DNA MMR genes: mainly MLH1 and MSH2. Germline hemiallelic methylation of MLH1 has been also reported to be an epigenetic cause of Lynch syndrome. The accumulation of microsatellite sequences in the genome can produce a loss of functionality of tumour suppressor genes leading to the formation of an early adenoma, BRAF mutation followed by alterations of the genes TGFBR2, IFG2R and BAX, participate in the progression toward intermediate and late stages of carcinogenesis (Fig.7) (3,33).

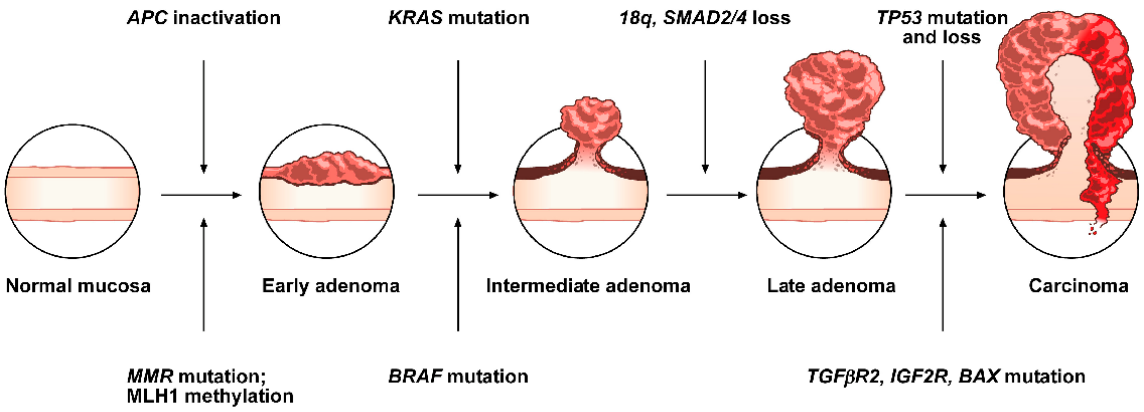


Figure 7 - Conventional adenoma-to-carcinoma sequence. Representation of CIN pathway above and MSI pathway underneath (30).

As mentioned before, serrated polyps are the result of another carcinogenic pathway known as the CpG island methylator phenotype (CIMP) or serrated pathway. CIMP is a substrate pathway of colorectal cancer, characterised by the hypermethylation of promoter CpG island sites, resulting in the transcriptional inactivation of tumour suppressor genes and the formation of serrated polyps with malignant potential (31).

High grade neoplastic polyps with carcinomatous cells that have not yet begun to invade the muscularis mucosa, and therefore have a lack of dissemination potential, are known as in situ carcinoma (i.e, intramucosal carcinoma). On the other hand, if a lesion overpasses the muscularis mucosa and extends to the submucosa layer, achieving dissemination capacity, it becomes an invasive carcinoma (cancer) (25,29) .

3.3.2. CARCINOGENESIS OF EARLY ONSET CRC

The pathogenic and genetic basis of most eoCRCs remains unknown. Some studies have reported that eoCRC may have a characteristic molecular profile and may be due to the cumulative effect of multiple genetic variants with different penetrance.
However, to date this information remains inconclusive and most cases appear to follow the same carcinogenic pathways as sporadic CRC, such as the classic adenoma-carcinoma sequence (19,34).

3.4. CRC RISK FACTORS

Several personal and environmental factors have been related to CRC development and therefore have been considered to enhance the carcinogenesis pathways mentioned above. More than a half (55%) of all CRC cases diagnosed in western countries are attributable to potentially modifiable unhealthy lifestyle factors. Non-modifiable factors have also been related to CRC, this group includes heredity and medical history such as family history of adenomas or CRC and personal history of IBD (1,14).
Understanding the implication of these factors in the physiopathology of the disease is key to devise efficient primary prevention strategies with the aim to reduce CRC incidence and to classify individuals according to their risk level (1).

3.4.1. NON-MODIFIABLE RISK FACTORS

- **Age:** The risk of CRC increases with age similarly to the rest of the cancers. 90% of CRC are diagnosed in patients over 60-70 years old. The incidence rates of CRC double for every 5-year age group until 50 years, afterwards the incidence raises by 30% approximately. The median age of CRC diagnosis in Spain was 68 years in men and 72 in women in 2020 (8). However, incidence data from US SEER database and other Western cancer registries reveals that the median age group at diagnosis is becoming younger, shifting from a median age of 72 years in 2000 to 66 years in 2020 (21,35), a trend that Spain could also follow in the coming years. The reasons underlying this trend may be multifactorial, where both, genetic influences and environmental and lifestyle exposures, contribute. However, no unique risk factor or specific combination of them have been associated with this phenomenon yet (19,36).
- **Sex:** CRC incidence rates are 30% higher in men than women. The disparity observed between men and women is probably due to different risk factor exposures (e.g, smoking) and sex hormones influence. However, lifetime risk for both sexes is similar because women have a longer life expectancy. About 4,4% of men and 4,1% of women will be diagnosed with CRC during their lifetime (13). CRC incidence rates among men and women under 50 years are similar (37).

HEREDITY, FAMILY AND PERSONAL HISTORY

- **Family History:** as mentioned before, 25% of the patients with CRC reveal a family history of the disease. First degree relatives of patients with CRC have 2 to 4 times the risk for developing the same disease, this risk increases when CRC is diagnosed before the age of 50 and/or when multiple relatives are affected. For this reason, family history is considered to be an important actionable risk factor, and therefore early screening at age 40 is indicated in individuals with first degree relatives (parent, sibling, or child) affected by CRC (38).
- **Hereditary syndromes:** 10% of CRC cases are due to an inherited gene mutation. Half is associated with a high-risk hereditary condition and the rest with moderately increased risk.
    - **Lynch syndrome:** responsible for 3% of all CRCs. Lynch Syndrome (i.e. HNPCC) is considered to be the most common inherited cause of CRC. As mentioned

before, this condition follows the MSI pathway of carcinogenesis, and apart from CRC many other cancers are also at increased risk such as endometrial, ovarian, stomach, urinary bladder, and female breast. Around 20% of the individuals affected by high-risk genes (MLH1 or MSH2) mutations will develop CRC by age of 50, and 40% by the age of 70 (1). Despite the median age of CRC among these individuals is 61 years, 8% occur in adults under the age of 50. Therefore, germline genetic testing and genetic counselling should be initiated as appropriate for any case of eoCRC (39). However, due to the high prevalence of this heredity form, every patient with CRC is screened for this condition using immunohistochemistry techniques for reparative proteins.

  - **Polyposis syndromes:** group of hereditary conditions related to higher CRC risk. Familial adenomatous polyposis (FAP) is the most common type among them and represents about 1% of all CRCs. The carcinogenic pathway is led by a mutation in the APC suppressor gene, which causes the development of up to thousands of colorectal polyps in younger ages (2^{nd}-3^{rd} decades of life). The majority of these mutations are inherited, however, about 10% can appear spontaneously and therefore these patients do not always reveal familiar history (29). Other colorectal polyposis less prevalent but also related to an increased risk for CRC include Peutz-Jeghers syndrome, juvenile polyposis syndrome, and serrated polyposis syndrome. All of them are also causes of eoCRC, therefore genetic testing for these conditions must be performed in patients under 50 years with CRC (40).
  - **BRCA1 and BRCA2:** despite their influence on CRC risk is not well established, it is estimated that BRCA1-2 carriers have a 50% increased risk to develop CRC. Approximately 1% of CRC patients under the age of 50 are positive for these mutations and for this reason must be also ruled out in the gene panel study of eoCRC (41).

- **Personal medical history**
  - **Personal history of cancer:** individuals with personal history of CRC are more likely to redevelop the same disease, this risk intensifies with an initial diagnosis at young age, yet a second primary colorectal tumour will only be

developed by 2% of these patients. Increased risk for CRC is also related to personal history of adenomas, and this risk increases along with the number and size of the polyps (42). CRC risk is also higher among individuals with a history of other cancers, mainly due to the carcinogenic effects of some oncologic treatment. Childhood cancer survivors who received pelvic/abdominal radiotherapy, men with prostate cancer treated with radiotherapy, or certain chemotherapy drugs (e.g., cisplatin, procarbazine) are some of the examples (43).

- **Chronic inflammatory bowel disease (IBD):** IBD has also been associated with CRC , particularly ulcerative colitis and Crohn's disease with colonic involvement. Due to prolonged and repetitive episodes of colorectal inflammation, individuals with IBD present almost two times the risk of developing CRC compared the general population (1,44). The incidence of CRC in these patients have decreased in the last decades due to the use of effective medication to control and prevent inflammation, as well as the implementation of specific screening strategies to detect premalignant lesions (45).
- **Diabetes:** A slightly increased risk for CRC has been detected among individuals with type 2 diabetes, and this association remains the same after considering other shared risk factors like body mass index, physical activity, etc. (46).

3.4.2. MODIFIABLE RISK FACTORS

- **Physical inactivity:** Sedentarism is strongly related to a higher risk of colon but not rectal cancer. Studies reveal that physically active people have around 25% lower risk of developing a colonic tumour, and this relation may improve in individuals being physically active from young ages. The same effect is observed among individuals becoming active later in life may reduce their risk, too (47). In addition, physically active patients diagnosed with CRC who continue with regular physical activity are less likely to die from the disease than those who were and remain less active.

- **Overweight and obesity:** excess of body weight, especially obesity, is a risk factor strongly related to CRC even in individuals who are physically active. Body fatness is typically measured using the body mass index (BMI), considering overweight a BMI range between 25.0 – 30.0 Kg/m^2 and obesity a BMI from 30.0 Kg/m^2 upwards (1). Abdominal fat seems to be more important than overall body weight, therefore other measurements could be used to identify high-risk patients like waist circumference or waist-to-hip ratio. Studies suggest that the influence of body fatness in CRC can depend on the timing of exposure, demonstrating a stronger influence for overweight and obesity during adolescence among women, but later in life for men. Excess body weight also plays a relevant role in the CRC prognosis reducing the likelihood of survival (48).
- **Diet:** dietary patterns influence CRC risk both indirectly, through overweight and obesity, and directly through specific nutritional elements. Diets enriched with certain foods, like processed sugar, red meat or carbohydrates promote inflammation and are associated with higher risk of CRC (49). Additionally, diet influences the composition of microbiomes inhabiting the large intestine. Microbiome has become an important area of research, as it is implicated in both preventing and promoting CRC through its influence on inflammation and immune response (50). Summarising the current evidence of dietary elements linked to CRC:
    - **Diary/Calcium:** Adequate calcium intake from dairy foods (700-1000 mg daily) is considered to be a protective factor against CRC (49).
    - **Whole grains/Fibre:** despite the reasonable idea that fibre may reduce CRC risk by allowing less exposure to carcinogens due to a faster transit and a larger stool volume, studies still remain inconclusive, and associations are weak. Evidence associated with whole grains is stronger than fibre itself, and has been considered to decrease CRC risk by 5% for every 30 g/day intake (49,51).
    - **Fruits and vegetables:** The majority of the studies assessing the relation between fruits and vegetables intake with CRC risk have shown inconsistent results. Some studies revealed a higher risk for CRC among individuals with

low intake (<300 g/day) and no further risk reduction is observed among patients with intakes over 700g/day (51).

- **Red and processed meat:** red meat refers to all mammalian muscle meat (including beef, pork, etc) and processed meat refers to meat that has been transformed through salting, curing, smoking, or other processes. Strong associations have been established for red and/or processed meat consumption and the risk of CRC. CRC risk increases by 18% for every 50 g/day of processed meat and by 12% for every 100 g/day of red meat (52). In 2015 the WHO classified processed meat as carcinogenic to humans (alongside with tobacco) and red meat as probably carcinogenic (53). Due to the concerning increase of meat consumption (especially in Western countries) The Cancer Prevention Recommendations, among other guidelines, advises to limit the consumption of red meat to no more than about three portions per week (equivalent to 350-500 grams) and to consume little, if any, processed meat (49,52).
- **Vitamin D:** association between CRC and vitamin D levels still remain inconsistent. However, a recent meta-analysis revealed a reduced risk of CRC among women with higher blood levels of vitamin D (25(OH)D up to 100 nmol/L) and a 37% increased risk among those with vitamin D deficiency (54). Further studies are needed in order to help clarify the implication of vitamin D supplementation on cancer prevention.

- **Smoking:** In 2009, The International Agency for Research on Cancer released a statement reporting that there is sufficient evidence to consider tobacco smoking as a direct cause of CRC (55). CRC risk among current smokers is about 50% higher than that in never smokers, and approximately 12% of CRC overall is attributed to cigarette current or former smokers (56). Smoking has also been related with the development and aggressiveness of adenomas, as well as a lower CRC specific survival, especially for current smokers (1).
- **Alcohol:** A meta-analysis including 66 studies about CRC and alcohol consumption determined association for both moderate (12,5-50 g/day) and high (>50g/day) alcohol consumption with a higher risk to develop CRC, as well as polyps (1,57).
-

- **Medications**
    - **Nonsteroidal anti-inflammatory drugs (NSAIDs):** long term use of acetylsalicylic acid and other NSAIDS is strongly proven to be related to a lower risk to develop CRC. A study released by Rothwell et al. revealed that the 20-year incidence of CRC was reduced by about 30% by treatment of high-dose (>500mg) acetylsalicylic acid for about 5-years(58). Survival improvement was also observed. However, guidelines currently do not recommend the use of NSAIDs for CRC prevention due to the potential side effects (especially gastrointestinal bleeding) associated (1,14).
    - **Hormones:** There is inconsistent evidence regarding the association between natural and/or exogenous steroid hormones and CRC. Some studies revealed that postmenopausal women with higher natural estrogens levels as well as hormone replacement therapies combining estrogen and progesterone formulations present reduced CRC, however other studies have found no association (59,60).
    - **Antibiotics:** recent studies pointed that oral antibiotic overuse could be related to higher risk of CRC, by disrupting the balance of gut microbiome and promoting the growth of proinflammatory bacteria strains. A recent study revealed that antibiotic use increased colon cancer risk after the minimal use of antibiotic with anti-anaerobic activity. Another study revealed that long-term antibiotic use (>2 months) in early middle adulthood (20-39 years) was associated with increased risk of colorectal adenoma (61). In contrast, the use of antibiotics for long periods of time (>60 days) was associated with a reduced risk for rectal cancer (62). This data suggests substantial heterogeneity in the pattern of the antibiotic's effects, and further studies are needed to describe the magnitude of this factor.
    - **Other drugs:** Some studies suggest that bisphosphonates (used for osteoporosis treatment and prevention) could reduce CRC risk (63).
- **Socioeconomic status:** Individuals with lower socioeconomic status are 40% more likely to be diagnosed with CRC compared to those with a higher socioeconomic status. Approximately, up to 50% of this difference can be attributed to differences

in the exposure of CRC risk factors (e.g., overweight, smoking), the rest has been related to differences in screening participation (64).

Table 3- Relative risk for established colorectal cancer risk factors (14)

	Relative risk
Heredity and Medical History	
Family history of CRC	
- 1 or more first degree relatives	2.2
- 1 or more first degree relatives diagnosed before age 50	3.6
- 2 or more first-degree relatives	4.0
- 1 or more second-degree relatives	1.7
Inflammatory Bowel Disease	1.7
Type 2 diabetes	1.4
Modifiable factors	
Heavy alcohol (>3 drinks /day)	1.3
Obesity (BMI>30Kg/m^2)	1.3
Red meat (100g/day)	1.1
Processed meat (50g/day)	1.2
Smoking	
- Current vs. Never	1.5
- Former vs. Never	1.2
Factors that decrease risk:	
- Physical activity	0.7
- Dairy (400g/day)	0.9

Note Relative risk compares the risk of disease among people with a particular "exposure" to the risk among people without that exposure. If the relative risk is more than 1.0 then the risk is higher among exposed than unexposed persons. Relative risks less than 1.0 indicate a protective effect. Dietary factors compare the highest with the lowest consumption.

3.4.3. eoCRC RISK FACTORS

The above points are well-established risk factors for CRC in general and their specific contribution to eoCRC still remains unknown (39). However, the following worrisome trends have been observed:

- Obesity, type 2 diabetes and metabolic syndrome have increased among young adults (65).
- The adoption of poor dietary habits and the consumption of fast food has increased up to 3-5 times among children and teenagers (52).
- A lowering of the CRC age onset has been associated with smoking (66).
- Body weight excess has also been related with eoCRC. A Nurses' Health Study released in 2019 revealed that obesity (BMI $\geq$30 kg/m^2) was independently associated with a nearly two-fold greater risk for eoCRC among women (67).

- Patients with IBD present higher risk to develop CRC at earlier ages (44).

These trends may explain part of the increased incidence of CRC in younger adults, but further studies are needed for a better insight into the pathogenesis of eoCRC.

3.5. CLINICAL AND PATHOLOGICAL FEATURES

CRC symptoms and signs are nonspecific, and early stages of the disease often remain asymptomatic reaffirming the important role that screening plays in the prognosis of the disease. CRC symptoms usually manifest only in large tumours and/or relatively advanced stages of the condition and may not be specific for colorectal cancer which can easily lead to a delayed diagnosis and a worse prognosis of the disease. The variety of symptoms depend on the location and stage of the tumour, the most common are: changes in bowel habits, general or localised abdominal pain or discomfort, and lower GI bleeding (either as visible rectal bleeding, hematochezia, melena or faecal occult blood loss) that can lead to anaemia. Like any other neoplastic process individuals can typically manifest a constitutional syndrome (unintentional weight loss, anorexia and fatigue) (1,2,14).

Up to 86% of average-risk patients under the age of 50 with CRC have been diagnosed after presenting symptoms (17). A review of 55 articles by O'Connell *et al.* revealed that rectal bleeding (50,8%) and abdominal pain (32,5%) are the most frequent symptoms among young adults because of a preponderance of left-sided tumours among younger patients. When compared to patients over 50 years, young patients are more likely to have left-sided tumours (20% vs 31.1%) and rectal cancer (22,4% vs 31,2%) (68).

The majority of the symptoms presented by patients with eoCRC were attributed to benign conditions such as haemorrhoids or irritable bowel syndrome, and up to 21% of these symptoms were present for more than 6 months (21). This, along with the lack of screening among younger individuals, could explain the trend of eoCRC to present at more advanced stages: 71,5% of eoCRC presented as stages III or IV disease compared to 62,5% of individuals diagnosed over 50, and 61,2% of young onset patients had metastatic disease at presentation compared to 44,5% of patients over 50 years (69).

The major concern arising from this situation is the poorer prognosis and higher mortality rates associated with a higher prevalence of advanced CRC stages.

Despite the more advanced stage and aggressive histology rates, eoCRC seems to have better outcomes when stratified by stage. Younger patients with lower stage disease present a better prognosis than older patients on the same stage of the illness, which strongly supports the idea that younger individuals could also benefit from the use of early detection strategies (17,21).

3.6. CRC DETECTION AND STAGING TECHNIQUES

The most applied and the most efficient method in diagnostic of CRC is endoscopy. In symptomatic patients, colonoscopy with biopsy is the most sensitive diagnostic method and should always be performed when CRC is suspected. In the case of incomplete colonoscopy, barium enema may be useful, as it allows exploration down to the cecum and rules out synchronous neoplasia. Another alternative is to perform a computed tomographic colonography (CTC) (1,2).

Once colon cancer has been diagnosed, tests must be done to determine the stage of the disease. Knowing the stage of the disease is essential in order to plan treatment.

If colon cancer is diagnosed, the extension study should be completed with a thoracoabdominal CT scan. If the diagnosis is a rectal cancer, a pelvic MRI (magnetic resonance imaging) scan should be performed for locoregional evaluation and a thoraco-abdominal CT scan for distant extension (2).

When small liver nodules suspicious for metastases are present in the CT, a liver MRI should be performed to characterise and establish the number of lesions. Further tests can be performed depending on the patient's symptoms and clinical suspicion to rule out other distant lesions (2).

Whenever a CRC diagnosis is established, and before starting any treatment, it is necessary to determine the tumour markers through a blood test to determine the serum CA19.9 (Carbohydrate antigen 19-9) and CEA (carcinoembryonic antigen). The latter marker is decisive, as its elevation after surgery, may be indicative of recurrence

of the disease. However, it should be noted that CEA determination is not a useful method for the diagnosis and screening of colorectal cancer (2).

3.6.1. STAGES OF COLORECTAL CANCER

Staging is key in order to assess the prognosis and determine best treatment choices. The most common cancer staging systems used in clinical settings are the American Joint Committee on Cancer (AJCC) system, and tumour, node and metastasis (TNM) system (Fig.8). According to the 8th edition of AJCC staging system (70):

- **Stage 0** (i.e, carcinoma in situ or intramucosal carcinoma): abnormal cells limited to the mucous layer. It is known to have no risk of lymph node metastasis; therefore, complete endoscopic resection can achieve cure without risk of recurrence and/or metastasis. However, it can spread into surrounding tissues.
- **Stage I:** cancerous cells spread to the submucosa or the muscle layer of the colon or rectum wall. From this stage lesions are considered invasive carcinoma.
- **Stage II:** when cancerous cells reach the serosa (the outermost layer), it is divided into stages **IIA** (cancer is limited in the serosa) , **IIB** (cancer has spread through the serosa but has not spread to nearby abdominal structures) and **IIC** (cancer has spread to nearby organs are affected).
- **Stage III:** cancer has spread to nearby lymph nodes. This stage is subdivided in IIIA, IIIB, IIIC depending on the number of lymph nodes and the layers affected.
- **Stage IV:** cancer has disseminated through blood and lymph nodes to distal regions of the organisms, typically liver, lung, abdominal wall, and ovaries. This stage at the same time is divided in IVA, IVB, IVC.

For descriptive and statistical analysis of tumour registry, a simplified classification was released by the Surveillance, Epidemiology, and End Results (SEER) programme (14):

- **Localised stage:** Cancer that has grown in the colon or rectum wall (but not completely through) and has not extended to lymph nodes or nearby structures.
- **Regional stage:** Cancer that has grown through the intestinal wall and/or spread to nearby structures and/or lymph nodes.
- **Distant stage**: Cancer that has disseminated to other distal parts of the body, such as the liver, lungs, peritoneum, or ovaries.

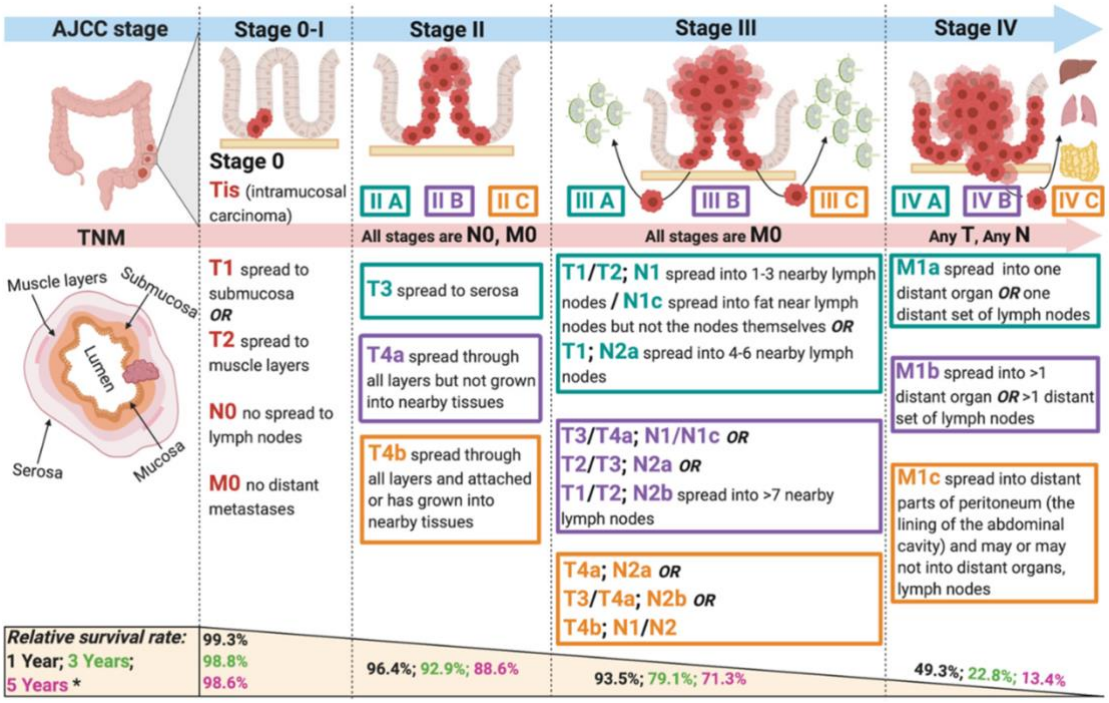


Figure 8- Colorectal cancer stages, TNM and prognosis. (103)

Colorectal cancer stages are expressed according to the American Joint Comittee on Cancer (AJCC), 8th Edition.TNMstaging is based on the size of the tumour, growth into lymph nodes and distant metatases. Relative Survival rate is represented for each stage of the disease, and expressed at 1, 3, and 5 years afterthe diagnosis.

3.7. CRC TREATMENT

CRC treatment has improved rapidly over the past years; however, the outcomes still depend on tumour molecular features, location, and patient characteristics (2,21).

- **Colon cancer:** Most patients diagnosed with CRC will undergo a surgical procedure to remove the tumour. Adjuvant chemotherapy can also be used to reduce spread and recurrences. Radiation, although it may be indicated in some cases, is not used as frequently as for rectal cancer.
- **Rectal cancer:** Surgery is the principal treatment and can be complemented with neoadjuvant and/or adjuvant chemotherapy and radiotherapy to reduce the risk of recurrences and spread.

It must be considered that the complexity of CRC treatments is high and that there are multiple strategies to follow. The standard treatment of colon and rectal cancer has been summarised and simplified in Table 4 (2).

Table 4- Summary of colorectal cancer treatment according to SEER staging of the disease.
Made by the author (2,14).

	COLON CANCER	RECTAL CANCER
Carcinoma in situ	- Colonoscopy polypectomy. Large polyps not removable by colonoscopy procedures: - Surgical resection of a segment of the colon.	- Colonoscopy polypectomy - Surgical local excision - Transanal excision**
Localised	- Partial colectomy* + nearby lymph node excision.	Surgery is usually the main treatment. Depending on the tumour location the surgical treatment can be: - Transanal excision - Low anterior resection - Proctectomy with colo-anal anastomosis - Abdominoperineal resection
Regional	- Partial colectomy + nearby and surrounding lymph nodes excision. +/- Adjuvant chemotherapy if the risk of recurrence is high.	- Neoadjuvant treatment with concomitant chemotherapy and radiotherapy. + Surgical treatment (using the same strategies explained in the localised stage) and nearby lymphadenectomy. + Adjuvant chemotherapy
Distal	If there are only few removable metastases to the liver or lungs, and the colonic lesion is removable too, surgery to resect these may improve survival: - Surgical removal of the tumour and metastatic lesions +/- neoadjuvant and /or adjuvant chemotherapy. If either the lesions are not tributary to surgery, the indicated treatment strategies are: - Chemotherapy and/or targeted therapies - Immunotherapy At this stage, surgery can also be performed as a palliative treatment to prevent a colon obstruction. Otherwise, sometimes surgery can be avoided placing a stent endoscopically.	If there are only few removable liver or lung metastases, and a colonic removable lesion surgery can be an optimal treatment: - Multiple combinations of surgery + chemotherapy + radiotherapy can be performed. In rare cases the cancer can be successfully treated by removing all the tumours with surgery. Some of the treatment options include: - Chemotherapy and /or targeted therapies - Immunotherapy At this stage, palliative treatments are used to relieve, delay, or prevent symptoms and increase life expectancy (surgery, chemotherapy, and radiation therapy).

*Note:*Partial colectomy: surgical excision of the affected region and part of the adjacent healthy tissue. **Transanal excision: Full-thickness rectal resection using a transanal approach surgery. ***Low anterior resection: the affected part of the rectum containing the tumour is removed using an abdominal approach, then the lower part of the colon is reattached to the remaining rectum (in the same intervention or at a second intervention).*

3.8. PREVENTIVE STRATEGIES AND EARLY DETECTION FOR CRC

3.8.1. PRIMARY, SECONDARY AND TERTIARY PREVENTION

The scientific progress achieved during the last decades regarding CRC risk factors and their influence on the carcinogenic pathways has allowed a more detailed comprehension of CRC natural history. This makes it possible to address and implement both primary (by reducing the incidence of CRC through modifiable lifestyle risk factors) and secondary (by detecting CRC in the pre-malignant and pre-symptomatic phase) prevention strategies (1).

Primary prevention for CRC is not easy due to the population lack of information and the intrinsic difficulty to modify certain risk factors. This highlights the need to develop new plans of action in order to promote healthier lifestyle habits and improve society's consciousness about the potential CRC risk factors mentioned above. However, due to the worrisome trends of CRC and the inherent difficulties of primary prevention, the need to use secondary prevention strategies, like screening, arose (1,10).

Secondary prevention of CRC consists of diagnostic examinations in asymptomatic individuals (4). The slow course of growth to advanced-stage disease provides a unique opportunity for the prevention and early detection of CRC (Fig.9) (Fig.10).

Finally, tertiary prevention aims to reduce the impact of existing lesions and involves the surveillance after the resection of CRC or adenomas to detect possible metachronous lesions at an early stage (25).

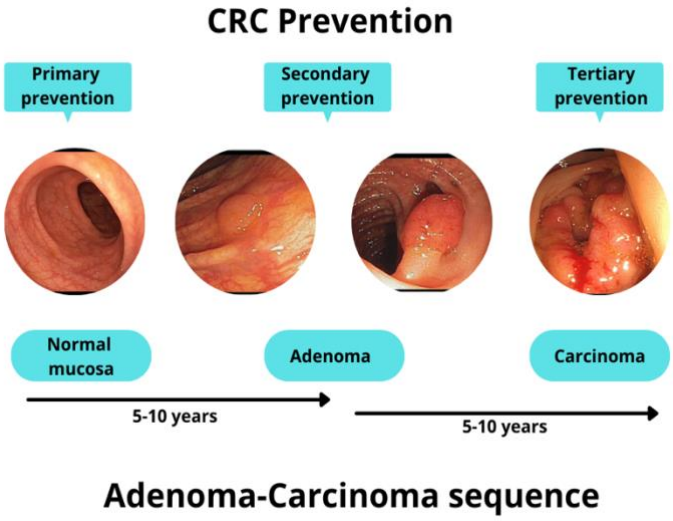


Figure 9- Adenoma-carcinoma sequence and prevention strategies. *Made by the author.*

3.8.2. SCREENING STRATEGIES

Screening is defined by the World Health Organization as "the use of simple and rapid tests across an apparently healthy population in order to identify individuals who have early stages of disease, but do not yet have symptoms".

The characteristics of CRC make it eligible for screening (Wilson and Jungner criteria, 1968)(71):

1) It is a frequent and serious social problem considering the mortality, morbidity, disability, and the social cost that it implies.
2) The clinical course of the disease is well known, and a pre-symptomatic stage is defined.
3) CRC treatment at pre-symptomatic stages reduces mortality and complications compared to the treatment of symptomatic stages.
4) Screening tests are available, safe, and easy to perform. They have high sensitivity, specificity, and high positive predictive value, are well accepted by professionals and patients, and have demonstrated a good cost-effectiveness.

The main objective of CRC screening programs is to reduce the mortality of the disease by detecting cancer at early stages and therefore achieving a better chance of curative treatment. In addition, CRC screening has the particularity to reduce the incidence of the disease by detecting and resecting CRC precursor lesions (polyps) (Fig.10).

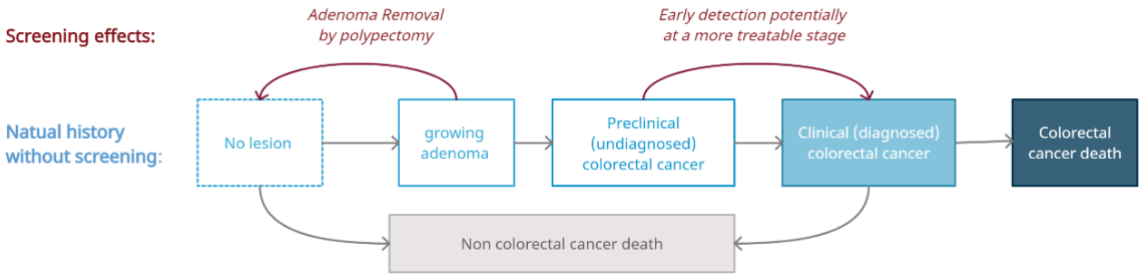


FIGURE 10- NATURAL HISTORY OF COLORECTAL CANCER AND THE EFFECTS OF SCREENING.
ADAPTATION FROM (89)

Strategies for CRC early diagnosis should be adapted to the different risk profiles. Currently, European guidelines divide population in three groups according to its individual risk to develop CRC. Notice how in the absence of personal and/or family history, the age is the most important CRC risk determinant (1):

1) **Low risk group:** Individuals under 50 years of age, without additional risk factors, have a low risk to develop CRC and are not considered eligible for screening interventions in our country. However, since 2018 American Cancer Society recommends starting regular screening at age 45 due to the increasing incidence of CRC among the younger population.
2) **Average risk group:** individuals aged $\geq$ 50 years without additional risk factors are considered to have medium risk to develop CRC. In this case, population-based CRC screening programs are recommended.
3) **High risk group:** Individuals with personal and/or family history (first degree relatives) with adenomas, CRC, CRC hereditary syndromes and/or IBD, are considered high risk and are subject to other specific screening programs.

There is evidence that CRC screening is effective and cost-effective among the average risk population when compared to non-screening(72). Multiple randomised clinical trials (the best way to evaluate screening strategies) demonstrate a decrease in CRC incidence and mortality (1,73,74).All types of screening programs result in additional years of life at an acceptable cost for most industrialised countries and may even result in some savings for the health care system by avoiding the cost associated to advanced disease care (75).

In 2000, the Prevention Advisory Committee recommended the use of screening for CRC in asymptomatic populations from 50 years of age in the European Union countries. However, it was not until July 2013, after the successful results obtained from several pilot tests among Spanish territories, that the National Health Council agreed to incorporate said screening into the basic services of Spain's National Health System. In 2019, although it was already active in many territories, the full distribution of the CRC screening program in Catalonia was achieved (12,76,77).

A screening technique ideally should have high sensitivity for the detection of adenomas and CRC lesions, and a high specificity to avoid false positive results. Moreover, the technique must be accepted by the population in terms of safety, and it must have low complication rates and an affordable cost. Currently, population-based screening

strategies that are revealed to be useful and cost effective are based on annual or biennial FOBTs (faecal occult blood tests), sigmoidoscopy every 5 years or colonoscopy every 10 years (14,78).

3.8.3. CRC SCREENING TECHNIQUES

There are multiple recommended CRC screening methods for the average risk population (Table.), that can be divided into two groups: 2) Stool tests, which are collected at home, and 1) structural or visual examinations performed at a health care facility. All tests have comparable ability to improve life expectancy when performed at appropriate times intervals and with the recommended follow-up. Principle characteristics of each screening test are summarized in the Table 5.

1) **STOOL TESTS (Non-invasive)**

Both advanced adenomas and CRC invasive tumours, are characterised by intermittent and unnoticeable bleeding in the stool that can be identified using different stool tests. The main advantage of these tests, apart from being non-invasive, is their simplicity, low cost, and effectiveness in reducing CRC mortality. Studies suggest that biannual or annual screening with high sensitivity stool tests can reach levels of efficacy like the ones achieved with colonoscopy (79).

- **Guaiac-based faecal occult blood test (gFOBT):** This test uses a chemical reaction (peroxidase reaction) to detect the haeme group (a component of the haemoglobin) in the stool. This test requires samples from 3 consecutive bowel movements and patients must avoid the intake of specific foods or drugs 3 days prior to the test; NSAIDs and red meat can lead to a false positive test result and vitamin C supplements or abundant intake of citrus to a false negative test result. Other limitations of these tests are its low sensitivity and the subjective reading of the results (1).

  A meta-analysis of 4 randomised clinical trials reported that the regular use of gFOBT annually and biennially reduced the risk of CRC death by 18% and 13% respectively (80).

- **Faecal immunochemical test (FIT)** (Fig.11)**:** also known as immunochemical FOBT, or iFOBT. This test is based on the detection of human globin by using the detection of monoclonal or polyclonal antibodies, therefore, is much

more specific for lower gastrointestinal bleeding. This technique can detect low concentrations of globin and is about twice as likely as most gFOBT tests to detect both advanced adenomas and cancer (sensitivity increase from 31.7% to 61.5%) (81,82). No dietetic or pharmacological restrictions are needed before the test and it only requires a single stool sample. Results can be qualitative or quantitative according to the FIT type, being the latter the most used in clinical practice (4).

Multiple studies demonstrate the superiority of quantitative FIT over other stool tests, not only because of its higher detection rate and specificity, but also because of its convenience, which leads to higher participation and adherence to the screening programs. About 77% of the patients declared preferring this immunological method over any other FOBT (83). Clinical trials assessing biennial FIT reported a reduction in CRC mortality reduction of 30%(84).

- **Multitargeted stool DNA:** This test does not only detect blood, but also multiple genetic mutations in the DNA cells found in the stool coming from adenomas and invasive colorectal lesions. This test has a slightly higher sensitivity to detect cancer and precancerous lesions compared to FIT, but it also results in a greater number of false positive tests, which can result in unnecessary colonoscopies (85). Although it is regarded as an acceptable tool for screening, it is not as economical as the previous tests and further studies are needed to assess its performance characteristics in community settings.

2) VISUAL EXAMINATIONS (Invasive)

Direct vision of the lining of the colon and rectum through endoscopic or radiological imaging techniques.

- **Colonoscopy:** procedure performed by a gastroenterologist that allows direct visual examination of the colon and rectum. It can be used either as a follow-up to a positive result from stool or other visual tests or as a unique screening test itself with a rescreening interval of 10 year for average-risk individuals with negative results (1).

Colonoscopy **requires a special preparation** with oral laxative drugs to cleanse the colorectum and achieve an optimal visualisation of the intestinal lining. The technique is done with the patient under sedation.

However, results from studies assessing sigmoidoscopy (similar test explained below) support indirectly the benefits of this technique. Some observational studies reported that colonoscopy itself as a screening test could reduce CRC by about 40% and mortality by about 60% (73).

As any other technique, colonoscopy has its limitations like the detection of polyps that would have never turned malignant or the unintentional omission of lesions (especially those located in the proximal colon or in bad preparations). In comparison to other screening techniques, colonoscopy presents a higher risk of potential complications such as bowel tears and bleeding, especially when a polypectomy is performed in older patients. However, side effects are unusual, and only take place in 1 to 2 of every 1.000 colonoscopies (86).

- **Flexible Sigmoidoscopy:** This technique is very similar to the colonoscopy but differs from it because it can only visualise the rectum and distal part of the colon (sigmoid). The preparation is done using rectal enemas and it is usually performed without sedation. It is less invasive and carries a lower risk of the colon being torn. It was a common screening technique in the past, but now it has been replaced by colonoscopy, especially because if any lesion is found during the sigmoidoscopy, the patient must be referred for a colonoscopy to examine the entire colon as well (1).

  Data obtained from randomised clinical trials reported a CRC incidence and mortality reduction by 20-25% and 25-30% respectively (87).

- **Computed Tomographic Colonography (CTC):** Imaging technique that allows visualisation of the intestine in 2D and/or 3D, the reason why it is also referred to as virtual colonoscopy. A small, flexible tube is inserted into the rectum to inflate the colon using carbon dioxide, afterwards the patient undergoes a CT scan. Colonic cleansing preparation is equally necessary, yet no sedation is required. This technique is less invasive and faster (10-15 minutes) compared to the other types of visual examinations. Patients with positive findings for

abnormal results or >5mm adenomas, are referred for colonoscopy (performed optimally the same day to avoid the need of a new preparation) (88).

The principal limitations of this technique are the radiation implied and the risk to obtain false positive results due to benign extracolonic lesions interfering with the image. It is also important to consider its high economic cost .

The performance of CTC for the detection of advanced adenomas or invasive CRC lesions seems to be similar to colonoscopy, but it shows lower sensitivity to detect small adenomas(89). Nonetheless, more studies are needed to establish the efficacy of this technique compared to others.

Table 5- Characteristics of recommended screening techniques (14).

	Benefits	Performance & Complexity*	Limitations	Test Time Interval
Visual Examinations				
Colonoscopy	• Examines entire colon • Can biopsy and remove polyps	**Performance**: Highest **Complexity**: Highest	• Full bowel cleansing • Can be expensive • Sedation usually needed, necessitating a chaperone to return home • Patient may miss a day of work • Highest risk of bowel tears or infections compared with other tests	10 years**
Computed tomographic colonography (CTC)	• Examines entire colon • Fairly quick • Few complications • No sedation needed • Non-invasive	**Performance:** High (for large polyps) **Complexity:** Intermediate	• Full bowel cleansing • Cannot remove polyps or perform biopsies • Exposure to low-dose radiation • Colonoscopy necessary if positive	5 years
Flexible sigmoidoscopy	• Fairly quick • Few complications • Minimal bowel preparation • Does not require sedation	**Performance:** High for rectum & lower one-third of the colon **Complexity:** Intermediate	• Partial bowel cleansing • Views only one-third of colon • Cannot remove large polyps • Small risk of infection of bowel tear • Slightly more effective when combined with annual faecal occult blood testing • Colonoscopy necessary if positive • Limited availability	5 years
Stool Tests (Low-sensitivity stool tests, such as single-sample FOBT done in the doctor's office or toilet bowl tests, are not recommended				
Faecal immuno-chemical test (FIT)	• No bowel cleansing or sedations • Performed at home • Low cost • non-invasive	**Performance:** Intermediate for cancer **Complexity:** Low	• Will miss most polyps • May produce false-positive test results • Slightly more effective when combined with a flexible sigmoidoscopy every five years • Colonoscopy necessary if positive	Annual / biennial

High-sensitivity guaiac-based faecal occult blood test (gFOBT)	• No bowel cleansing or sedation • Performed at home • Low cost • non-invasive	**Performance:** Intermediate for cancer **Complexity:** Low	• Requires multiple stool samples • Will miss most polyps • May produce false-positive test results • Pre-test dietary limitations • Slightly more effective when combined with a flexible sigmoidoscopy every five years • Colonoscopy necessary if positive	Annual / biennial
Multitarget stool DNA test (Cologuard)	• No bowel cleansing or sedations • Performed at home • Requires only a single stool sample • non-invasive	**Performance:** Intermediate for cancer **Complexity:** Low	• Will miss most polyps • More false-positive results than other tests • Higher cost than gFOBT and FIT • Colonoscopy necessary if positive	3 years, per manufacturer's recommendation

Note:
*Complexity involves patient preparation, inconvenience, facilities, and equipment needed, and patient discomfort.
**For average-risk individuals, e.g., does not apply to those who have a history of adenoma

3.8.4. SCREENING PROGRAMME FOR AVERAGE RISK INDIVIDUALS IN CATALONIA

The population-based screening programme for CRC (*"Programa de Detecció Precoç de Càncer de Còlon i Recte, PDPCCR")* began in Catalonia began in 2000 in l'Hospitalet del Llobregat and was progressively extended to the rest of the Catalan territories until it reached a total coverage in 2019. It is currently aimed to people at average-risk for CRC, including men and women between 50 and 69 years of age without other high-risk factors, and using a faecal-immunochemical test (FIT) biennially (Fig 11.) (76,78).

The main characteristics of the programme are (78):

- **Target population:** men and women aged 50-69.
- **Enrolment:** using a personal invitation (nominal letter).
- **Screening test:** quantitative faecal-immunochemical test (FIT). The criterion for FIT positivity is set at a cut-off point of 20 µg of haemoglobin per gram of stool. Any sample with a concentration equal or greater than 20 µg of haemoglobin per gram of stool shall be considered positive.
- **Frequency:** biennial.
- **Study test in case of a positive FIT result (diagnostic test):** colonoscopy under sedation without the need for hospitalisation.

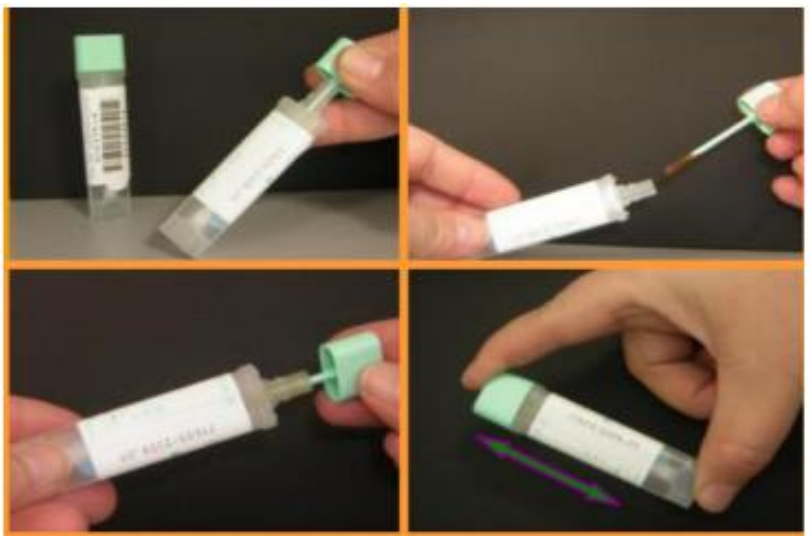


Figure 11- Faecal immunochemical test (FIT) (77).

The call for applications to participate in the programme is done using a personal letter sent by the screening office of the territory. The letter indicates the instructions to follow and where to collect the stool sample container and where it must be returned for the analysis. In Catalonia the programme operates through two different circuits: one that incorporates pharmacies in the management of stool samples (in Girona and Barcelona), and another based on the Primary Care Centres (PCC) (in Lleida and Tarragona). If the FIT result is negative, an invitation is re-sent after 2 years. On the other hand, if the FIT result is positive, a colonoscopy is recommended to identify the bleeding source. Before the colonoscopy performance, an assessment of possible contraindications must be done, and it is carried out in a face-to-face interview performed by the Nursing Department of the Service. During this interview information about the test and its preparation is facilitated and the informed consent document is provided. If the colonoscopy results are normal, a second visit is not necessary, and the result is communicated through a nominal letter. In these cases, the screening is resumed after 10 years with a new invitation letter. This is because a negative colonoscopy it is considered to provide long term "protection" from CRC for about 10 years, the time needed to complete the adenoma-carcinoma sequence (77,78,90).

On the other hand, If the colonoscopy result is not negative, depending on the outcome of the colonoscopy and pathology department, the patient may be referred to an appropriate specialist unit (Fig.12) (32,78):

- Non-neoplastic findings (like a diverticulum or a hyperplastic polyp), will be referred to their primary care doctor and will re-join the programme 10 years later.
- In case to find a sum of ≤4 non-advanced polyps an invitation letter to rejoin the programme will be sent after 10 years (94).
- Findings compatible with advanced polyps or a sum of >4 non-advanced / invasive adenocarcinoma /polyposis syndrome/ IBD findings, will be excluded from the programme and will follow specific monitoring strategies (76,94).

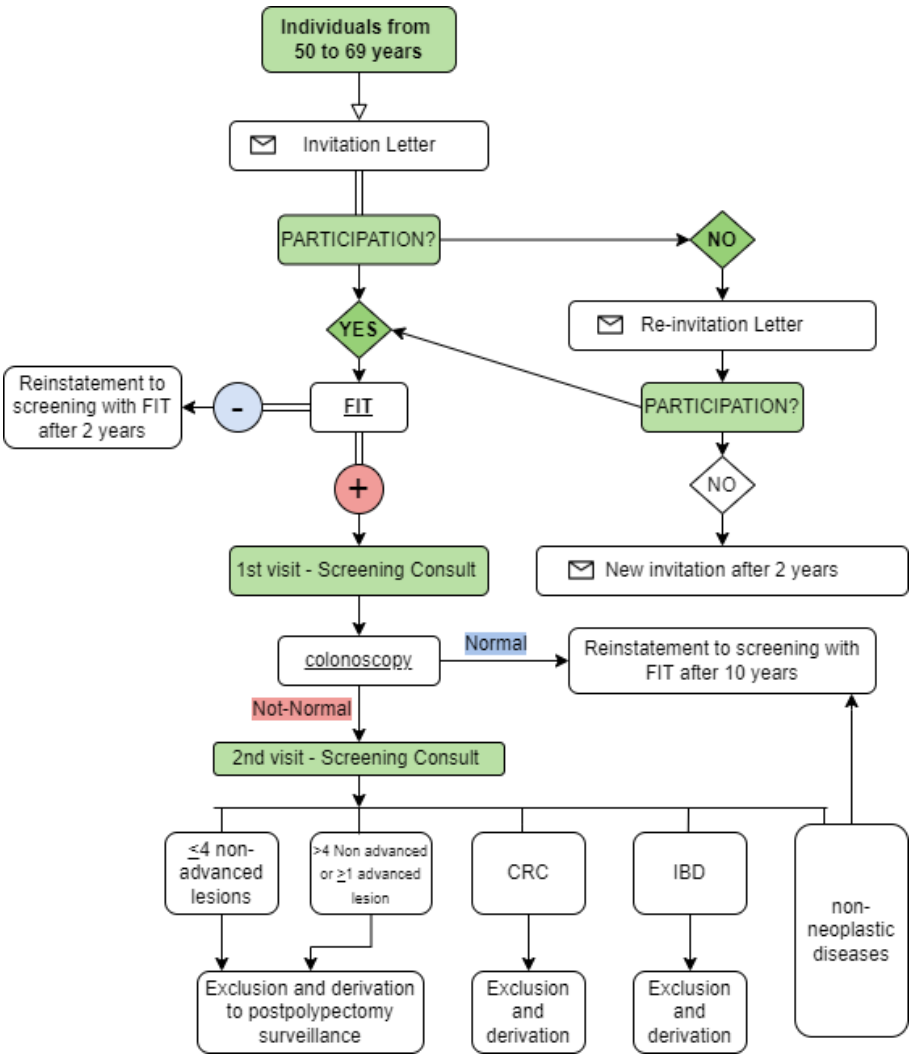


Figure 12 Functional Outline of CRC screening programme in Catalonia. (104)

3.9. CRC PROGNOSIS

An average of 54% of the patients with CRC in Spain survive more than 5 years after the diagnosis. Survival depends largely on the stage: if the carcinoma is stage I, survival is 90-95% (at 5 years); in stage II It is reduced to 75-50%; in stage III the survival is between 22-20%; and in stage IV it is reduced to less than 8% (91).

The prognosis of eoCRC has been widely debated. Although the overall prognosis is worse for eoCRC compared to those cases diagnosed after the age of 50, survival rates stratified by stage are better in younger patients (Table 6). The average survival stratified by stage is better for eoCRC for both stage III (34 vs 28 months) and IV (30 vs 11 months). Better is probably due to the fact that younger patients present better health conditions, fewer comorbidities, better surgical recovery, and better tolerance to oncological treatments. This enables patients to cope better with the disease and therefore be more able to complete aggressive adjuvant treatments. However, as mentioned above, the overall mortality for eoCRC is much lower. This situation has been mainly related to the higher rates of advanced stages due to a delayed diagnosis of CRC, which reaffirms the idea that a system to detect these cases earlier could be highly beneficial for younger individuals (19,92).

Table 6. term stratified survival of eoCRC and late onset CRC (19).

	5-years overall survival (%)	
	Early onset CRC	**Late onset CRC**
Stage I	93.3	94.9
Stage II	88.6	82.7
Stage III	58.9	57.2
Stage IV	18.1	6.2

Note: early onset refers to CRC diagnosed before the age of 50 and late onset after the age of 50.

3.10. CHALLENGES FOR IMPROVEMENT OF eoCRC

The management of CRC in young patients presents significant challenges (Fig.13). The lack of knowledge about this disease makes it difficult to individualise and come up with specific measures for this population group. To date, the management of eoCRC is very similar to the rest of CRC's diagnosed among older patients. (19,39).

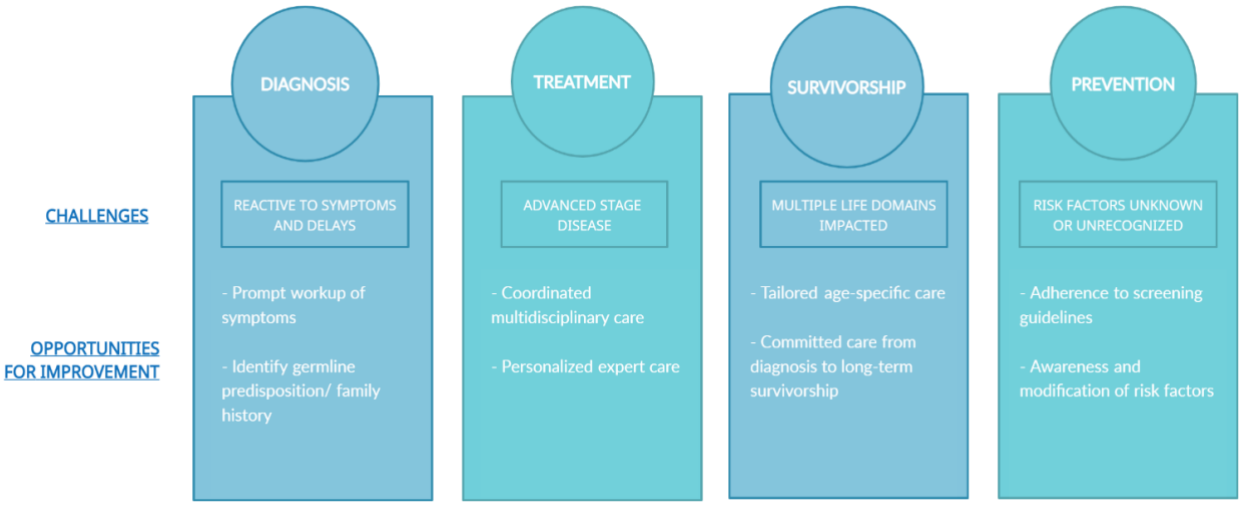


Figure 13- Challenges and associated opportunities for improvement throughout the spectrum of care for young adult patients with colorectal càncer.
Adaptation from (39)

Since 2018, the American Cancer Society recommends US population starting screening at 45 years of age(93). This recommendation was based on modelling analyses adjusted for the increasing incidence of CRC in young patients. The results determined that lowering the age of screening to 45 years, using colonoscopy as a single screening tool, increased life-years gained by 6,2% at the cost of 17% more colonoscopies per 1.000 adults over an individual's lifetime. This recommendation was recently supported by an updated modelling study released by the US Preventive Services Task Force in May 2021 (89). These modelling results were considered efficient and model-recommendable not only for colonoscopy but also for high-sensitivity stool-based test strategies, like faecal immunochemical test (FIT). Any positive results obtained from a non-colonoscopy test must be followed up by a colonoscopy exploration (25). The decrease in the age threshold for screening aims to improve the increasing incidence of eoCRC cases. Currently no age-specific results have been published, and as soon as screening among

45 years old becomes more regular, the evidence and efficiency of this measure will be evaluated (93).

4. JUSTIFICATION

CRC is the most frequently diagnosed cancer and the second leading cause of cancer death for both sexes in Spain (7). Fortunately, over the last few decades there has been a decline in both incidence and mortality associated with CRC. The overall decrease of CRC observed in "high-income" countries, has been attributed mostly to the implementation of population-based screening strategies, which particularly involves adults over 50 years of age. These patterns can easily mask the concerning increase of CRC incidence in young adults (<50 years) that has been taking place in parallel in these same communities. CRC diagnosed before the age of 50 is also denoted as early onset CRC (eoCRC), which used to be very uncommon. Recent data from the US population (2012-2016) reveal an annual 2,25% increase of CRC in those under 50 years of age, which contrasts sharply with the annual 3,3% decline observed in individuals over 65 years of age (15). The future outlook for these trends is not optimistic, and eoCRC it is estimated to rise by up to 270% by 2030 in the US (20), and similar trends are also emerging in European countries (6,22,94). Regarding to Spanish trends, we should consider that oncology registries in Spain are scarce and do not contain enough information from recent years (22). Therefore, the available data is not representative of the current CRC trends among young adults. Nevertheless we can consider that the upward trends of eoCRC, observed in the US and other European countries, could be a direct consequence of an earlier westernisation of lifestyles (dietary habits, sedentarism…) adopted by these societies in comparison to ours. For this reason, the patterns noted in these populations could be considered as an anticipatory reflection of what will happen in the near future in our population.

Mortality from eoCRC has likewise increased, and contrasts sharply with the parallel reduction observed in the older counterparts with access to screening. The worse overall prognosis of eoCRC is due to more frequently delayed diagnosis which implies higher rates of advanced stages. CRC in young patients can be challenging for healthcare professionals, as it is usually asymptomatic at early stages and most patients consult when symptoms appear which is when the disease is already in advanced stages. In addition, most of these symptoms are wrongly attributed to benign conditions, further

delaying diagnosis (2,17). Due to the higher rates of advanced stage at diagnosis, the management of eoCRC can be very demanding. The need to use coordinated multimodality treatments, and the requirement to globally treat the patient for whom multiple life domains are significantly affected by the cancer diagnosis (more so than in older individuals) implies an important loss of productive life years and a huge expense of material and economic resources for any public health system. This places eoCRC as a serious public health issue and highlights the urgent need to find new approaches to diagnose these patients at earlier stages of the disease.

However, younger patients have a much better prognosis compared to older patients when stratifying by stage (19,92), and evidence suggests that eoCRC behaves similarly to "late onset" CRCs following the same slow adenoma-carcinoma sequence. Therefore, screening could also be useful for this population group not only to detect the disease at early stages but also to prevent it. In addition, no specific factor (or combination of them) has been directly associated to eoCRC (39), so neither primary prevention measures nor diagnostic strategies based on individual risk seem suitable to ameliorate this problem now. This, along with the increasing burden of eoCRC, places population-based screening as a potentially useful strategy for young individuals. In Spain, like major part of European communities, the population-based screening programme is recommended for average-risk individuals between 50 and 69 years. The results so far have been showing effectivity in reducing both mortality and incidence. The biennial FIT (faecal immunochemical test) strategy is easy to perform, low-cost and risk free, and the colonoscopy that follows any positive FIT it is considered to outweigh the possible risks associated. Given the characteristics of eoCRC mentioned before and the successful results of the current population-based screening programme, it is reasonable to think that younger patients could also benefit from the same strategy.

This study aims to assess whether the application of a screening strategy in the young population can reduce the mortality caused by eoCRC. Knowing that the majority of eoCRCs occur between 40-49 years of age (17), It has been decided to focus our study on this age group. Indeed, the American Cancer Society in 2018 launched the recommendation to start screening from 45 years of age in the US (89,93), based on

computer modelling simulations. It stands to reason that guidelines and recommendations should be derived from well-collected and reproducible data, obtained from experimental-designed trials and not from mathematical predictions. Therefore, an experimental design was used for this study, and will be the first field trial to assess the efficacy of CRC screening among individuals between 40-49 years.

The threatening increase in eoCRC incidence and mortality demonstrate an obligation to take actions. For now, early screening seems to be a reasonable strategy to help improve these worrisome trends by helping to save lives from eoCRC and starting at the age of 40 may be a robust screening option.

5. HYPOTHESES

5.1. MAIN HYPOTHESIS

The 5-year mortality rate for CRC will be lower among those individuals between 40-49 years who have received screening in comparison to those of the same age who have not received screening.

5.2. SECONDARY HYPOTHESES

1. The incidence of **CRC cases**, as well as the incidence of premalignant lesions (**polyps**), is expected to be **higher among the screened group** compared to the unscreened group during the study period.

2. **Screened individuals diagnosed with CRC will present higher rates of early-stage** carcinoma in comparison to those **who do not undergo early screening who will present higher rates of late-stage** carcinoma when diagnosed.

3. The benefit of the colonoscopy as a screening technique outweighs the possible risks associated; **secondary effects related to colonoscopy will be minimal and mild** among individuals undergoing this test.

4. In the population aged 40-49 years, **faecal immunochemical test (FIT) will have a positive predictive value for premalignant and malignant lesions similar to** that obtained in the population over 50 years of age (which in Catalonia is known to be 10-14% for CRC and 30-40% for premalignant lesions).

5. **Subjects with CRC belonging to the screening group, who are still alive 5 years after the diagnosis, will exhibit an improved quality of life** in comparison to those alive 5 years after the diagnosis who did not receive the screening intervention.

6. The individuals diagnosed with CRC during the study will present **a higher prevalence of risk factors associated with CRC** in comparison to those individuals with negative findings for CRC.

6. OBJECTIVES

The proposed project has the following objectives:

6.1. MAIN OBJECTIVE

The main purpose of this project is to assess whether the application of **a screening strategy in the general population aged 40-49 years reduces CRC mortality at 5 years** in comparison to those individuals of the same age who do not undergo screening.

6.2. SECONDARY OBJECTIVES

1. To assess the **number of both neoplastic lesions (CRC) and premalignant lesions (polyps)** encountered among the screened group and unscreened group.

2. To assess the incidence of **early and late-stage colorectal carcinomas** diagnosed among the screened group in comparison to those who do not undergo screening.

3. To assess **the type and number of secondary effects** among screened individuals undergoing a **colonoscopy** procedure.

4. To assess the **number of positive FIT results, the overall number of colonoscopies and the type and number of colonoscopy findings.**

5. To assess if i**ndividuals from the screening group who are still alive 5 years after the diagnosis of CRC present an improved quality of life** in comparison to those alive 5 years after the diagnosis who did not receive the screening strategy.

6. To assess and compare the **prevalence and combination of CRC risk factors** between the participants who are diagnosed with CRC during the study and those who are not.

7. MATERIAL AND METHODS

7.1. STUDY DESIGN

This project is designed as a multicentric, population-based, randomised, parallel group, open, field trial aiming to compare two strategies: CRC screening strategy vs. only following strategy among individuals between 40-49 years.

7.2. STUDY POPULATION

The target population of this study will be individuals between the ages of 40 and 49 years from the Health Region of Girona (Province of Girona), which includes approximately 100,000 individuals (95).

The current CRC screening programme for individuals over 50 years, has a participation rate between 30%-40% in the Province of Girona (12). Knowing that we need a total number of 20.236 participants for our study and assuming a 35% of participation, we should send an application to at least 57,818 individuals. However, as this is a field trial, a much lower participation is expected. Therefore, to have margin, every Primary Care Centre (PCC) and Screening Unit[1] in the Health Region of Girona will be asked to join the study, and all individuals between 40-49 years of age living in the basic health areas (BHA) of the collaborating centres will be invited to participate. Hospital Universitari Doctor Josep Trueta (Girona) will be the coordinating centre of the study.

All data will be supplied from the CatSalut's Central Registry of Insured individuals' (CRI). CRI contains personal data (full name, address, date of birth, etc.) of the users of the Catalan Health Service in possession of an individual health card (IHC).

In summary, an invitation letter (ANNEX 2) will be sent to any individual between 40 and 49 years of age in possession of an IHC and currently residing in one of the Basic Health Areas from the Health Region of Girona participating in the study, according to the CRI database.

- **INCLUSION CRITERIA**
    - Men or women between 40-49 years.

[1] *Screening Unit: sanitary team that engages all those professionals involved in the development of the CRC screening programme (clinical analysis unit, screening nursing, endoscopy unit, pathological anatomy service and gastroenterology service).*

- Possession of an individual health card (IHC) (being registered in the Central Registry of Insured, CRI).
- Currently living in one of the Basic Health Areas belonging of the Health Region of Girona (according to the address registered in the CRI).
- Ability to understand the study procedure.
- Accepted and signed informed consent (ANNEX 3).

- **EXCLUSION CRITERIA**

Individuals will be excluded automatically, if they do not accomplish the inclusion criteria of our target population due to possible incidences of the CRI database:

- Age error
- Address error
- Exitus

Individuals will be excluded permanently from the study if they accomplish any of the following criteria:

- Low abdominal signs or symptoms present before the beginning of the study, like: rectorrhagia, stool changes, abdominal pain, weight loss accompanied by asthenia and anorexia, symptoms of iron-deficiency anaemia of unknown origin, abdominal mass, or any other symptom suggestive of CRC.
- Colonoscopy performed during the last 5 years.
- Personal history of CRC and/or colorectal adenomas.
- Personal history of known IBD (Ulcerative Colitis, Crohn's disease, etc.).
- Personal history of total colectomy.
- Terminal illness of serious disability or morbidity affecting life expectancy that contraindicates colonoscopy.
- Pregnancy.
- Familiar history of familial adenomatous polyposis or other polyposis syndromes, or hereditary nonpolyposis CRC.
- Familiar history of CRC defined as:
  - 2 or more first degree relatives diagnosed with CRC (regardless of age of diagnosis).
  - 1 first degree relative diagnosed with CRC before the age of 60.

- **WITHDRAWAL OF THE STUDY**

Individuals participating in the study should continue the follow-up established by the protocol. Whenever possible, an attempt should be made to have patients complete the study unless there is a justified reason:

- **Patient follow-up loss:** when it is not possible to contact the patient and/or complete the intervention follow-up. For a participant to be considered excluded from the study, all the following conditions must be met:
  - **The participant does not show up for one of the activities included** in the intervention or fails to attend in the following screening round.
  - **The participant does not respond to any of the 3 reminder calls that will be made in case the previous point happens.** The reminder calls should be made at least 24 hours apart from each other and at different times of the day.
- **Request to withdraw consent for the study** (ANNEX 4): The participant can express a voluntary decision to be excluded from the study. To whenever possible, this information should be obtained in written form.
- **Death**

Every patient loss must be declared and recorded along with their data and the withdrawal reason. All data obtained during the study prior to the withdrawal will be used for the study results.

7.3. SAMPLING

- **SAMPLE SIZE**

The sample size was estimated using the GRANMO software, and the setting for two independent proportions.

Based on the number of CRC deaths among 40-49 years patients in 2014 obtained from Girona's cancer registry (4,2 annual deaths / 100,000), we assumed:

⇒ The 4-year cumulative risk of CRC death among patients between the 40-49 years age range is 0.0168%.

Based on the DESCRIC (90) project aiming to evaluate the efficacy of screening, we expect a 30% risk reduction of CRC mortality by lowering the CRC screening threshold to 40 years.

⇒ Considering that, we will see a cumulative mortality risk of 0,0117% in the study group.

We assumed a risk alpha of 0.05 and a risk beta of 0.2 in a two-sided test. The estimated loss at follow-up is 15%.

Using these variables, GRANMO calculated **10,118 subjects in each group** to ensure a significant difference in the mortality risk. Therefore, **a total of 20,236 patients** will be needed.

- **ESTIMATED TIME OF RECRUITMENT**

The estimated time of recruitment will be **1 year**. The sample analysis will be initiated once individuals accept their participation in the study by signing the informed consent. The time of recruitment is an estimation therefore it can be adjusted to the enrolment rates during the first months of the study.

- **SAMPLE SELECTION AND ENROLMENT**

The sampling method selected for the study will be a **consecutive sampling**. The choice to enter the study will be offered to the general population aged between 40 and 49 in possession of an individual health card (IHC) and who are currently living in the province of Girona according to the CRI database.

Considering that the participation rate for this study will be much lower than the 40% achieved by the ongoing CRC screening program, an invitation will be sent to all the individuals in the province of Girona meeting the inclusion criteria (approximately 130,000 people) in order to recruit the necessary sample size. The sampling collection will be conducted until the sample size is totally achieved. The first 20,236 subjects to sign the informed consent will be enrolled and become participants of the study.

Eligible people will be contacted to participate in the study throughout a **nominal letter invitation** (ANNEX 2)**.** A brief and understandable summary of the study will also be enclosed in the invitation letter. Those individuals interested in participating must call their referral PCC to arrange a visit. The visit will be carried out by the specially trained staff from the Nursing Department of the centres involved. There, inclusion, and exclusion criteria will be assessed, an understandable explanation of the study will be

offered, and the informed consent will be handed and signed. The selection process will end after completing this exact same process with a total number of **20,236 individuals**.

- **RESPONSE RATE ASSURANCE**

As mentioned before, to enhance the enrolment of participants, information about the study and its safety will be sent along with the invitation letter. In addition, the team members from the Nursing Department, in charge of selecting and receiving the subjects willing to participate in the study, are going to re-explain the study plan and conditions in a simple and understandable way and transmit a feeling of assurance to the potential participants.

- **RANDOMIZATION AND MASKING**

Every individual who enters the study will be randomised into one of the following two groups:

- **Screening Group (study group):** patients whose stool sample will be biennially analysed using a quantitative FIT and therefore will undergo a screening intervention. In case of a positive FIT result, a colonoscopy will be indicated to rule out the possibility of asymptomatic CRC.
- **Fake screening Group (control group):** patients whose stool sample will be biennially collected but not analysed and therefore will not undergo a screening intervention. At the end of the study, it will be determined whether any of the control group participants have developed CRC.

It will be an open study; however, participants will be blinded at the beginning of the study. In the first visit, after being randomly assigned to a group, all the participants will be provided with a "stool sample collection kit". All participants will return the stool sample to their primary care centre within 2 weeks, but never exceeding 3 days from the date of the defecation. This procedure will be repeated after 2 years, however only those samples from individuals belonging in the "study group" will be analysed using quantitative FIT. In case of positive FIT results, a colonoscopy will be indicated among the screened individuals. When this happens, the patients involved will be aware of their

participation in the screening group. Therefore, the **study will lose the blind in case of a positive FIT result.**

7.4. STUDY DURATION

- **Kick- off:** November 2021
- **Intervention:** The intervention will be applied during 4 years from March 2022 to March 2026. The screening intervention will be applied biennially for 4 years, so 2 screening rounds will be performed.

  Patients who have not been diagnosed with CRC after these 4 years of intervention will no longer be followed up. Patients who have developed a CRC during the study will be followed up to evaluate the mortality and quality of life 5 years after the diagnosis.
- **End of study:** October 2031. The study will end **5 years after the diagnosis of the last CRC case** found during the study, and after the analysis and publication of the results.

In case of demonstrating a great efficacy of screening strategy or in case of detecting important side effects before these periods of time, the study will be concluded, and the results will be published.

7.5. VARIABLES AND MEASUREMENTS

7.5.2. PRINCIPAL VARIABLES

- **Independent variable: Intervention**

Intervention → **screening strategy vs. Fake screening strategy**.

It will be a dichotomous qualitative variable and will be expressed by the number of patients undergoing screening (whose stool sample will be collected and analysed using quantitative FIT), and the patients undergoing a fake screening strategy (whose stool sample will be collected but not analysed).

- **Dependent variable: mortality**

Mortality → **CRC specific mortality at 5 years after the diagnosis**

The specific CRC mortality at 5 years will be the **main variable of the study** and will be evaluated among all those patients diagnosed with CRC during the study (either from the study and the control group).

It will be a dichotomous qualitative variable: **Dead Vs Not Dead.**

In the **study group,** this variable will be assessed 5 years after the diagnosis of any CRC found through screening. In the **control group**, medical records (from SAP) of each participant will be reviewed at the end of the last screening round to detect any CRC diagnosis. Mortality for this group will be assessed 5 years after each diagnosis too.

7.5.2. SECONDARY DEPENDENT VARIABLES

- **Positive FIT results**

  The test used to detect faecal occult blood is **the quantitative faecal immunochemical test (FIT)** which will be **performed biennially among the screening group** participants.

  Only one stool sample per participant and per round will be analysed. A new stool sample determination will only be performed in case the sample cannot be analysed due to poor quality conditions (incorrectly collected sample, tube breakage or any other incident that makes the analysis impossible).

  The same method (FIT) will be used throughout all the duration of the study to guarantee the homogeneity of the study and to avoid variability between methods.

  The positivity criterion for FIT will be unique throughout the study. This will be established according to the cut-off point of 20 µg of haemoglobin per gram of stool, that depending on the method used for the analytical determination it corresponds to different concentrations of haemoglobin in ng per ml of preservation solution (e.g., 100ng/ml according to the analytical method "EIKEN" (78)). However, to avoid confusion, the result will always be expressed in µg of haemoglobin per gram of stool. **Any sample with a concentration equal to or higher than 20 µg haemoglobin per gram of faeces will be considered positive.**

  This variable will be categorised as:

  - **Positive FIT result:** > 20 µg of haemoglobin per gram of stool.
  - **Negative FIT result:** <20 µg of haemoglobin per gram of stool.

- **Indicated colonoscopies**

  The test of choice for individuals in the screening group with a positive faecal-immunochemical test (FIT) result is the colonoscopy. This test will only be considered in case of a positive FIT result. In order to determine this procedure indicated, it is necessary to assess the potential contraindications or other situations requiring specific action. This assessment will be carried out in a face-to-face visit managed by a trained professional from the Nursing Department of the referral Endoscopic Unit a few days before the test performance.

  During this visit, the personal history and current medication will be assessed and it will be determined whether the colonoscopy is indicated for the patient in question. Colonoscopy is a test performed under sedation, so anaesthetic risk will be assessed too using the American Society of Anaesthesiologists physical status classification (ASA PS) (96)(ANNEX 5).

  According to the Catalan PDPCCR the following situations are considered contraindications for colonoscopy (78).

  Absolute contraindications:

  - **Severe systemic disease or ASA >IV**
  - **Severe active infection**
  - **Signs or symptoms suggesting intestinal perforation**
  - **Severe irreversible coagulation disorder**

  Relative contraindications:

  - **Peritoneal dialysis**
  - **Severe dementia**
  - **Severe general condition or ASA III.**

  The colonoscopy will be indicated for those participants in the screening group with a positive FIT result and no contraindications for colonoscopy. Participants showing contraindications for colonoscopy will be excluded from the study and will be referred to a gastroenterologist and to their primary care doctor.

  This variable will be categorised as:

  - **Indicated colonoscopy:** any participant with a previous positive FIT result and no contraindications for the colonoscopy

- **Contraindicated colonoscopy:** participants with a negative FIT result or participants with a positive FIT result presenting one or more contraindication for the colonoscopy.

- **Accepted colonoscopies**

Once the indication for the colonoscopy is confirmed, the individuals involved will accept or deny the willingness to undergo this procedure. The informed consent, signed by the subject undergoing the test and by the endoscopist in charge of the examination, will be needed. The physician performing the procedure will hand the document and properly explain it to the patient before the test. The colonoscopy will only be performed in the presence of this document duly signed and will be properly kept for the whole duration of the study.

This variable will be categorised as:

- **Performed colonoscopy:** the colonoscopy informed consent was duly signed, and the participant did undergo the procedure.
- **Not-performed colonoscopy:** the colonoscopy informed consent was not signed, and the participant did not undergo the procedure.

- **Colonoscopy and pathology results:**

Colonoscopy findings will be classified, quantified, and reported. The department of digestive endoscopy and anatomical pathology will be responsible to develop this task. The colonoscopy results will be categorised as it follows according to the criteria followed by PDPCCR of Catalonia and the "Societat Catalana de Digestologia" (10,32,78):

- **Non-Advanced lesions:**
  - **Non-advanced adenoma:** 10mm, tubular and low-grade dysplasia.
  - **Non-advanced serrated lesion:** <10mm and no dysplasia.
  - Any resected but uncollected polyp under 10mm of size.
- **Advanced lesions:**
  - **Advanced adenoma:** ≥10mm, villous component or high-grade dysplasia
  - **Advanced serrated lesion:** ≥10mm or with dysplasia.

- **Non-invasive adenocarcinoma (stage 0).**

- **Invasive adenocarcinoma,** findings compatible with invasive colorectal adenocarcinoma: cancerous cells invading or overpassing the submucosal layer (stage I-IV of the American Joint Committee on Cancer (AJCC)).

  In case of any invasive adenocarcinoma, to detect possible cases of Lynch syndrome, the MSI pathway (microsatellite instability) will be studied using molecular or immunohistochemical tests (DNA repair proteins: MLH1, MSH2, MSH6 and PMS2). If a positive case is detected, it will be specified too.

- **Polyposis syndromes,** endoscopic findings compatible with polyposis. The diagnosis of colorectal polyposis is accepted when there are more than 20 polyps. Syndromes will be classified according to the polyp histology as
  - **Familial adenomatous polyposis:** further subclassified into classical (>100 polyps) or attenuated (20-100 polyps).
  - **Hamartomatous polyposis:** Peutz-Jeghers syndrome, Juvenile polyposis, Cowden syndrome.
  - **Serrated polyposis**

- **Inflammatory bowel disease (IBD)**, pathological findings compatible with Crohn's disease or Ulcerative Colitis.

- **Other findings:** defined as patients with other lesions either benign - haemorrhoids, diverticula, anal fissure, etc. – or malignant - anal squamous cell carcinoma, carcinoid tumour, etc. – that are not related with an increased risk of CRC.

  Therefore, this group will also include hyperplastic polyps of <10mm limited to the rectum or sigma.

- **Negative colonoscopy:** Colonoscopy in absence of abnormal findings. It will be defined as the absence of adenomas/serrated polyps/cancer/ IBD / other lesions. Colonoscopies without endoscopic findings where no sample has been collected will also be included.

- **Localization of invasive colorectal carcinoma lesions:**

  The location of any lesion found in the colonoscopy must be informed in the colonoscopy report.

  The location of any invasive CRC detected during the colonoscopy will be classified and categorised according to the following anatomical regions.

  - **Rectum**
  - **Sigma**
  - **Descending/Left colon**
  - **Splenic flexure**
  - **Transverse colon**
  - **Hepatic flexure**
  - **Ascending/Right colon**
  - **Cecum**

- **Colorectal cancer stage:**

  Any individual diagnosed with a lesion compatible for an invasive adenocarcinoma will be referred for a visit with a gastroenterologist at their referral Hospital. There, they will undergo an extension study to assess the locoregional and/or distant extension.

  The tests carried out for the staging will be applied according to the clinical criteria of each Hospital. However, most in the common clinical practice the following tests are usually performed (2):

  - If colon cancer is diagnosed the extension study will consist of thoraco-abdominal CT scan.
  - If rectal cancer is diagnosed the extension study will be performed with a pelvic MRI scan + thoraco-abdominal CT scan.
  - All patients will undergo a blood test that must include hepatic profile, nutritional parameters and tumoral markers (CEA and CA19.9).
  - Other tests will be performed depending on the patient's signs and symptoms: e.g., bone pain -gammagraphy, pneumaturia-cystoscopy.

Once the extension study has been completed, the lesions will be classified according to the American Joint Committee on Cancer (AJCC) staging system (70) in the following group:

- **Early Stages**
  - **I:** cancerous cells have spread to the submucosa or the muscle layer of the colon or rectum wall.
  - **II:** cancerous cells have reached the serosa and may have spread to nearby organs. There is no lymphatic affection. It can be subdivided into IIA, IIB and IIC.
- **Advanced stages**
  - **III:** cancer has spread to nearby lymph nodes. Depending on the number of lymph nodes and the layers affected this stage is subdivided in IIIA, IIIB, IIIC
  - **IV:** cancer has disseminated to distal regions of the organisms, and can be subdivided in IVA, IVB, IVC.

Patients with CRC will be classified according to this staging system. This variable will be categorised as:

- **Early stage:** stage I or II.
- **Advanced stage:** stage III or IV.

- **<u>Type of colonoscopy complications</u>**

The principal recognized harms of CRC screening, although being very rare, are those associated with colonoscopy as a follow-up of a FIT positive test. The harm conventionally associated with a possible false positive test result, is partly mitigated because a normal follow-up colonoscopy would remove the patient from the next screening rounds as it can be assured that he/she will most likely not develop any malignant lesions within the following 10 years.

However, to assess the risk-benefit balance of this screening tool, the type of complications secondary to colonoscopy will be registered among the screening group.

Immediate and delayed complications of colonoscopy include colonic perforation, postbiopsy and/or postpolypectomy bleeding, and diverticulitis (described among patients with previous diverticulosis). As colonoscopy is performed under sedation, cardiopulmonary complications secondary to anaesthesia can also be produced. Although it is extremely rare, death related to colonoscopy has also been described (86).

To express this variable, the **most significant complications appearing within the first 30 days after the colonoscopy** will be assessed and categorised as:

- **Important colonic bleeding:** any colonic bleeding requiring hospitalization.
- **Colonic perforation**
- **Important cardiopulmonary complications:** secondary to sedation.
- **Other significant complications**: defined as any life-threatening complication secondary to colonoscopy.
- **Death**

After the procedure, patients will remain under observation for a few hours until being fully recovered from sedation and they will be instructed to report any unwanted effect to one of the members of the referral Endoscopic Unit. In addition, 2 days after the colonoscopy a call from the endoscopic unit will be performed, to rule out any complication.

In the event of post-discharge complications, a face-to-face visit will be arranged, and the patient will be properly checked and treated. Afterwards, any complication will be recorded.

- **Colonoscopy complications**

To assess the **risk-benefit balance of this screening tool**, **the number of complications secondary to colonoscopy mentioned in the previous paragraph will be registered and quantified** among the screening group.

- **Quality of life evaluation:**

Quality of life is frequently cited as, “the state of well-being, compounded by 2 components: the ability to perform daily activities reflecting physical, psychological

and social well-being; and the patient's satisfaction with levels of functioning and disease control" (97).

Our study aims to assess the quality of life of those participants who have been diagnosed with CRC during our study and who are still alive 5 years after diagnosis. We will assess quality of life using the **EORTC QLQ-C30 questionnaire** (ANNEX 6). This questionnaire was developed by the European Organisation for Research and Treatment of Cancer (EORTC) to evaluate the quality of life (QoL) of oncologic patients, and it was specifically designed to be used in clinical trials. It is composed of 30 questions or items that assess QoL in relation to physical (symptoms), emotional, social and the overall level of functioning of patients with cancer. The questions refer to the week prior to the questionnaire. For the completion of the QLQ-C30 questionnaire, values between 1 and 4 (1: not at all, 2: a little, 3: quite a lot, 4: a lot) are assigned according to the patient's responses to the item, only items 29 and 30 are evaluated with a score of 1 to 7 (1: very bad, 7: excellent). The scores obtained are standardised and a score between 0 and 100 is obtained, which determines the level of impact of the cancer on the patient for each of the scales. High values on the overall level of functioning indicate improved QoL, while high values on the items referring to cancer-associated symptomatology indicate a decreased QoL (97,98).

To complete the QoL assessment of our participants, the CRC specific questionnaire, **EORTC-QLQ-CR29** (ANNEX 7), will be used as well. This questionnaire was also designed by the EORTC group and allows a more specific assessment of the QoL of CRC patients. It consists of 20 additional questions (plus 13 more in case of colostomy), scored, and interpreted the same way as the previous questionnaire.

Both questionnaires will be evaluated among the study participants diagnosed with CRC who are still alive 5 years after diagnosis, afterwards the average scores obtained in the study group and in the control group will be compared (97,98).

Table 7- Dependent variables of the study

DEPENDENT VARIABLES	MEASUREMENT	DESCRIPTION	CATEGORIES
CRC mortality	Clinical records	Qualitative dichotomous	- Dead - Alive
Positive FIT results	Analytical Laboratory results	Qualitative dichotomous	- Positive - Negative
Indicated colonoscopies	Anamnesis and physical exploration	Qualitative dichotomous	- Indicated - Contraindicated
Accepted colonoscopies	informed consent and colonoscopy inform	Qualitative dichotomous	- Performed - Not performed
Colonoscopy and pathology results	Colonoscopy and anatomical pathology confirmation	Qualitative polytomous	- Negative colonoscopy - Non-advanced lesions - Advanced lesions - Polyposis syndromes - Invasive adenoCa - IBD - Other
Localization of CRC lesions	Colonoscopy report	Qualitative polytomous	- Rectum - Sigma - Left colon - Splenic flexure - Transverse colon - Hepatic flexure - Right colon - Cecum
CRC stage	Extension study tests	Qualitative dichotomous	- Early Stage - Advanced Stage
Type of colonoscopy complications	Self-Recalled, Anamnesis, Physical examination and specific complementary tests	Qualitative polytomous	- Colonic bleeding - Colonic perforation - Cardiopulmonary events - Other - Death
Colonoscopy complications		Quantitative discrete	
Quality of life	EORTC QLQ-C30 EORTC QLQ-CR29	Quantitative discrete	

NOTE: CRC (colorectal cancer), FIT (faecal immunochemical test), adenoCa (adenocarcinoma), IBD (inflammatory bowel disease).

7.5.3. COVARIABLES

The following variables may play an important role in the modification of the results due to their influence over CRC incidence and mortality, therefore, must be considered when results are analysed.

- **AGE:** CRC risk increases with age; therefore, CRC incidence could be higher in the older patients (around the 49 years of age) compared to the younger patients (around the 40 years of age) of our sample. Similarly, age is also associated with higher comorbidity, lower response to treatment and worse prognosis (1). **This variable will be expressed in years.**
- **SEX:** CRC risk is up to 30% times higher among man than women (37). This variable will be recorded **as "F" for women and "M" for men.**
- **SOCIOECONOMIC STATUS:** individuals with lower socioeconomic status are more likely to be diagnosed with CRC in comparison to those with higher socioeconomic status (64) due to present a higher prevalence of CRC risk factors. The education has been related to the socioeconomic status; therefore, this variable **will be divided according to the achieved educational level:**
    - Without studies
    - Primary qualification
    - Secondary qualification
    - Diploma/Degree
    - Post-graduate
- **TOBACCO:** Tobacco is considered a direct cause of CRC, especially for current smokers (55).It will be classified as:
    - **Active smoker**
        - In the case of being an active smoker the consumption is going to be recorded with the measurement of **cigarettes per year.**
    - **Ex-smoker**
        - In case of being an ex-smoker the **years since the last cigarette** will be recorded.
    - **Non-smoker**
- **ALCOHOL:** There is evidence that moderate and high alcohol consumption are associated with a higher risk to develop CRC (1). The information will be obtained

and expressed as **grams of alcohol daily and weekly consumed**, and it will be classified as proposed by V.Bagnardi et.al (57):

- **Light drinking:** ≤12,5 g/day
- **Moderate drinking:** 12- 50 g/day
- **Heavy drinking:** >50 g/day

- **BODY FATNESS:** Body mass index (BMI), as a measurement of body fatness, is related with higher risk and poorer prognosis for CRC (48). BMI is calculated using the following formula BMI= Weight/ Height^2 and expressed in Kg/m^2. This covariable will be registered using the BMI classification:
  - **Underweight:** <18,5 BMI
  - **Normal weight:** 18,5-24,9 BMI
  - **Overweight:** 25,0-29,9 BMI
  - **Obesity class I:** 30,0-34,9 BMI
  - **Obesity class II:** 35,0-39,9 BMI
  - **Obesity class III:** >40 BMI.
- **PHYSICAL ACTIVITY:** Physical inactivity is considered a strong risk factor for CRC, and it has also been associated with worse therapy outcomes. On the contrary there is strong evidence that being physically active decreases the risk and death for CRC (47). The American Institute for Cancer Research recommends engaging up to 150-300 minutes of moderate-intensity activity or 75-150 minutes of vigorous-intensity activity (or combination of both) weekly (52). This variable will be expressed as:
  - **Active:** the subject engages up to 150-300 minutes/week of moderate-intensity activity or 75-150 minutes/week of high-intensity activity, or combination of both.
  - **Slightly Active:** the subject performs less physical activity than active individuals but more than sedentary individuals. This group includes individuals performing daily activities like transport (walking, travelling by bike, etc) and household (cleaning, washing, etc).
  - **Sedentary:** the subject does not engage in any moderate or high intensity activity per week and is not active in a day-to-day basis.
- **DIABETES:** Individuals with type 2 diabetes present higher risk for CRC (46). It will be recorded as a **yes/no question**.

- **MENOPAUSE:** Hormonal factors could have an impact in CRC (59). The information will be assessed among females participating in the study and will be obtained from the anamnesis:
    - **Non-menopause:** patient with monthly menstrual cycles.
    - **Pre-menopause:** patient with less than 12 months without menstrual period
    - **Menopause:** patient with more than 12 months without menstrual period.
- **DIETARY HABITS**
    - **RED MEAT:** Red meat is considered a "probably carcinogenic" factor since 2015 by the WHO (53). Red meat refers to all types of mammalian muscle meat (beef, veal, pork, lamb, etc.). Guidelines recommend not to exceed the 350-500 grams (equivalent to three portions) of cooked weight of red meat per week (52). Participants will be asked for the number of red meat portions consumed per week and it will be expressed as:
        - **Risk red meat consumption:** >3 read meat portions weekly.
        - **Non-risk red meat consumption**: ≤3 meat portions weekly.
    - **PROCESSED MEAT:** Processed meat is considered a "carcinogenic" factor since 2015 by the WHO(53). Processed meat refers to meat that has been transformed using salting, curing, or any other process to improve preservation (ham, salami, bacon,etc.). Guidelines recommend consuming very little, or none, processed meat (52). Daily processed meat intake will be asked as a **yes/no question.**
    - **CALCIUM:** A calcium intake under 700-100 mg/day has been associated with increased CRC risk (51). Participants will be asked for the number of dairy foods consumed daily (milk, cheese, etc) and for the use of calcium supplementation. This covariable will be expressed as:
        - **Adequate daily intake of calcium (>700-1000 mg/day)**: consumption of 2 or more servings of dairy foods per day and/or calcium supplements intake.
        - **Deficient daily intake of calcium (<700 mg/day):** consumption of <2 servings of dairy foods per day without calcium supplementation.
    - **FIBRE:** diets poor in fibre (whole grains), have been associated with higher incidence of CRC (51). According to WHO, adults should consume at least 3

portions of whole grains per day (to meet the recommended fibre intake of 25-35 grams/day). This variable will be expressed as:

- **Adequate daily intake of fibre:** the participant consumes ≥3 portions of whole grains daily.
- **Deficient daily intake of fibre:** the participant consumes <3 portions of whole grains daily.

- **FRUITS AND VEGETABLES:** diets poor in fruits and vegetables have been associated with a higher risk for CRC (49,51). According to WHO adults should consume at least 400 g (5 portions) of fruits and vegetables daily. This variable will be expressed as:
  - **Adequate daily intake of fibre, fruits and/or vegetables:** the participant consumes at least five portions of vegetables and fruit every day.
  - **Deficient daily intake of fibre, fruits and/or vegetables:** the participant does not consume the daily intake of five portions of vegetables and fruit.
- **VITAMIN D:** Compelling data from several studies suggest vitamin D as a potential protective factor against CRC (54). Vitamin D supplements intake will be assessed as a **yes/no question.**

- **CONCOMITANT TREATMENTS:** all the medications consumed by the participants will be reported to be assessed as possible interactions of the study. Specially attention will be paid to the following drugs:
  - **ANTIBIOTICS:** oral antibiotic overuse could increase the risk for CRC by disrupting the balance of gut microbiota. Although the definition of the role played by this factor remains heterogeneous, one study revealed that long-term antibiotic use (>2 months) in early middle adulthood (20-39 years) (61). We will ask the participant if he/she has received one or more antibiotic treatments for more than 2 months between the age of 20-39 years. It will be assessed as a **yes/no question.**
  - **NSAIDS:** High dose (>500 mg/day) and long-term acetylsalicylic acid users (>5 years) appear to have a lower risk to develop CRC and a survival benefit compared to non- acetylsalicylic acid users (58). We will ask the participant

if he/she has been taking >500mg/day of acetylsalicylic acid for more than 5 years. It will be recorded as a **yes/no question**.

- **BISPHOSPHONATES:** Studies suggest that bisphosphonates could be a protector factor for CRC (63). It will be assessed as a **yes/no question**.

All the covariables will be reported using a case report form (CRF) (ANNEX 8), that will be filled by one of the team members based on the participant's information obtained from the anamnesis, medical history, and measurements (weight and height for BMI calculation) of the patient.

Table 8- Covariables of the study

COVARIABLE	DESCRIPTION	CATEGORIES	MEASURAMENT
Age	Quantitative variable		CRF collected by one of the study members through anamnesis and anthropometric measures*. **Weight and height will be measured in the consulting room and used to calculate the BMI.*
Sex	Qualitative dichotomous	- F: Women - M: Men	
Socioeconomic Status	Qualitative polytomous	- Without studies - Primary qualification - Diploma/Degree - Post-graduate	
Tobacco		- Active Smoker - Ex-Smoker - Non-Smoker	
Alcohol		- Light drinking - Moderate drinking - Heavy drinking	
Body Fatness (BMI)		- Underweight - Normal weight - Overweight - Obesity I - Obesity II - Obesity III	
Physical Activity		- Active - Slightly Active - Sedentary	
Menopause		- Non-menopause - Pre-menopause - Menopause	
Diabetes **Red Meat** **Processed Meat**	Qualitative dichotomous	- Yes - No	

Calcium **Fibre** **Fruits and vegetables**	Qualitative dichotomous	- Adequate daily intake - Deficient daily intake	
Vitamin D **Antibiotics** **NSAIDS** **Bisphosphonates**	Qualitative dichotomous	- Yes - No	

Notes: *BMI (body mass index)*

7.6. INTERVENTION

All the participants, regardless of their assigned group, will be provided with a "stool sample collection kit" during the first visit in their primary care centre (PCC). There, one of the trained members of the Nursing Department will explain to them how to perform the test correctly (ANNEX 9). All participants must return the stool sample within 2 weeks to the same centre where the collection kit was provided, but never exceeding 3 days from the date of defecation. In case of non-delivery of the sample, a reminding phone call will be done by the nurse in charge of the participant

The strategy followed by each group of the study are explained below and represented in Figure 14:

7.6.2. SCREENING STRATEGY

Participants of the screening group will follow the following circuit:

- **Stool sample delivery and analysis:** Once the participants of the screening group have handed their stool sample in their referral PCC, this will be analysed using a quantitative FIT.
- **Delivery of FIT results:**
    - **Negative results will not be reported,** and the participant will receive a reminder email two years after to repeat the same stool collection process (if the patient is less than 50 years old at that moment).
    - **In case of a positive FIT result**, participants will be informed about the positive FIT via a telephone call from their referral endoscopy unit in less than 2 weeks.

During this call, the meaning and implications of FIT positivity will be explained, and a colonoscopy will be recommended. The affected participants will then be scheduled as soon as possible (maximum 7 days after the communication of the positive result) for a face-to-face visit with the nursing team of the reference endoscopy unit.

Participants who cannot be contacted by telephone will receive an email requesting them to contact their referral centre to arrange a visit with the screening nurse.

- **Colonoscopy indication-visit:** As mentioned, participants with positive FIT will be scheduled for a visit, carried out by the nursing staff of one of the referral endoscopic units involved in the study. During this call:
    - The meaning of the positive FIT result will be re-explained.
    - Information about the colonoscopy procedure and possible complications will be provided.
    - Information about the preparation of the colonoscopy will be handed.
    - Personal and medical data, concomitant medication, and anaesthetic risk (ASA level) will be registered through the anamnesis and clinical history. Exclusion criteria and contraindications for the colonoscopy will be assessed.
    - Participants in treatment with anticoagulants, antiplatelet agents, or oral iron, will be informed about the posology modifications that need to be made before the procedure.

  If no contraindication is detected and the patient agrees, the colonoscopy will be scheduled (within the next 2 weeks) and will take place in the referral screening centre for the patient. Patients meeting any contraindication for colonoscopy will be excluded and referred to a gastroenterologist and their primary care doctor.
- **Colonoscopy preparation:** once the colonoscopy is indicated, during the same visit with the nursing team of the endoscopy unit, patients will be explained how to perform the colonoscopy preparation and the evacuation solution will be provided. Patients undergoing a colonoscopy, must follow a specific diet low in vegetable fibre for 2 days prior to the test, and a liquid diet together with the administration of an evacuation solution in the previous 12-24 hours (ANNEX 10). The evacuation solution used for the colonoscopy will be a polyethylene glycol-based preparation

(PLEINVUE®). Other specific situations, involving medication, will also be considered before a colonoscopy, and the patient will receive instructions on how to proceed:

  - Individuals receiving oral iron therapy should discontinue it for seven days prior to the colonoscopy.
  - Individuals receiving anticoagulant or antiplatelet therapy, will be assessed in order to modify their therapeutic regimen according to the established guidelines and protocols (ANNEX 11) and will be asked to arrange a visit with their primary care physician in order to modify the medication regimen prior to the test.

- **Colonoscopy procedure:** Before the colonoscopy, the physician performing the procedure will hand the informed consent document (ANNEX 3) and properly explain it to the patient before the test. The colonoscopy will only be performed in the presence of this document duly signed (by both the participant and the physician) and will be properly kept for the whole duration of the study.

  The colonoscopy will be performed under deep sedation if the patient has consented to it. The level of colon cleaning will be assessed using the "Boston scale" (ANNEX 12). If the colonoscopy is poorly prepared (Boston <3%) it will be necessary to repeat the colonoscopy insisting on the colon preparation.

  During the procedure, biopsies or polyp's resection may be performed at the discretion of the endoscopist. Resection of all polyps will be recommended whenever possible; the polypectomy technique will be chosen according to the clinical criteria of the endoscopist. All lesions must be photographed, morphologically described according to "Paris classification" (ANNEX 1) and all resected polyps should be recollected for a posterior pathological analysis.

  At the end of the procedure, the patient will remain under observation for few hours to ensure a good recovery from the sedation and discard immediate complications. Afterwards, the patient will be able to go home, preferably with a companion, due to the remaining effects of the sedation.

  The patient will be instructed to report any adverse effects or complications related to the procedure, as soon as possible, to one of the members of the screening unit.

In any case, the patient will receive a call from the endoscopy team, 2 days after the test, to assess their clinical status or any possible complications.

- **Colonoscopy results:**

  Participants with negative results will be informed through a phone call from their referral screening centre. Patients with normal findings in the colonoscopy will no longer have to undergo the next screening rounds of the study and will not receive the reminder email after 2 years.

  In the case of colonoscopies with abnormal findings, these patients will receive a call to arrange a visit with a specialised unit which will vary depending on the results. During the visit, the endoscopy and pathology reports will be assessed, and the patient will receive information about the outcomes, and their meaning.

  - **Patients with ≤4 non-advanced lesions**: a visit with the nursing team of the endoscopy unit will be arranged. The participant will no longer continue to follow the next screening rounds and he/she will not receive the reminder email after 2 years. These patients will be followed by the gastroenterologist in charge of post-polypectomy surveillance strategies (*ANNEX 13*).
  - **Patients with an advanced lesion and/or a total sum of >4 non-advanced lesions:** will be scheduled for a visit with a specialised gastroenterologist in charge of the post-polypectomy surveillance strategies (*ANNEX 13*). They will be excluded from the upcoming screening round and will not receive a reminder email after 2 years.
  - **Patients with polyposis syndromes:** will be referred to the gastroenterologist in care of hereditary forms of CRC. These patients will be excluded from the following screening round too.
  - **Patients with invasive adenocarcinoma (CRC):** will be referred to a specialised gastroenterologist from their referral hospital. There, they will undergo an extension study. The tests will be applied according to the clinical criteria of each specialist.

    The date of diagnosis, and the stage (at the time of diagnoses) will be duly recorded, and five years after the CRC diagnosis, the patient's survival will be assessed. Quality of life will be evaluated for all patients who are still alive at 5 years.

These patients will be excluded from the upcoming screening rounds and will not receive the 2-year reminder email.

- **Patients with IBD compatible findings:** will be scheduled for a visit with the corresponding gastroenterology specialist. These patients will be excluded from the upcoming screening round.
- **Patients with other findings:** The abnormal findings will be communicated to their referral primary care doctor and a visit will be arranged. These patients will no longer follow the upcoming screening round.

7.6.3. FAKE SCREENING STRATEGY

Participants in the fake screening group (control group) will submit their sample, but this will not be analysed, instead, it will be eliminated. The participant will be invited to perform the same procedure after 2 years until all screening rounds are completed through a reminder email. At the end of all screening rounds, it will be determined whether any of the patients of the "fake screening group" have developed CRC during this time. If CRC is detected, the date of diagnosis, and the stage (at the time of diagnoses) will be recorded. Five years after the CRC diagnosis, the patient's survival will be assessed, and all patients who are still alive will undergo a quality of life evaluation.

7.7. SAFETY

The risks of the intervention can be associated to:

- **FIT:** to develop this test a stool sample is needed. There are no major risks associated with the collection of the stool sample and it is completely secure.

  As FIT is used as a screening tool, the only "downside" associated to this test would be the risk to obtain a false positive result in this test. A false positive would imply to submitting a healthy patient to an invasive procedure (colonoscopy) with its potential risks and complications. However, this effect is partly mitigated because a normal follow-up colonoscopy would remove the patient from the next screening rounds as it can be assured that he/she will most likely not develop any malignant lesions in the few years.
- **Colonoscopy:** is an invasive technique and therefore it has associated risks that will be considered. The main complications related to the realisation of a colonoscopy

include bleeding, colon perforation, diverticulitis, post-polypectomy syndrome and adverse effects from sedation (mainly cardiovascular) (86). However, to minimise the complications, a detailed assessment of the patient and potential risks (comorbidities, medication, and anaesthetic risk) will be carried out by one of the trained nurses of the Screening Unit before the intervention.

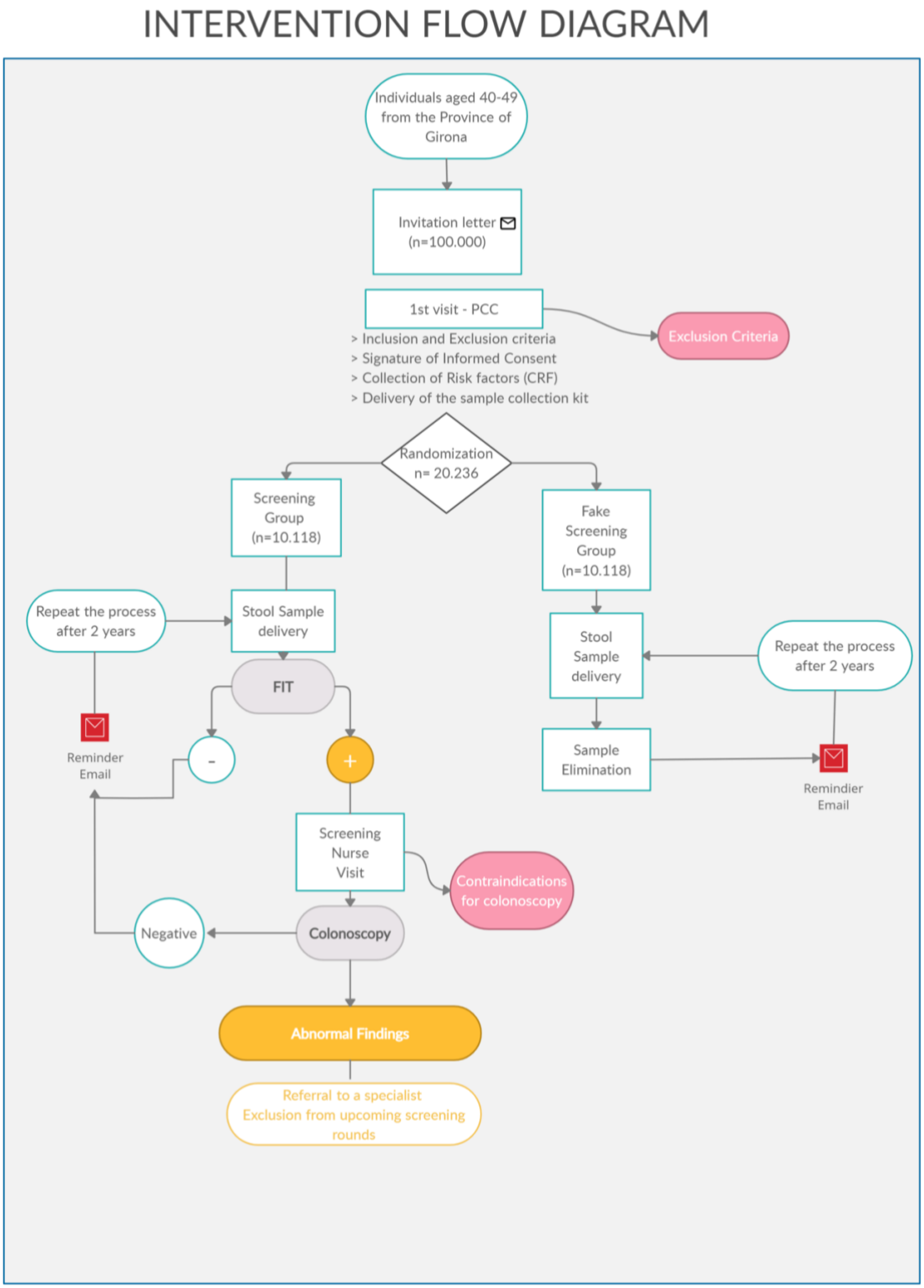


Figure 14- Intervention Flow Diagram

7.8. DATA COLLECTION

For data collection, we will create a computer-based database using SPSS ® Statistics program. Participant's name and personal data will be codified using an identification number to respect anonymity as much as possible.

- **INVITATION**

Data of our study population (name, age, address, phone number and email) will be collected from the CatSalut's Central Registry of Insured individuals' (CRI), which contains personal data of the users of the Catalan Health Service in possession of an individual health card (IHC). Eligible patients for our study will be invited to join the study through a nominal letter. Interested individuals will be directed to contact their referral primary care centre and a visit will be arranged with one of the trained members of the study team.

- **FIRST VISIT**

Those individuals interested in participating, will assist to a face-to-face visit with one of the trained members of the Nursing Department of the referral PCC.

During the first visit:

a. Information and an understandable explanation of the study will be offered, and the trained member of the team will assess the following topics:

i. Motivation and aims of the study, as well as the benefits that may lead in the future.

ii. Stages of the study, including detailed information (duration, follow-up, confidentiality, etc.) about the strategies followed for both groups of the study.

iii. Possible unwanted effects of the intervention.

iv. Inclusion and exclusion criteria of the study.

In case the subject meets the inclusion criteria and none of the exclusion criteria and agrees to participate in the study, the **Protocol Information Sheet** (ANNEX 14) and the informed **consent document** (ANNEX 3) will be handed.

b. The collection of all the covariables will be recorded during the first visit using a case report form specifically designed for the study (ANNEX 8). The questions in the CRF will be formulated and signed in by the responsible

members of the Nursing Department. Most of them will be assessed through the anamnesis except for the BMI for which weight and height will be measured in the consult.

c. **Randomisation**

Once the subject accepts to participate in the study, he/she will be randomised to one of the following strategies.

i. **Screening Strategy (study group):** participants whose stool sample will be analysed using a screening tool (FIT).

ii. **Fake screening Strategy (control group):** participants whose stool sample will not be analysed.

The strategy followed by each participant will be registered in their personal profile of the study database.

d. **Stool sample collection kit:** during the first visit all the participants will be provided with a "stool sample collection kit" and an "instruction sheet" about how to use it (ANNEX 9). Verbal indications about how to use it will also be facilitated by the nursing team. Every collection kit will be identified using the participants study number.

The member of the study in charge of the first visit, will register all the information obtained during this visit and the date on which the kit was provided.

- **SAMPLE DELIVERY AND RECEPTION**

All participants must deliver the stool sample in their referral PCC in less than 2 weeks since the first visit. Otherwise, a reminding phone call will be executed by the responsible member of the Nursing Department of the referral PCC. Participants will deliver the tube in their PCC where the professional in charge will identify the patient (and which study group he/she belongs to) and collect the sample. All samples received will be duly registered in the database.

- **SCREENING STRATEGY (study group)**

  - **Sample reception and custody:** The professional in charge will attach an identification label to the tube. This label will include the personal number and a barcode that will link each sample to the personal data of each participant.

The tube should be stored in a cool, dry place away from direct exposure to light while waiting to be collected by the transport service. It is preferable that the sample is kept always refrigerated (4-8 °C).

- **Sample distribution:** All samples collected by the transport service and leaving the PCC will be registered. The samples should be transported as quickly as possible (and never overpass the 15 days) to their referral laboratories following the same preservation conditions as mentioned above. The samples will be collected from the PCC by the same transport service in charge to transport other samples from the centre to the referral laboratory.
- **Sample processing (FIT):** Once in the laboratory, samples will be kept refrigerated (4-8ºC) and analysed in the shortest possible time to reduce the rate of false negative results due to haemoglobin degradation. The presence of occult blood in the sample will always be analysed using the same screening test: **quantitative FIT.** Any sample with a concentration equal to or higher than 20 µg haemoglobin per gram of faeces will be considered positive. All results will be registered in the study database. To avoid confusion, results shall always be expressed in the same units (µg /g). Positive results will be reported to the endoscopy units involved in the study. The laboratories participating in the study must incorporate the quantitative FIT into their quality system, and one of the specialists will be responsible of for the analytical process of the samples. To ensure the quality of the results all the laboratories collaborating with the study must participate in external quality programs and indicate which ones.

  Any incident that makes the analysis of the sample difficult or impossible shall be recorded in order to ensure the action to resolve it (repeat collection) and must be reported the referral PCC as:

  - Sample misidentified or illegible.
  - Broken tube or tube in bad conditions.
  - Sample excess or shortage

- **FIT results:**
  - **Negative FIT results:** will be registered but not informed, and participants will be sent a reminder email to repeat the exact same proceaduree 2 years after.
  - **Positive FIT results:** The laboratory will inform the referral endoscopy unit about any positive FIT, who will be responsible to arrange the pre-colonoscopy visit with one of the endoscopy unit nurses.
- **Colonoscopy Indication visit:** During this visit, the nursing team of the endoscopy unit will evaluate all the information about the medical history and clinical status of the patient, as well as the anaesthetic risk, ASA classification level and concomitant medication. All this information will be duly recorded in the study database. If the patient meets any potential risk for colonoscopy this will be contraindicated and excluded from the study and visit will be arranged with a gastroenterologist and their referral primary care doctor. On the other hand, if the patient does not meet any exclusion criteria for the procedure, the colonoscopy will be considered indicated. Both cases will be duly recorded in the study database. If the patient agrees, a visit to perform the procedure will be arranged within the next 2 weeks.
- **Colonoscopy:** Prior to the test, the responsible endoscopist will hand over and explain the colonoscopy informed consent document (ANNEX 15). The colonoscopy will only be performed in presence of a duly signed (by both the patient and the endoscopist) informed consent. This document will be kept by the endoscopic unit associated with the study for the whole duration of this one. The colon cleansing will be assessed using the Boston Scale and registered in the colonoscopy report. During the procedure, any diagnostic action that the endoscopist deems necessary (polypectomy, biopsy, etc.) will be carried out and registered in the colonoscopy report.

  At the end of the examination, the subject will remain under observation in the endoscopy unit for a few hours to assess their sedation recovery. Any complication during or after the procedure will be recorded.

The colonoscopy report will be registered in the database and must contain the information described in the ANNEX 16.

- **Pathological analysis:** Any colonoscopy sample arriving at the anatomical pathology department will be accompanied by:
  - **The request form:** which must include the identification data of the participant (identification number and barcode) and information about the polyps/samples extracted.
  - **The histological sample:** each sample must arrive in an individual tube, also duly identified.

  The anatomical pathology report should follow a specific format and it should provide information on:
  - Affiliation details of the participant
  - Location of the lesion
  - Endoscopic procedure performed (resection/ biopsy/etc.)
  - Size (mm)
  - Histological type and grade
  - Resection margins

  The report should be issued in no less than 1 week after arrival of the sample.

  If the sample is positive for colorectal carcinoma, in order to detect possible cases of Lynch syndrome, the MSI pathway (microsatellite instability) will be studied using molecular or immunohistochemical tests (DNA repair proteins: MLH1, MSH2, MSH6 and PMS2). If a positive case is detected, it will be reported too.
- **Colonoscopy complication's registry:** 2 days after the colonoscopy a call from the endoscopic unit will be performed by one of the nurses to assess the evolution of the patient. In addition, patients will be instructed to notify any possible complications related to the procedure. In such a case, the participant will be visited, examined, and treated if necessary and the type and severity of the condition will be recorded in the study database.

- **Colonoscopy and Pathology results:** Participants with negative results will be informed through a phone call from the endoscopy unit and they will be explained about how to proceed for the next controls.

  The Screening Unit team (endoscopy and anatomical pathology departments) will be the responsible for the classification of the abnormal findings that will be classified as:

  - Non-advanced lesions
  - Advanced lesions
  - Invasive adenocarcinoma (CRC)
  - Polyposis syndromes
  - IBD compatible findings
  - Other findings

  Participants with abnormal findings in the colonoscopy will receive a phone call from the administrative department of the endoscopy unit.

  - **≤4 non-advanced lesions:** patients with these findings will be informed about the colonoscopy outcomes through a phone call and a meeting with the nursing team of their referral endoscopic unit will be arranged. During this visit the screening nurse will explain the results and how to proceed to the patient.
  - **Advanced lesions or >4 non-advanced lesions / invasive adenocarcinoma / polyposis syndromes / IBD:** these patients will not be announced about the results during the phone call, and a visit with the referral gastroenterologists will be arranged, only there the specialist will explain the outcomes to the patient and how he/she must proceed.
  - **Other findings:** patients with other outcomes will be arranged for a visit with their primary care doctor.

  This activity and those participants who no longer have indications to follow the screening rounds will be registered in the study data base.

  For any case of invasive CRC, the date of diagnosis and the stage by that time will be recorded.

In order to know if any CRC is "missed" in the screening group. All the participants will be asked to inform the study team in case they are diagnosed with CRC outside the framework of the study. However, at the end of all screening rounds the electronic medical records (SAP) of the participants with FIT negative results will be checked in order to assess the number of "false negative" FITs.

- **FAKE SCREENING STRATEGY (control group)**
    - **Stool sample delivery:** All the samples submitted by the participants of the "fake screening group" will be recorded as "delivered", and the samples will be eliminated. The same process will be performed and registered during the following screening rounds. Participants will be reminded to repeat the process through an email.
    - **CRC detection:** in order to know if any CRC is diagnosed outside the study framework, at the beginning participants from the control group will be instructed to inform the study team if they are diagnosed with CRC at some point during the course of the study.

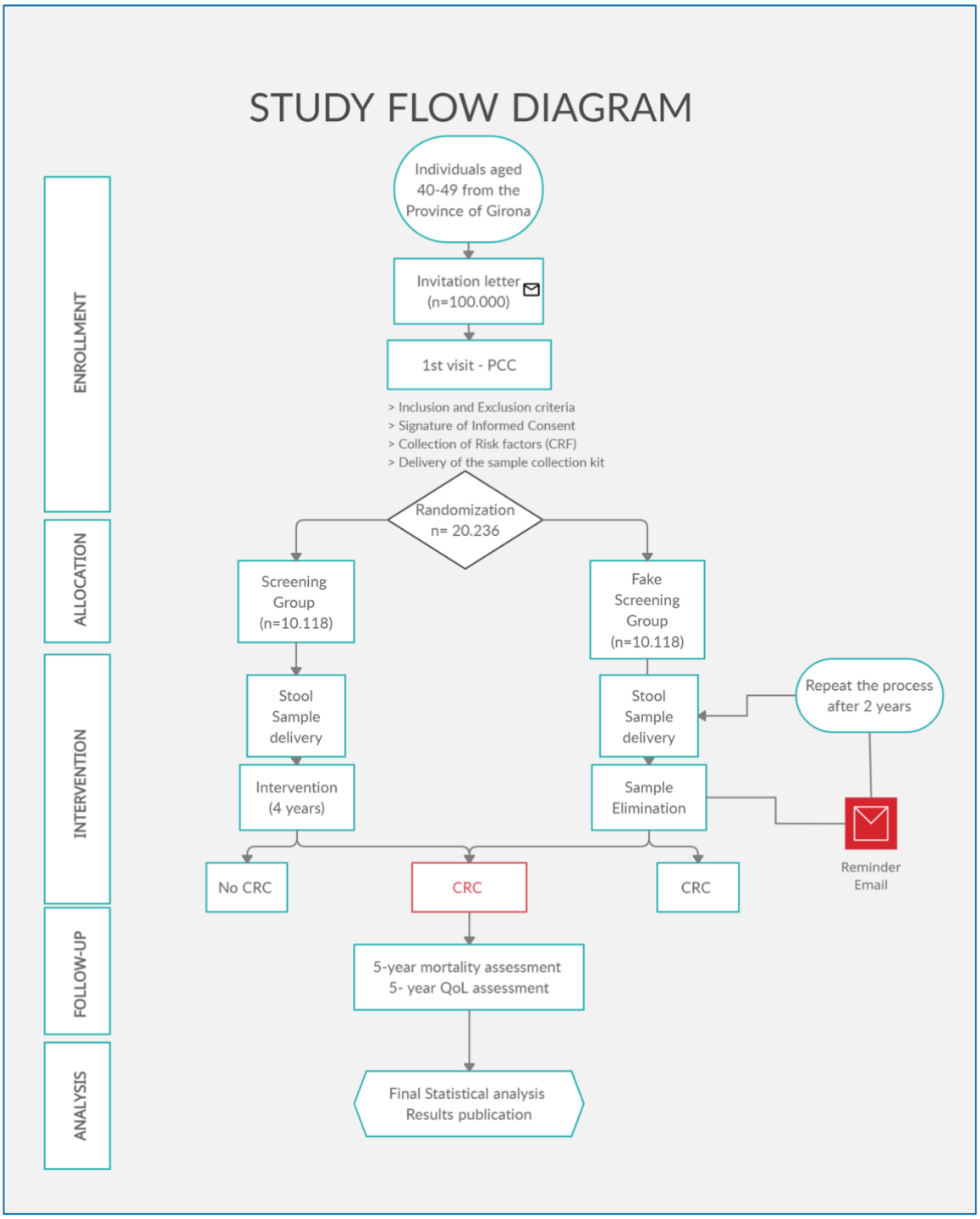
      In any case, at the end of all screening rounds, an analysis will be made to check if any CRC has been diagnosed among the control group using the electronic medical records of the SAP system, and the date of diagnosis and the stage by that time will be recorded. This will allow us to know the incidence of CRC in our control group.
- **CRC'S FOLLOW-UP**

Death at 5 years of the CRC cases diagnosed through the screening intervention will be determined through the electronic medical records of the SAP system. The same will be performed for the CRCs aroused in the control group during the study. Information will be recorded in the study database.

All patients alive 5 years after the CRC diagnosis (either from the control or the study group) will be contacted through email. Attached to this email will be a link directing the patient to a secure website where they will find the web-questionnaire version of EORTC QLQ-C30 (general QoL) and QLQ-CR29 (specific QoL for CRC patients). The study member assessing the data from these questionnaires will be blinded. The

scores for each section of the questionnaire will be recorded. Finally, the average punctuation obtained for each group of the study will be calculated and compared.

- **STUDY FLOW DIAGRAM:**



8. STATISTICAL ANALYSIS

- **Descriptive analysis**

We will summarise the qualitative dependent variables (CRC specific mortality at 5 years, positive FIT results, indicated colonoscopies, accepted colonoscopies, colonoscopy results, localization of invasive adenocarcinoma, stages of CRC, and specific type of colonoscopy side effects) by proportions. The discrete dependent variables (the number of colonoscopy side effects and quality of life) using median and interquartile range.

We will repeat these analyses stratifying by the intervention. This last analysis will be stratified by the covariables. Quantitative variables will be properly categorised.

- **Bivariate inference**

The difference of proportions of the qualitative dependent variables between screened and not screened will be tested using the chi-square. When the expected number of counts in one cell will be less than 5 we will use Fisher's exact test.

The difference of medians of the discrete dependent variables will be tested by the Mann-Whitney's U.

These analyses will be stratified by the covariables. Quantitative variables will be properly categorised.

- **Assessment of the predictive capacity of FIT**

Positive predictive values (PPVs) will be calculated as the number of individuals diagnosed with CRC/ advanced polyps /non-advanced polyps over the number of participants with a positive FIT result. The results will be shown as percentage. The results will be compared with the PPV for premalignant and malignant lesions obtained in the population over 50 years of age, which in Catalonia is known to be 10-15% for CRC and 30-40% for premalignant lesions (76,78).

As we do not have a randomised sample, we will use the following formula based on the Bayes theorem:

$$PPV = \frac{S\ x\ P\ (Disease)}{S\ x\ P\ (Disease) + (1 - E)\ x\ (1 -\ P\ (Disease))}$$

- **Multivariate analysis**

The efficacy of the intervention on the mortality at 5 years, positive FIT results, indicated colonoscopies, accepted colonoscopies, stages of CRC will be assessed by logistic regression controlling for the covariables.

In the case of discrete dependent variables (colonoscopy complications and quality of life) the effect of intervention will be assessed in a Poisson regression, adjusting for the same covariables as above.

In the case of the qualitative polytomous variables (colonoscopy and pathology results, localization, and type of side effects) we will use a multinomial regression controlling for all the covariables. This type of regression is used when the dependent variable is a nominal polytomous or categorical variable. The interpretation of the OR (odds ratios) estimated in this regression is the same that in logistic regression.

Possible effect modifications between the risk factors (i.e., between age and sex) will be considered including interactions between this risk factors.

9. ETHICAL AND LEGAL CONSIDERATIONS

This protocol will be presented and submitted for consideration, evaluation, and approval by the Clinical Research Ethics Committee (CEIC) from Hospital Universitari Doctor Josep Trueta (HUJT) as the coordinating study centre. The Committee will ensure that the protocol fits the ethical requirements for being approved. In the case of the CEIC having objections, they will be considered, introduced, and modified. Management's Department authorization of all the medical centres enrolling in the study will also be required.

The study will be performed under the requirements expressed in the Declaration of Helsinki of Ethical Principles for Medical Research Involving Human Subjects signed by the World Health Association in October 2013, and the Principles of Biomedical Ethics from Beauchamp and Childress from 1970 and reviewed in 2009:

- **Autonomy:** the values and personal choices made by any participant will be respected throughout the study. An information sheet about the study protocol (ANNEX 14) in an understandable language for the participant will be given and explained by one of the members of the study. Written informed consent document (ANNEX 3) must be obtained by investigators from each participant before taking part in the study. It will also be explained to the individuals that they are free to refuse entry into the study and free to withdraw from the study at any time without prejudice.
- **Non-maleficence:** no malicious intent is being done to the patients participating in the study. Patients who may be affected by any of the tests in the study will be excluded.
- **Beneficence:** It is the moral obligation to act for the benefit of others. All actions will be carried out thinking about what is best for the patient. In our study this principle is being complied because we will apply a screening strategy that we hope will help to prevent and reduce CRC mortality.
- **Justice:** an equitable distribution of well-being benefits will be respected in the study, and any discrimination in access to health resources or against any group of people will be avoided to guarantee the principle of justice.

The development of the field trial will also obey with the credentials marked in "***The*** *Real Decreto 1090/2015, de 4 de diciembre, por el que se regulan los ensayos clínicos con medicamentos, los Comités de Ética de la investigación con medicamentos y el Registro Español de Estudios Clínicos".*

Privacy and confidentiality

The processing of personal data required in this study, the personal data cession of all the patients and their confidentiality and communication will obey: The Regulation (EU) 2016/679 of the European Parliament and of the Council of 27 April 2016, on the protection of people with regard to the processing of personal data and on the free movement of such data, The repealing Directive 95/46/EC (General Data Protection Regulation) and The *"Ley Orgánica 3/2018, de 5 de diciembre, de Protección de Datos Personales y Garantía de los derechos digitales"* and the *"Real Decreto 1720/2007, de 21 de diciembre por el que se aprueba el Reglamento de desarrollo de la Ley Orgánica 15/1999*".

The study will provide anonymity to patients by identifying them with a code number in the database. The data access will only be available to the research team. The access to this information by a third person will not be allowed. Therefore, this study guarantees the confidentiality and anonymity of all data related to the participants, and any data will be exclusively used for the purpose of the research.

Transparency

Investigators will have to declare no conflict of interest, and authors will declare the main goal of this research is to develop generalizable knowledge to improve human health and quality of life.

Investigators will also have to agree to publish all data and results with total transparency including unfavourable data or events. If, by any chance, the initial planning of the project suffers a deviation during the study, the research team will contact participants to inform them with total transparency and a new signed informed from every participant consent will be needed to continue with the study.

10. WORKING PLAN

10.5. PARTICIPATING CENTRES

The study will be conducted on 2 levels:

1) **PRIMARY CARE CENTRES (PCC):** All the PCC located in any of the basic health areas (BHA) belonging to the Health Region (HR) of Girona will be invited to participate in the study.

   The HR includes the following territories:

   - 7 counties in the Province of Girona (Alt Empordà, Baix Empordà, Garrotxa, Gironès, Pla de l'Estany, Ripollès and La Selva.)
   - Some municipalities of Marseme (Calella, Canet de Mar, Malgrat de Mar, Palafolls, Pineda de Mar, Sant Cebrià de Vallalta, Sant Iscle de Vallalta, Sant Pol de Mar, Santa Susanna and Tordera).

   In the PCC of all these regions, the "first level" of the study will take place - the participant's selection and enrolment, and the biennial collection of stool samples. The Nursing Department of these centres will be the main responsible, however primary care physicians will be aware about the study as well.

   Each PCC, according to its basic health area, will have a Screening Unit of reference. The same distribution designed for the screening programme for >50 years will be used.

2) **SCREENING UNITS:** each screening unit is formed by a **Clinical Laboratory Centre + Screening Nurse + Endoscopy Unit + Anatomical Pathology Unit + Specialised Gastroenterologists.** All the Screening Units in the Health Region of Girona will participate in our study.

   There, the "second level" of the study will take place → The Screening Units will be responsible for the proper development of the intervention of the screening group.

   The HR of Girona includes the following Screening Units:

   a. Hospital Universitari Doctor Josep Trueta
   b. Hospital Santa Caterina
   c. Hospital d'Olot i Comarcal de la Garrotxa
   d. Hospital de Figueres

e. Hospital de Palamós
f. Hospital de Campdevànol
g. Hospital de Sant Jaume de Calella
h. Hospital Comarcal de Blanes

10.6. RESEARCH TEAM

- **Research manager:** who will lead the execution of the project and will be responsible for ensuring the global coordination of the centres participating in the study, the correct application of the protocol and the correct storage of data and information.
- **Project Coordinator:** who will responsible for the supervision of the project regarding compliance with regulations and protocols.
- **Principal investigator:** who will be ultimately responsible for the overall research and the design, administration and conduct of the research protocol the publication of results and the writing of the extracted conclusions.
- **Co-Investigators:** for each BHA and Hospital participating in the study one of the co-investigators will be a "**Head Co-investigator**" in charge to properly coordinate each task. Head Co-investigators will be distributed as follows:
    i. PCC: there will be a Head co-investigator from the Nursing Department for each BHA.
    j. Screening Units: there will be a Head co-investigator for each Hospital. Additionally, each department involved will also have a main responsible:
        i. Laboratory manager
        ii. Responsible Nurse in charge of screening consultation
        iii. Endoscopy manager
        iv. Pathology manager
        v. Gastroenterology manager

  The Head Co-investigators will meet once every 6 months with the research manager and the study coordinator.
- **Research technician:** who will be in charge to assess all the information and data recorded during the study, ordering supplies, general clerical work, etc.

- **Statistic specialists:** in charge to perform the statistical analysis of the study

10.7. STUDY STAGES

The research team will carry out the tasks of coordination, interpretation, and dissemination of the results. The sequence of activities is detailed below:

Stage 0: Study design (November 2021 – January 2022)

- 1st meeting (November 2021): the study development was planned and agreed by the project coordinator (Dra. Virgínia Piñol) and the principal investigator (Anna Cufí). During this meeting the main objectives, hypothesis and methodology were established.
- Protocol elaboration (November 2021 – January 2022): Bibliographic research and protocol elaboration has been carried out during this time.

Led by: project coordinator and principal investigator.

Stage 1: Ethical evaluation (January 2022 – February 2022)

During this stage we will submit our protocol to the Clinical Research Ethical Committee (CEIC, *Comitè Ètic d'Investigació Clínica*) at Hospital Universitari Doctor Josep Trueta de Girona for its approval. During this phase an insurance will be contracted as well. The time requested in this stage may vary according to the time taken by the CEIC to approve the project. Any modification of the protocol will be done to achieve the CEIC's required conditions.

Led by: project coordinator and principal investigator

Stage 2: Initial coordination: February 2022-March 2022

- 1st meeting with the research team (February 2022)

  We will hold the first meeting with the study coordinator and all the head co-investigators involved with the study. During this meeting we will clarify the different phases of the study with the chronogram, and we will review the roles of each participant. All head co-investigators will be asked to hold a second meeting with their respective co-investigators to provide the with the same information. The whole research team will keep in contact via email and/or telephonic messages.
- Training (February 2022)

Co-investigators will be informed about the study protocol. They will be taught how to give the information to the patient and how to collect and record their data in the study database. Protocols and consensus documents will be provided for each unit in charge of one of the study phases. This is intended to homogenise the process and reduce differences in results.

Led by: all the team.

Stage 3: Participant's recruitment and data collection: March 2022 – May 2031

1. Patient recruitment (March 2022- March 2023)

   A consecutive sampling will be used. An invitation letter will be sent, and the enrollment visit performed for those participants interested in participating. Participants meeting the inclusion criteria and none of the exclusion criteria, after signing the informed consent, will be enrolled and randomised into one of the groups of our study.

2. Intervention (March 2022- March 2026):

   The screening intervention will be applied to our study group; the stool sample will be analysed using FIT, and in case of a positive result, participants will undergo a colonoscopy. This intervention will be applied biennially for 4 years so 2 screening rounds will be performed. If few CRC cases are found during this period, adding a third round of screening will be considered. During this period, once every 6 months the head co-investigator of each BHA and hospital will meet the study coordinator and research manager to assess whether the protocol is being correctly followed and discuss any inconvenience.

3. Follow-up (March 2022- March 2031)

   All the participants with CRC will be evaluated 5 years after the diagnosis to determine mortality at 5 years and to assess their quality of life.

   Notice how the duration of the study depends on the date of the last diagnosis of CRC. However, the maximum duration of the study could be up to 9 years (4 years of screening rounds + 5 years if the last diagnosis of CRC is made at the end of the last screening round).

4. Record of data (March 2022-March 2031)

The specialists will record all the data collected from the different variables in the database.

Led by: Head co-investigators and Co-investigators

Stage 4: Statistical analysis and data interpretation: April 2024-May 2031

The statistical analysis will be performed by a subcontracted statistician who will be blinded for the study groups.

1. Biennial Statistical analysis (April 2024 and April 2026):

   It will allow the assessment of the results obtained in each screening round: number of FIT positive results, number of indicated and performed colonoscopies, type of lesions found during the procedure, etc. In addition, It will allow us to determine the efficacy and side effects of the intervention. In case of observing great results for screening intervention, or in the contrary, in case of observing serious unwanted effects the study will be concluded and the results published

2. Final Statistical analysis (April 2031-June 2031):

   It will be carried out 5 years after the last diagnosis of CRC. During this stage all the information collected about the mortality at 5 years and the quality of life of the participants with CRC will be analysed.

3. Data interpretation (July 2031-August 2031):

   The principal investigator and the study coordinator will oversee the interpretation of the results. Afterwards the discussion and conclusion of the study will be released.

Led by: the statistician and the principal investigator.

Stage 5: Final article elaboration and publication of the results: September 2031 – October 2031.

k. Publication in reviews – Writing a Journal Article. Different reviews will be applied to publish the findings.

l. Attendance to 1 national congresses, "*Asociación Española de Gastroenterología"* to present the results and conclusions of the study.

Led by: The principal investigator and the study coordinator.

10.8. CHRONOGRAM

STAGE	TASK	PERSONNEL	PERIOD																									
			2021		2022				2023		2024			2025			2026			2027	2028	2029	2030	2031			
			Nov.	Dec.	Jan.	Feb.	Mar.	Apr.-Dec.	Jan.-Mar.	Apr.-Dec.	Jan.-Mar.	Apr.	May. -Dec.	Jan.-Mar.	Apr.	May. -Dec.	Jan.-Mar.	Apr.	May. -Dec.	Jan.-Dec.	Jan.-Dec.	Jan.-Dec.	Jan.-Dec.	Jan.-Mar.	Apr.-Jun.	Jul.-Aug.	Sep.-Oct.
STAGE 0 Study Design	1st meeting	Principal investigator Project coordinator																										
	Protocol elaboration	Principal investigator																										
STAGE 1 Ethical evaluation	Presentation to CEIC	Principal investigator Project coordinator CEIC																										
STAGE 2 Initial coordination	1st meeting	All team																										
	Training																											
STAGE 3 Recruitment and data collection	Patient recruitment	Head co-investigators and co-investigators																										
	Intervention																											
	Follow-up																											
	Record of data																											
STAGE 4 Statistical analysis and data interpretation	Biennial statistical analysis	Statistician																										
	Final statistical analysis																											
	Data interpretation	Principal investigator and Project coordinator																										
STAGE 5 Results publication	Publication and results dissemination	Principal investigator and project coordinator																										

11. BUDGET

11.5. NOT INCLUDED COSTS

Staff: the personnel participating in the research team will not be extra rewarded for their involvement in the project as they will perform their duties as part of their work activity. In doing so, we try to avoid any economic incentive to join the study.

Travel and meals allowances: Team meetings will be held telematically, therefore these expenses will not be covered.

11.6. INCLUDED COSTS

Subcontracted services

- **Insurance**
- **Statistician:** The study will contract a statistician in charge to perform the statistical analyses of the outcomes. These analyses will take place biennially during the first 4 years of the study. After this period, the statistical analyses will only be performed 5 after the last diagnosis of CRC.
- **Communications provider:** the study will contract a company in charge to send the reminder email 2 years after the first screening round, and to create secure website, link and email directing the patients with CRC to the QoL questionnaire. A data protection agreement will be previously signed to prevent the use of participants personal data for any non-study purposes.

Materials

This project aims to assess the efficacy of CRC screening among individuals between 40-49 years. The screening technique used for our intervention is the biennial FIT, followed by a colonoscopy in case of a positive result. This screening strategy is daily used among the hospitals involved in our study as part of the already established screening programme, however it is not used to screen individuals between 40 and 49 years. Therefore, the costs of FIT and the colonoscopy have been included in the budget.

The number of colonoscopies (and therefore the number of colonoscopy preparations, and the pathology analyses) is an approximation based on the incidence of positive FIT results obtained in the screening programme for population over 50 years of age (5%) (99). In our study, as the incidence of CRC is still inferior to the population over 50, we

expect to find an inferior number of positive results, however this gives us an idea of the "maximum" number of colonoscopies that our study could reach.

The rest of included costs are summarised in Table 9.

It should be emphasised that this is a "field trial", a study involving a very large population sample and therefore its total cost is also important. This protocol will be presented to multiple applications and calls for public and private funding in order to be carried out.

Table 9 – BUDGET OF THE STUDY

EXPENSES	COST PER UNIT	NUMBER OF UNITS	SUBTOTAL
	Personnel costs		
Investigators	0€	0	0€
Research technician	22,000€ /year	4 years full time 5 years part time	143,000 €
	Subcontracted services		
Insurance policy	25,000€/trial	1	25,000 €
Statistical analysis	30 €/hour	(70h in total) 30h/biennially for 4 years + 10h/year for an additional year	2,100 €
Communications provider	300€	1	300€
	Materials and Tests		
Shipping costs	0,10 €/letter	100.000	10,000€
Printing costs*	0,05 €/page	150.000	7,500€
Emails	0,03€/email	20.000	600€
Stool collection Kit	0,5€/unit	20.300/round	20,300
FIT	20€/ test	10.150/round	406,000€
PLEINVUE®	6€/unit	507/round	6.084€
Colonoscopy service	185€	507/round	187,590€
Pathology analyses**	6€	507/round	6,084€
	Dissemination and publication		
Article publishing fees	2,000 € /publication	1 publication	2,000 €
Inscription to national congresses	600€ /congress per attendant	1 congresses; 2 inscriptions	1,200 €
		TOTAL	817,758 €

NOTE: **Printing costs include invitation letter, study information sheet, Informed consent, colonoscopy informed consent.*
***Citology.*

12. LIMITATIONS

The present study has several limitations that should be acknowledged:

BURDEN OF THE DISEASE

Although the relative risk for eoCRC is increasing in some westernised countries, the absolute incidence of eoCRC is still moderate and considerably smaller than the older counterpart. In addition, most eoCRC are sporadic, and we still do not have sufficient evidence to individualise the indication for screening, thus, the intervention is needed for the general population. For this reason, our study sample is so large, and yet we may find that the incidence of CRC in this sample is too low and not significant. In case this happens, the study will consider increasing the sample size and/or the duration of the intervention by adding another screening round. As we assess a population-based intervention, we need a large sample to carry out an experimental design and therefor and demonstrate the efficacy of the screening intervention.

SAMPLE

The study uses a non-probabilistic sampling method, for this reason, the subjects in our study population do not have the same probability of being chosen to be part of the sample. However, the consecutive sampling is the non-probabilistic method that associates less bias, as it is theoretically a free-of-choice selection.

This type of sampling can give rise to a **selection bias**, which could lead us to the following situation: those subjects who are more concerned about their health and who are more likely to have a higher prevalence of healthy lifestyle habits and less comorbidities may be more likely to participate in the study, guided by the concerning for their health; while those subjects who are less concerned about their health, with poorer lifestyle habits and a higher prevalence of comorbidities may be less likely to participate. The opposite situation could happen as well. In either case, we would have a sample that does not resemble the reality of our population, and that could lead us to obtain both underestimated and overestimated, but in any way, unrepresentative results. To detect and remedy this bias, the results will be analysed considering possible

confounding variables. The results will be stratified by each of the covariables, and their possible associations will be assessed.

BLINDING

Since the screening intervention is only applied to one study group and not to the other, the researchers cannot be blinded. This could lead to **observer bias**, especially in the case of endoscopies as it is an "explorer-dependent" diagnostic test. Knowing that a patient is participating in the study can lead the endoscopist to perform a more thorough examination for malignant lesions.

All participants will be blinded at the beginning of the study. In case of a positive FIT result, the participant will have to undergo a colonoscopy, so the blind will be lost every time this happens as the participant will know of his/her participation in the screening group. By blinding all patients initially, we try to reduce the **attentional bias**. Attentional bias, or Hawthorne effect, occurs when study participants may alter their behaviour when they know they are being observed. In any case, this bias could appear in those patients with a positive FIT, but we do not consider that it could have any impact on the results, as the time between the notification of the positive FIT result and the colonoscopy is minimal.

To try to minimise any bias related to the absence of triple-blinding, we will blind the statistician to each participant's intervention.

COLLABORATING CENTRES

It is a multi-centre study involving multiple units and departments. To avoid **detection bias and collection bias,** a protocol will be drawn up in as much detail as possible explaining how to carry out each step of the study and how to collect data. Meetings will be held every 6 months to ensure a faithful application of the protocol.

Due to the involvement of multiple centres, we cannot rule out the occurrence of **interobserver bias**. To try to reduce this, consensus documents will be designed for each unit responsible to perform a measure or diagnostic test (clinical laboratory, Endoscopy units, and anatomical pathology units).

BIASES ASSOCIATED WITH SCREENING

- **Lead-time bias:** This bias occurs when screening advances diagnosis, but does not improve prognosis, leading to an increase in disease duration without any benefit. The survival would have been the same as with symptomatic diagnosis.

  We believe that this bias will not occur in our study, since stratifying by stage shows a clear difference in improved survival of eoCRC cases in early stages. eoCRC, as in those aged >50 years, presents as symptomatic only in advanced stages and this has been proven to be associated with poorer survival rates. Thanks to the CRC screening programme already established, it has been proven that diagnosing the disease in an asymptomatic phase implies a much more favourable prognosis as the disease is detected in early stages. In addition, screening even helps to prevent CRC as it allows the excision of premalignant lesions. This is crucial, because the increasing incidence of eoCRC pertains to advanced stage diseases, which account for the greatest mortality burden.

  A successful screening programme should increase lifespan; results expressed as "5-year survival rate" can possibly lead to misleading statistics as they can easily overlook a lead-time bias. To avoid this, the results in our study will be expressed as "mortality rate in the screened group" and "mortality rate in the control group" showing the differences by absolute mortality reduction.

- **Length-time bias:** Screening is more likely to select slowly progressive cases, which have a longer duration, are less lethal and have a better prognosis, which may result in treatment that appears to be useful but is in fact ineffective.

  Considering that the natural history of eoCRC and CRC over 50 years are very similar, and that the results of the current screening system (with biennial FIT) has demonstrated efficacy, we consider that our study uses a sufficiently sensitive test and narrow enough intervals to detect rapidly progressive cases.

  However, to identify this, participants will be instructed to report if at any time during the study they are diagnosed with CRC (outside the trial) and participants will be asked the same question biennially when they come to submit their stool. This will allow us to identify those cases within the screened group that we have “missed” with our screening protocol, assess them, and determine their progression and prognosis. As our study will perform an analysis of results after

each screening round, if this type of bias is detected we will adjust the intervals for the following rounds and exclude the first round from the results.

- **Overdiagnosis:** overdiagnosis is the diagnosis of the disease that would have never been diagnosed without screening, and as it is expected that such a diagnosis will not result in death, it is treated unnecessarily. Overdiagnosis is a bias of screening itself and an unintended effect of any secondary prevention strategy or improved sensitivity of any diagnostic technique. To minimise the effect of overdiagnosis we targeted the screening to the population of young adults considered to be at highest risk, the age range of 40-49 years (where most cases of eoCRC occur).

STUDY LENGTH

In order to ensure conclusive results, our study was designed as a 4 year intervention (2 rounds of screening) and a 5-year follow-up of those patients diagnosed with CRC. As we are screening the general population, several rounds of screening are needed to detect enough cases of CRC. As we are assessing mortality a few years need to pass after the diagnosis of CRC, and we decided to wait an average of 5 years as in most studies of oncological mortality. Although this is a long-term study, we believe that we can obtain conclusive results during the study course. For this reason, a biennial statistical analysis of results will be carried out, if conclusive results are obtained, the study will be considered completed and results will be published.

BUDGET

Our study will cost a total 817,758 euros. We are aware that the cost of the study is high and that this is partly due to the experimental design of our study. Several screening guidelines base their recommendations on the evidence from predictive models, in fact the recommendation to start screening at the age of 45 launched by the American Cancer Society in 2018 was based on computational results. Computational evidence might be accurate, cheap and a good option for a first study, however it may not reflect reality, and for this reason we believe that it is a mistake to base any recommendation on their results as the level of evidence cannot be as valid as an experimental study. It stands to reason recommendations should be modelled after collecting solid

experimental data from well-designed and replicated clinical trials. Therefore, although we are aware of its high costs, we have decided to use an experimental design to obtain quality evidence-based results.

APPLICABILITY- SUSTAINABILITY

The application of our intervention may lead to implementation and resource division issues:

- Modifying the current screening recommendations may lead to confusion among participants and shift attention away from the population over 50 years to a lower risk age group, rather than increasing participation in screening for those ate higher risk. However, we believe that both strategies are not mutually exclusive, and that expanding screening and increasing participation rates should be two parallel objectives to pursue independently.
- Lowering the screening threshold for the general population may overburden our health system, especially endoscopy units, and take resources away from other important actions. However, we consider that this effect would be mitigated after years of implementing the screening in this population. It is considered that the biennial FIT strategy is economically feasible, and it is very likely that our health care system has the resources to allow its implementation. In Spain, an average CRC treatment varies between 23,500-36,300 euros, but can reach up to 60,000 euros with new therapies (which are commonly used among eoCRC cases) and up to 150,000 euros in metastatic disease (stage IV), a stage in which many eoCRC cases are diagnose (100). In contrast to these numbers, a study from the Basque Country concluded that the cost attributable to their screening programme was only 28 euros per person screened, 941 euros per advanced adenoma found, and 7,324 euros per CRC diagnosed (101). It is also worth mentioning that CRC screening is more cost-effective than other screening programmes; a colonoscopy is 7 times cheaper than a mammography, and the cost per QALY (Quality-adjusted life year) of the CRC screening programme is 2,500 euros while for breast cancer screening programmes is 15.000 euros, which is clearly higher (101).

All these numbers work in favour of the probable profitability of early screening, however, the cost-effectiveness of the application of our strategy must be determined in a second study.

To improve this situation, an exhaustive collection of CRC risk factors for all participants will be performed throughout our study. We will stratify our results based on them, in order to see if there are any specific trends between them and CRC. We hope that this will open new doors to the investigation of risk factors associated with eoCRC or CRC in general, so that in the future we will be able to individualise the indication for screening based on each individual's risk. This would help to desaturate the healthcare system and reduce the costs of screening.

13. IMPACT

CRC is the most frequent type of cancer and the second leading cause of cancer mortality for both sexes in Spain. Over the last decades, CRC overall and its mortality have decreased mainly due to the implementation of screening programmes indicated from the age of 50 years onwards. Despite this, many westernised countries have reported an alarming increase in incidence and especially mortality of eoCRC in recent years. This has raised debate as to whether young adult patients could be better managed.

The increase of eoCRC mortality has been mostly associated with a delay in the diagnosis of the disease and a higher prevalence of advanced stages, but what is encouraging about this situation is that young patients have a much better prognosis than their older counterparts when diagnosed at earlier stages. In these circumstances, lowering the age of screening could be a straightforward solution to this problem.

No risk factor or association of risk factors has been identified to satisfactorily explain the increasing incidence of eoCRC shown in some westernised countries (up to 2,25% annual increase (20), therefore using individualised strategies according to risk does not seem to be an option. Moreover, this trend is expected to continue to increase in most of the affected countries. We must bear in mind that the recommendations to start screening were adequate according to 20th century data, but populations and their characteristics change, so clinical recommendations must be adapted in order to offer adequate management to our patients. In these circumstances, the hypothesis we put forward is that screening from the age of 40-49 years seems a valid, safe, and necessary solution to reduce mortality in this population group.

From this study we expect to obtain results with a much greater impact than the reduction in mortality, since saving a premature death carries more weight because it saves more productive years, which makes the trade-off against the increase in screening costs a favourable one. Furthermore, we propose that screening will not only reduce the mortality of CRC patients, but also improve their quality of life by allowing

them to be diagnosed at earlier stages, so they will have a better prognosis and suffer fewer complications and comorbidities derived from the disease.

Additional expected benefits from screening 40-49 age

- The incidence of CRC between the age range of 40-49 would increase the first rounds of screening, as it happens with any screening technique. However, we consider that after years of implementation the incidence would decrease, as observed with the current system in place. This is because CRC screening is not only a diagnostic technique but also a preventive technique as it allows the removal of premalignant polyps that would have become CRC instead.
- Additional benefits for the 50-60 age group could be expected to be obtained too by the screening of adults between 40-49 years. It should be recalled that screening is already indicated for this group, but its efficacy has been found to be much lower compared to individuals aged 60 years and older. Lowering the starting age is likely to favourably impact the incidence and mortality for CRC of the 50-60 age group. This is due to the slow adenoma-carcinoma progression (10 years), which implies that a polypectomy could benefit the same individual 10 years later, and therefore a polypectomy at age 45 would reduce CRC incidence and mortality at age 55.
- During our study we will assess the presence of risk factors associated with CRC for each of the participants (ANNEX 8) in order to evaluate in the near future any relation between the risk factors and the cases of CRC detected. The aim of this is to open doors to new studies focused on assessing the possible aetiology of eoCRC. In the future, this would allow the application of effective primary prevention measures and the individualisation of screening programmes based on the risk of each individual.
- Diagnosing, managing, and treating young patients with CRC is expensive because most of them are found in advanced stages and because it implies an important loss of productive years of life, since the patient is at a phase of maximum personal growth and probably the most productive phase of their life. Early screening aims to be an economic strategy to diagnose young patients with CRC at early stages, facilitating the management and treatment and leading to a much smaller loss of productive years of life.

It is important to remember that in the event of obtaining results in favour of our hypothesis, before implementing the measure, cost-effectiveness studies should be carried out to assess its possible application. However, we are aware that implementing a screening programme is a societal and political decision for which other public health issues must be considered too.

14. FEASIBILITY

This project will be carried out in the PCC and 8 Hospitals (Screening Units) found in the Health Region of Girona. Hospital Universitari Dr. Josep Trueta will be the reference centre of the study.

The project will take place in different units according to each stage of the process, and it will be carried out by a multidisciplinary team formed by primary care doctors and nurses, gastroenterologists, endoscopists, endoscopy nurses, pathologists, and clinical laboratory specialists. All these professionals are already participating in the ongoing screening program established for the general population over 50 years of age, and they have the knowledge and experience to develop every procedure of the study. All the tests used for our study are part of the daily routine of each of these centres so there will be no need to purchase any other device and team members will not need to undertake further training to perform them.

For our study it will only be necessary to hire a statistician to perform the statistical analyses, and a research technician to develop the revision of all the data collection. We are aware that the price of our study is high, thus we are confident that we will be able to find the necessary funding to make it possible by submitting our study to public and private funding calls.

15. FUTURE DIRECTIONS

Our study proposes the implementation of several measures to improve, relatively quickly, the worrisome increase of eoCRC, a condition for which the aetiology remains still unknown. These measures are:

- Education of the general population, physicians and health professionals.
- Re-evaluation of screening guidelines for eoCRC
- Evaluation of potential eoCRC risk factors.

However, we are aware that the solution for this problem does not (and should not) end here, and that there is an urgent need to broaden the field of research in order to get to the root of this problem. In the future, new lines of research should focus on:

- Expanding and improving oncology registry databases for a better description of eoCRC trends in all birth cohorts.
- Describing the dietary and lifestyle changes occurred in the past decades by carrying out long-term epidemiological studies assessing adulthood and early in life exposure to risk factors.
- Developing pathology studies aiming to discover and describe the genetics and molecular features of eoCRC.

The information obtained through these studies combined, may help to better characterise these tumours and the patients who suffer from them. On this basis, it would be possible to develop targeted primary prevention strategies and individualise the management of these patients according to their genetic and risk profile. In the era of personalised medicine, screening decisions might be based according to risk factors and predisposition of each individual. This would allow us to be more efficient in our interventions and more cost-effective.

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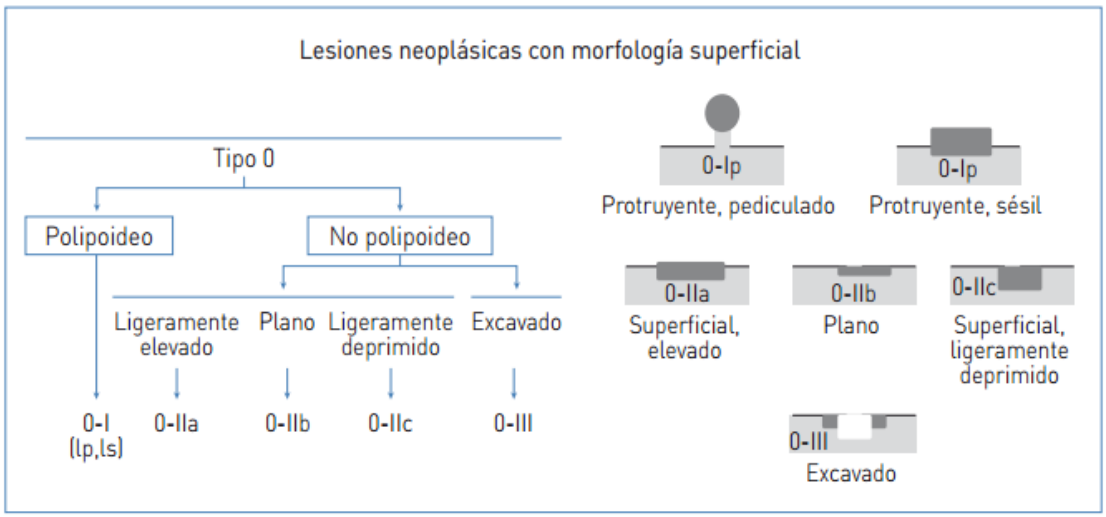
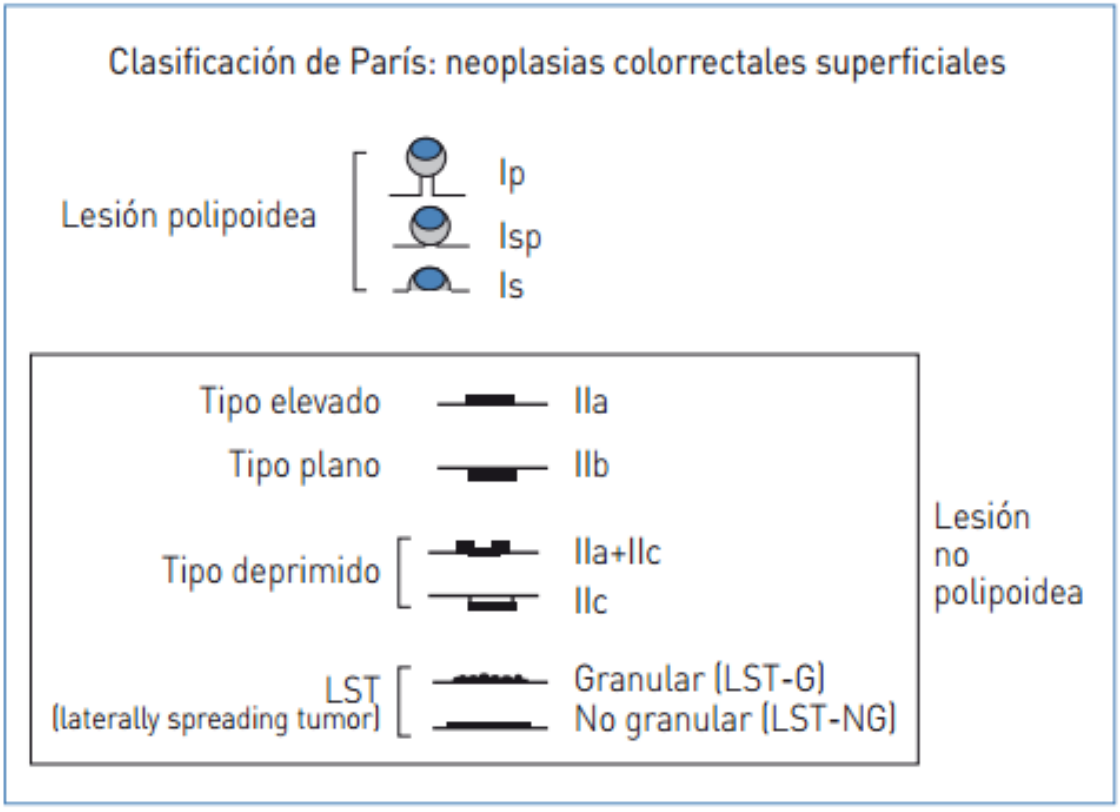
17.ANNEXES

17.5. ANNEX 1- Paris classification (28)





17.6. ANNEX 2- Invitation letter

Detecció Precoç càncer colorectal 40-49 anys

Benvolgut/uda senyor/a,

El càncer de còlon i recte és un dels càncers més freqüents en la nostra població. Aquest càncer típicament afecta a persones de més de 50 anys, però en els últims anys s'ha vist un increment de casos i mortalitat en pacients més joves, sobretot entre els 40 i els 49 anys. Si es detecta a temps, és molt fàcil de tractar i té moltes possibilitats de curar-se.

Malauradament, el càncer colorectal no acostuma a donar simptomatologia fins que la malaltia es troba en fases molt avançades. Per aquest motiu és important detectar-lo precoçment i abans que comenci a donar símptomes. Un dels sistemes del que es disposa i que ha demostrat ser eficaç per diagnosticar precoçment aquest càncer és el cribratge poblacional, actualment indicat a partir dels 50 anys.

Davant del preocupant increment de casos de càncer de colon i recte en pacients joves en els últims anys, hem començat un estudi poblacional amb la intenció de valorar l'eficàcia del mateix sistema de cribratge en la població d'entre 40 i 49 anys. Aquest estudi es desenvoluparà a nivell de la Província de Girona amb la col·laboració dels seus Centres d'Atenció Primària i de 8 Hospitals de la regió i comptarà amb més de 20.000 participants.

Amb aquesta carta us oferim participar en aquest estudi de detecció de càncer de còlon i recte adreçat a homes i dones d'entre 40 i 49 anys. L'estudi consisteix en realitzar una prova de detecció de sang oculta en femta cada dos anys, durant un total de 4 anys (2 proves en total). La detecció de sang oculta en femta és una prova innòcua i segura, que pot realitzar fàcilment en el seu domicili i entregar-la seguidament al seu centre de capçalera de referència.

*L'informem que **no seran candidats a l'estudi, i per tant no seran admesos, si:***
-S'ha fet una colonoscòpia en els darrers 5 anys.
-Pateix o ha patit alguna malaltia de còlon o recte.
-Té algun familiar de primer grau diagnosticat de càncer colorectal abans dels 60 anys o 2 familiars de primer grau diagnosticats de càncer colorectal (independentment de l'edat).
-Embaràs actual.

Participant en aquest estudi podria ajudar a aportar nous coneixements sobre el càncer colorectal i a buscar noves estratègies per prevenir-lo, contribuint a millorar la salut i qualitat de vida de persones com vostè així com el coneixement científic.
En cas d'estar interessat/ada en participar li preguem que es posi en contacte amb el seu Centre d'Atenció Primària a través d'una trucada telefònica.
Per qualsevol altre dubte o aclariment, si us plau, posis en contacte amb el seu Centre d'Atenció Primària o a través del nostre correu electrònic: **prevenciocolon4049@gmail.com**

Cordialment,
Anna Cufí Jou
Principal Investigadora de l'estudi "Cribratge de càncer colorectal als 40-49 anys"

17.7. ANNEX 3- Informed consent document

CONSENTIMENT INFORMAT

TÍTOL DE L'ESTUDI:

Jo,_____,

Amb DNI_____, de nacionalitat_____, major d'edat, amb domicili_____

Afirmo que:

- He rebut i llegit el Full d'Informació sobre l'estudi que se m'ha entregat.
- He rebut la informació suficient sobre les característiques i objectius de l'estudi, els possibles riscs i la importància de la meva contribució per l'avanç mèdic.
- He pogut fer les preguntes necessàries i desitjades al respecte de l'estudi i han estat respostes de forma satisfactòria.
- He esta informat/ada pe l'investigador_____ de les meves implicacions i finalitats de l'estudi.
- Entenc que la meva participació és voluntària.
- Dono permís perquè les meves dades i de la meva història clínica siguin utilitzades per l'equip investigador per fins relacionats amb aquest estudi. He estat informat/ada sobre l'ús de caire científic que es farà de les meves dades personals.
- Entenc que les dades facilitades per mi seran totalment confidencials i que puc sol·licitar la retirada i eliminació de les meves dades personals en qualsevol moment de l'estudi.
- Entenc que puc revocar el meu consentiment informat sobre la participació a l'estudi, sense necessitat d'especificar-ne el motiu i sense que això afecti a la meva assistència sanitària.
- D'acord amb el que s'ha esmentat fins ara, accepto voluntàriament la participació a l'estudi.
- Declaro que se m'ha entregat una còpia del Full d'Informació i una còpia d'aquest Consentiment informat.

SIGNATURA DE L'INVESTIGADOR/A:_____ DATA:_____

SIGNATURA DEL PARTICIPANT:_____ DATA:_____

17.8. ANNEX 4- Withdrawn consent

REVOCACIÓ DEL CONSENTIMENT

Jo, _____

amb DNI_____, revoco el consentiment informat de participar en l'estudi

SIGNATURA_____ DATA:_____

17.9. ANNEX 5- American Society of Anesthesiologists Physical Status (ASA PS) (96)

ASA PS CLASSIFICATION	DEFINITION	ADULT EXAMPLES
ASA I	A normal healthy patient	Healthy, non-smoking, no or minimal alcohol abuse
ASA II	A patient with mild systemic disease	Mild diseases only without substantive functional limitations. Current smoker, social alcohol drinker, obesity (30<BMI<40), well controlled diabetes or hypertension, mild lung disease.
ASA III	A patient with severe systemic disease	Substantive functional limitations. One or more moderate to severe diseases. Poorly controlled diabetes or hypertension, morbid obese (BMI> 40), active hepatitis, alcohol dependence or abuse, implanted pacemaker, moderate reduction of ejection fraction, etc.
ASA IV	A patient with severe systemic disease that is a constant threat to life	Recent (<3 months) myocardial infarction, ongoing cardiac ischemia or severe valve dysfunction, severe reduction of ejection fraction, shock, sepsis, etc.
ASA V	A moribund patient who is not expected to survive without the operation	Ruptured abdominal/thoracic aneurysm, massive trauma, intracranial bleed with mass effect, ischemic vowel in the face of significant cardiac pathology or multiple organ/system dysfunction.
ASA VI	A declared brain-dead patient whose organs are being removed for donor purposes	

17.10.ANNEX 6- EORTC QLQ-C30 questionnaire (97)

EORTC QLQ-C30 (versión 3)

Estamos interesados en conocer algunas cosas sobre usted y su salud. Por favor, responda a todas las preguntas personalmente, rodeando con un círculo el número que mejor se aplique a su caso. No hay contestaciones "acertadas" o "desacertadas". La información que nos proporcione será estrictamente confidencial.

Por favor ponga sus iniciales:
Su fecha de nacimiento (día, mes, año):
Fecha de hoy (día, mes, año): 31

		En absoluto	Un poco	Bastante	Mucho
1.	¿Tiene alguna dificultad para hacer actividades que requieran un esfuerzo importante, como llevar una bolsa de compra pesada o una maleta?	1	2	3	4
2.	¿Tiene alguna dificultad para dar un paseo largo?	1	2	3	4
3.	¿Tiene alguna dificultad para dar un paseo corto fuera de casa?	1	2	3	4
4.	¿Tiene que permanecer en la cama o sentado/a en una silla durante el día?	1	2	3	4
5.	¿Necesita ayuda para comer, vestirse, asearse o ir al servicio?	1	2	3	4

Durante la semana pasada:		**En absoluto**	**Un poco**	**Bastante**	**Mucho**
6.	¿Ha tenido algún impedimento para hacer su trabajo u otras actividades cotidianas?	1	2	3	4
7.	¿Ha tenido algún impedimento para realizar sus aficiones u otras actividades de ocio?	1	2	3	4
8.	¿Tuvo sensación de "falta de aire" o dificultad para respirar?	1	2	3	4
9.	¿Ha tenido dolor?	1	2	3	4
10.	¿Necesitó parar para descansar?	1	2	3	4
11.	¿Ha tenido dificultades para dormir?	1	2	3	4
12.	¿Se ha sentido débil?	1	2	3	4
13.	¿Le ha faltado el apetito?	1	2	3	4
14.	¿Ha tenido náuseas?	1	2	3	4
15.	¿Ha vomitado?	1	2	3	4
16.	¿Ha estado estreñido/a?	1	2	3	4

Por favor, continúe en la página siguiente

Durante la semana pasada:	**En absoluto**	**Un poco**	**Bastante**	**Mucho**
17. ¿Ha tenido diarrea?	1	2	3	4
18. ¿Estuvo cansado/a?	1	2	3	4
19. ¿Interfirió algún dolor en sus actividades diarias?	1	2	3	4
20. ¿Ha tenido dificultad en concentrarse en cosas como leer el periódico o ver la televisión?	1	2	3	4
21. ¿Se sintió nervioso/a?	1	2	3	4
22. ¿Se sintió preocupado/a?	1	2	3	4
23. ¿Se sintió irritable?	1	2	3	4
24. ¿Se sintió deprimido/a?	1	2	3	4
25. ¿Ha tenido dificultades para recordar cosas?	1	2	3	4
26. ¿Ha interferido su estado físico o el tratamiento médico en su vida familiar?	1	2	3	4
27. ¿Ha interferido su estado físico o el tratamiento médico en sus actividades sociales?	1	2	3	4
28. ¿Le han causado problemas económicos su estado físico o el tratamiento médico?	1	2	3	4

Por favor en las siguientes preguntas, ponga un círculo en el número del 1 al 7 que mejor se aplique a usted

29. ¿Cómo valoraría su salud general durante la semana pasada?

1	2	3	4	5	6	7
Pésima						Excelente

30. ¿Cómo valoraría su calidad de vida en general durante la semana pasada?

1	2	3	4	5	6	7
Pésima						Excelente

17.11. ANNEX 7- EORTC-QLQ-CR29 (97)

EORTC QLQ – CR29

Los pacientes a veces dicen que tienen los siguientes síntomas. Por favor, indique hasta qué punto ha experimentado usted estos síntomas o problemas durante la semana pasada. Responda rodeando con un círculo el número que mejor se corresponde con su caso.

Durante la semana pasada:	**En absoluto**	**Un poco**	**Bastante**	**Mucho**
31. ¿Orinó con frecuencia durante el día?	1	2	3	4
32. ¿Orinó con frecuencia durante la noche?	1	2	3	4
33. ¿Alguna vez se orinó sin querer?	1	2	3	4
34. ¿Tuvo dolor al orinar?	1	2	3	4
35. ¿Tuvo dolor de barriga o de estómago?	1	2	3	4
36. ¿Tuvo dolor en las nalgas/región anal/recto?	1	2	3	4
37. ¿Tuvo una sensación de hinchazón en el abdomen?	1	2	3	4
38. ¿Había sangre en las heces?	1	2	3	4
39. ¿Ha observado la presencia de mucosidad en las heces?	1	2	3	4
40. ¿Tuvo la boca seca?	1	2	3	4
41. ¿Ha perdido pelo como consecuencia de su tratamiento?	1	2	3	4
42. ¿Ha sufrido algún problema relacionado con el sentido del gusto?	1	2	3	4

Durante la semana pasada:	**En absoluto**	**Un poco**	**Bastante**	**Mucho**
43. ¿Ha estado preocupado/a por su salud futura?	1	2	3	4
44. ¿Se ha sentido preocupado/a por su peso?	1	2	3	4
45. ¿Se sintió menos atractivo/a físicamente a consecuencia de su enfermedad o tratamiento?	1	2	3	4
46. ¿Se sintió menos varonil/femenina a consecuencia de su enfermedad o tratamiento?	1	2	3	4
47. ¿Se sintió desilusionado/a con su cuerpo?	1	2	3	4
48. ¿Lleva Vd. una bolsa de colostomía/ileostomía? (Por favor, rodee con un círculo la respuesta correcta)	Sí		No	

Por favor, continúe en la página siguiente

Durante la semana pasada:	**En absoluto**	**Un poco**	**Bastante**	**Mucho**
Responda estas preguntas SOLO SI TIENE UNA BOLSA DE COLOSTOMÍA; en caso contrario, siga más adelante:				
49. ¿Ha sufrido alguna pérdida involuntaria de gases/flatulencias de la bolsa colectora?	1	2	3	4
50. ¿Ha sufrido alguna pérdida de heces a través de la bolsa colectora?	1	2	3	4
51. ¿Ha sufrido alguna inflamación de la piel situada alrededor de la bolsa colectora?	1	2	3	4
52. ¿Tuvo que cambiar la bolsa frecuentemente durante el día?	1	2	3	4
53. ¿Tuvo que cambiar la bolsa frecuentemente durante la noche?	1	2	3	4
54. ¿Sintió vergüenza a causa de su bolsa?	1	2	3	4
55. ¿Tuvo problemas con el cuidado de su bolsa?	1	2	3	4

Responda estas preguntas SOLO SI NO TIENE UNA BOLSA DE COLOSTOMÍA:				
49. ¿Ha tenido alguna pérdida de gases/flatulencia involuntaria a través del recto?	1	2	3	4
50. ¿Ha sufrido alguna pérdida de heces a través del recto?	1	2	3	4
51. ¿Ha sufrido alguna inflamación de la piel situada alrededor de la región anal?	1	2	3	4
52. ¿Fue de vientre con frecuencia durante el día?	1	2	3	4
53. ¿Fue de vientre con frecuencia durante la noche?	1	2	3	4
54. ¿Sintió vergüenza por tener que hacer de vientre?	1	2	3	4

Durante las últimas cuatro semanas:	**En absoluto**	**Un poco**	**Bastante**	**Mucho**
Sólo para varones:				
56. ¿Hasta qué punto estuvo interesado en el sexo?	1	2	3	4
57. ¿Le costó alcanzar o mantener la erección?	1	2	3	4

Sólo para mujeres:				
58. ¿Hasta qué punto estuvo interesada en el sexo?	1	2	3	4
59. ¿Tuvo dolor o molestias durante el coito?	1	2	3	4

17.12. ANNEX 8- Case Report Form (CRF)

QUADERN DE RECOLLIDA DADES

Aquest qüestionari forma part de l'estudi "Cribatge precoç del càncer de còlon". Les dades obtingudes seran utilitzades exclusivament per l'estudi, garantint la confidencialitat i anonimitat regulada per la "Ley Orgánica 3/2018, de 5 de diciembre, de Protección de Datos Personales y Garantía de los derechos digitales".

Nom i cognoms: **Sexe**: F / M **Data:**

Nivell d'estudis: Sense estudis | Estudis primaris | Estudis secundaris | Universitaris | Postgrau

Tabac: Fumador/a | Ex-fumador/a | No fumador/a

-En cas que hagi contestat "Fumador"; quants cigarretes per any? __
-En cas que hagi contestat "Ex-fumador"; quants anys fa de l'última cigarreta? __

Alcohol: No bebedor o bebedor lleu | Bebedor moderat | Bebedor important

*Lleu = <12,5 g/dia, moderat = 12-50 g/dia, sever = >50 g/dia.
**Aproximadament 1 copa de vi = 10gr d'alcohol, 1 cervesa = 10 gr, 1 combinat= 20 gr

IMC: Baix pes | Normopes | Sobrepès | Obesitat grau I | Obesitat grau II | Obesitat grau III

*Utilitzarem l'índex de Massa Corporal (IMC) o pes/talla^2 per mesurar el greix corporal. Baix pes = <18,5. Normopes = 18,5-24,9. Normopes = 18,5-24,9. Sobrepès = 25-29,9. Obesitat grau I = 30-34,9. Obesitat grau II = 35-39,9. Obesitat grau III = >40.

Activitat física: Actiu | Poc actiu | Sedentari

*Actiu = 150-300 minuts/setmana d'activitat física d'intensitat moderada o 75-150 minuts/setmana d'intensitat alta. Sedentari = no activitat física ni actiu a les activitat diàries. Poc actiu= entre actiu i sedentari.
**Exercicis d'intensitat moderada: pot parlar durant l'activitat / *Exercicis d'intensitat alta: no pot mantenir una conversa durant l'activitat.

Diabetis tipus II: Sí | No

*Diagnòstic confirmat per un professional sanitari

Menopausa: No menopausa | Pre-menopausa | Menopausa

*No menopausa = pacient amb cicle menstrual mensual. Pre-menopausa = <12 mesos sense cicle menstrual. Menopausa = >12 mesos sense cicle menstrual

Hàbits dietètics:

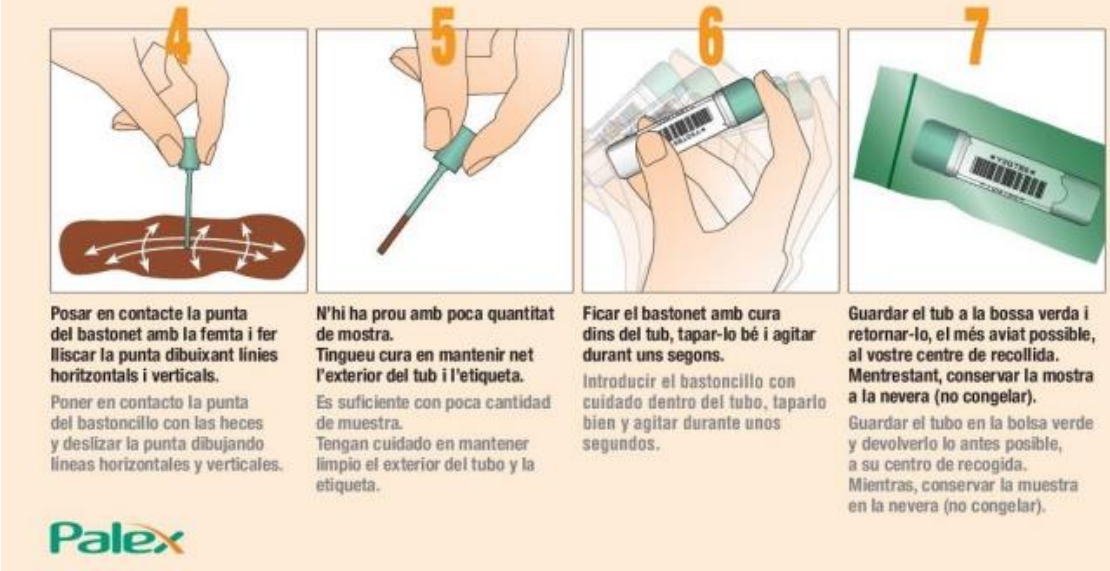
- Consum carn vermella: >3 porcions/setmana | ≤3 porcions/setmana
- Consum carn processada: Sí | No
- Consum de calci: ≥2 làctics/dia | <2 làctics/dia
- Consum de gra integral: ≥2 porcions/dia | <2 porcions/dia
- Consum de fruita i verdura: ≥5 porcions/dia | <5 porcions/dia
- Consum de suplements de vitamina D: Sí | No

*Carn vermella = xai, vedella, porc, etc. Carn processada = pernil salat, xoriç, frankfurt, fuet, etc. Làctics = llet, formatge, iogurt, etc. Gra integral = arròs integra, pasta integral, pa integral, civada, etc.

Tractaments concomitants:

- Presa durant >2 mesos seguits d'antibiòtic/s: Sí | No
- Presa durant >5 anys d'àcid acetilsalicílic (*Aspirina*) de ≥500mg/dia: Sí | No
- Pren actualment bifosfonats: Sí | No

17.13. ANNEX 9– Stool Sample collection Instructions (78)



17.14. ANNEX 10- COLONOSCOPY PREPARATION (78)

PREPARACIÓ DE CÒLON AMB **PLEINVUE®** · C.N. 721059-7

Els 7 dies previs al dia de la seva prova **no pot prendre cap medicació amb Ferro.**

48 HORES ABANS ES RECOMANA UNA DIETA COM S'INDICA A CONTINUACIÓ:

POT PRENDRE	NO POT PRENDRE
Llet i iogurt natural desnatats, Mantega en poca quantitat, Formatges frescos, Pa blanc o torrat, Galetes no integrals.	Brous sense verdures, Arròs i pastes no integrals, Carns i peix blanc a la planxa o bullits, patates en puré o bullides sense pell, cafè, té o infusions lleugeres.	Fruites, verdures i llegums, productes integrals, productes làctics sencers, formatges grassos, carns amb alt contingut en greix, embotits, peix blau, xocolata, pastissos, fruits secs, begudes isotòniques tipus aquarius.

QUAN I COM PRENDRE PLEINVUE®

PROVA AL MATÍ (8-11H)	PROVA AL MIGDIA (11-16H)	PROVA A LA TARDA (16-20H)
18:00 h Dosi 1 – Tarda prèvia	21:00 h Dosi 1 – Nit previa	7:00 h Dosi 1 – Dia de la prova
21:00h Dosi 2 - Nit prèvia	06:00h Dosi 2 – Dia de la prova	10:00 h Dosi 2 – Dia de la prova

1a dosi de PLEINVUE®

Sobre 1

1. Obriu el sobre corresponent a la dosi 1 i dissoleu-ne el contingut en 500 ml d'aigua freda.
2. Preneu el preparat en un període de 45 min. Preneu-ne un got cada 10-15 min.
3. A continuació, preneu com a mínim 1/2 litre addicional de líquids clars*.

500 ml

2a dosi de PLEINVUE®

Sobre A + sobre B

1. Obriu el sobre corresponent a la dosi 2 (sobre A + sobre B) i dissoleu el contingut dels 2 sobres en 500 ml d'aigua freda. Dividiu-lo en 4 gots de 125 ml.
2. A continuació, prepareu 1/2 litre de líquids clars*. Dividiu-lo en 4 gots de 125 ml.
3. Preneu el preparat lentament (4 gots del preparat + 4 gots de líquids clars*), alternant un got del preparat amb un got de líquids clars*. Es recomana un got cada 15-20 min (125 ml).

500 ml = 125 ml + 125 ml + 125 ml + 125 ml

Es recomana prendre aquesta dosi refrigerada

15 min

Líquids clars: aigua, brou, suc de fruita sense polpa, refrescs, te o cafè sense llet.

- **Un cop comenci la preparació només podrà prendre líquids clars.**
- **Amb cada dosi haurà de prendre com a mínim 1/2 litre de líquids clars com s'indica a l'esquema.**
- **Pot prendre més líquids clars que els recomanats a l'esquema durant la preparació i fins 4 hores abans de la prova.**
- **DEJÚ ABSOLUT (fins i tot d´aigua) 4 hores abans de la prova.**

HAURÀ DE SEGUIR ESTRICTAMENT AQUESTES INSTRUCCIONS PER EVITAR REPETICIONS, I RECORDI:

1. Portar un full amb els medicaments que preneu.
2. Portar estudi radiològic o endoscòpic previ si el té.
3. Haurà de venir acompanyat.
4. No podrà conduir fins a 12 hores després de la prova.

17.15. ANNEX 11– Anticoagulant/Antiplatelet therapy modifications Pre-Colonoscopy (78)

Individuals receiving anticoagulant therapy: in these patient's thromboembolic risk (high or low) will be assessed in order to modify their therapeutic regimen according to the established protocols:

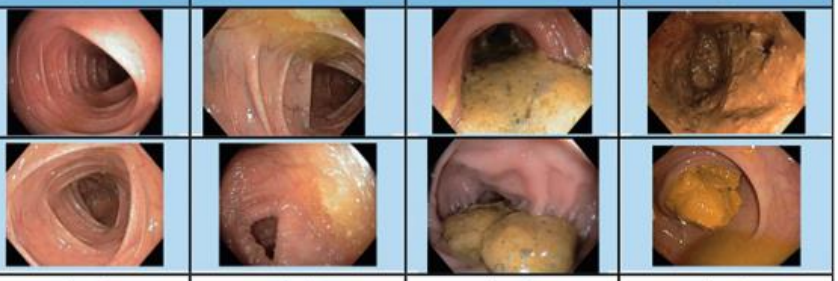
- Low thromboembolic risk: it will only be necessary to discontinue the treatment five days before the procedure and determine the INR before the colonoscopy.
- High thromboembolic risk: it will be necessary to stop the treatment five days before the procedure and initiate the administration of low molecular weight heparin subcutaneously.

Individuals receiving antiplatelet therapy: the thromboembolic risk will be assessed (high or low), as well as the specific drug received, to modify the therapeutic regimen.

- Patients on treatment with acetylsalicylic acid (ASA) at prophylactic doses (≤ 300 mg/day) will not need a discontinuation of the treatment. Patients following treatments at therapeutic doses (>300mg/day) will require a dose reduction to 100mg/day for seven days before the colonoscopy.
- Patients on treatment with clopidogrel, prasugrel and ticlopidine, in case of low thromboembolic risk the treatment will be discontinued the seven days before the colonoscopy, in case of high thromboembolic risk the patient will add 100mg/day of ASA during this period.
- Patients on treatment with double antiplatelet therapy with ASA + clopidogrel due to high risk of stent thrombosis: it the stent placement took place in <6 weeks the test will be delayed, otherwise clopidogrel will be discontinued for 7 days prior to the scan and the dose of ASA reduced to 100mg/day.

Patients on treatment with new oral anticoagulants (dabigatran, rivaroxaban and apixaban) will discontinue the treatment 24 hours before the test and restart it the following day.

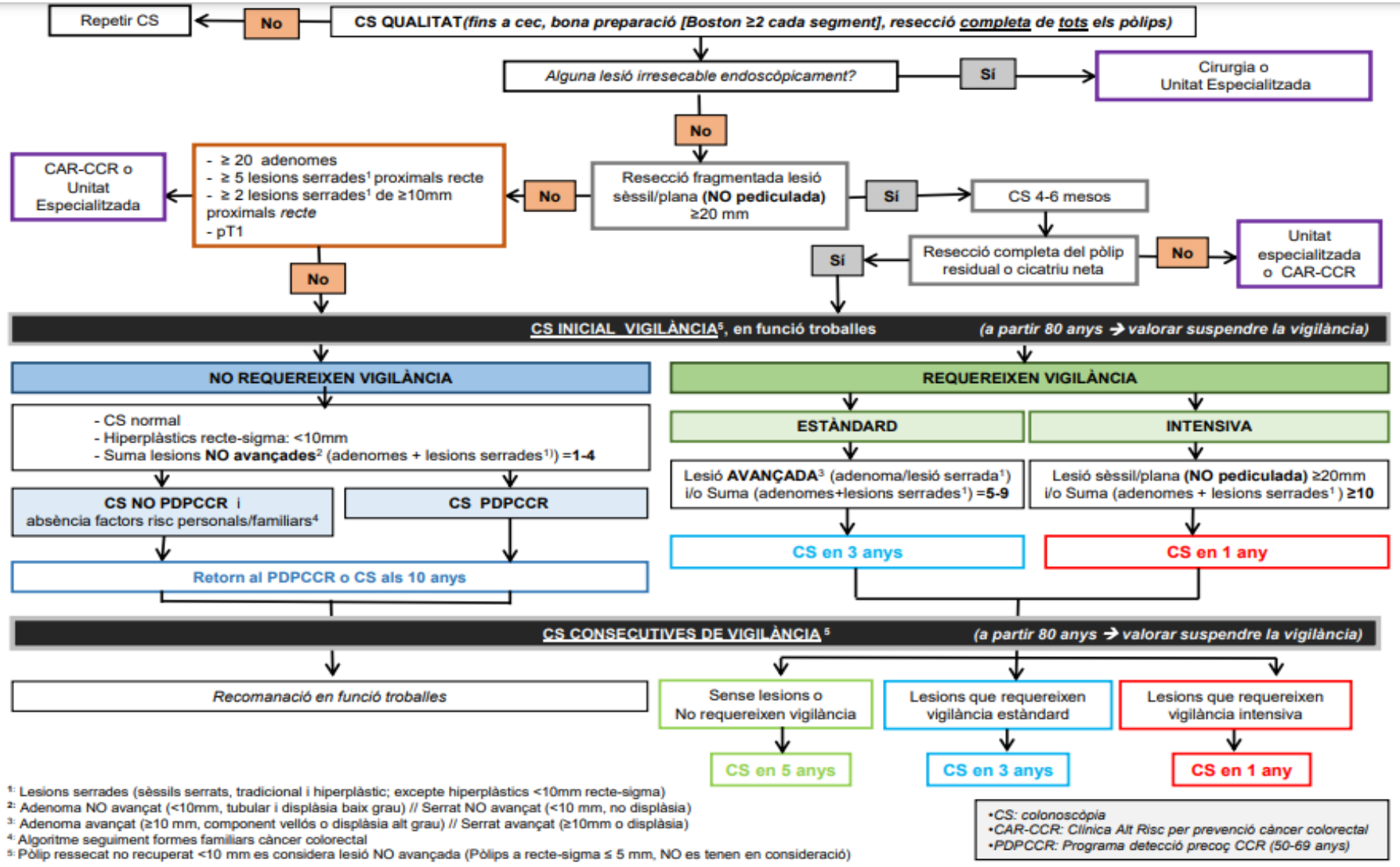
17.16. ANNEX 12 – Boston bowel preparation scale (BBPS) (102)

BBPS		3	2	1	0
3=Excellent 2=Good 1=Poor 0=Inadequate					
LC	☐	☐	☐	☐	☐
TC	☐	☐	☐	☐	☐
RC	☐	☐	☐	☐	☐
BBPS= ☐					

SCORE	DEFINITION
0	Unprepared colon segment with mucosa not seen due to solid stool cannot be cleared.
1	Portion of mucosa of the colon segment seen, but other area of the colon segment not well seen due to staining, residual stool and/or opaque liquid.
2	Minor amount of residual staining, small fragments of stool and/or opaques liquid, but mucosa of colon segment seen well.
3	Entire mucosa of colon segment seen well with no residual staining, small, fragments of stool or opaques liquid.

Boston Bowel Preparation Scale (BBPS). LC: left colon, TC: transverse colon, RC: right colon.

17.13. ANNEX 13– Postpolypectomy surveillance strategies (32)



17.18. ANNEX 14- Protocol Information Sheet

FULL INFORMATIU

NOM DE L'ESTUDI:

INVESTIGADOR PRINCIPAL: Anna Cufí Jou

CENTRE DE REFERÈNCIA: Hospital Universitari Doctor Josep Trueta, Girona.

1. INTRODUCCIÓ

Ens dirigim a vostè per convidar-lo a participar, de forma totalment voluntària, en un estudi d'investigació sobre la detecció precoç del càncer colon i recte en persones com vostè, d'entre 40 i 49 anys d'edat

L'estudi ha estat aprovat pel Comitè d'Ètica i Investigació Clínica (CEIC) de l'Hospital Universitari Doctor Josep Trueta de Girona, d'acord amb la legislació vigent, i amb respecte als principis enunciats en la declaració de Helsinki i a les guies de bona pràctica clínica. La intenció d'aquest document és fer-li arribar tota la informació necessària sobre l'estudi per tal que pugui avaluar i jutjar si vol participar-hi de forma totalment lliure.

Li preguem que llegeixi aquest full informatiu amb atenció i que en cas de qualsevol dubte o qüestió es posi en contacte amb nosaltres per tal de solucionar-los.

2. DESCRIPCIÓ GENERAL DE L'ESTUDI

Quin és l'objectiu de l'estudi?

Aquest estudi té com a principal objectiu valorar l'ús del cribratge del càncer colorectal en la població general d'entre 40 i 49 anys.

El cribratge són aquell conjunt de proves diagnòstiques que permeten detectar malalties en la població, aparentment sana, de forma precoç i en fases asimptomàtiques. Actualment, a Catalunya, ja es disposa d'un programa de cribratge pel càncer de colon i recte dirigit a la població general a partir dels 50 anys. No obstant això, en els últims anys s'ha observat un increment de casos d'aquesta malaltia en la població per sota d'aquesta edat, el que es coneix com a càncer colorectal d'aparició precoç. A més, molts dels casos de càncer de colon i recte en adults joves són asimptomàtics, fet que dificulta la seva detecció, i no es manifesten fins a trobar-se en estadis més avançats pel que solen ser casos amb un pitjor pronòstic.

El nostre estudi pretén aplicar el mateix sistema de detecció precoç (utilitzat entre la població a partir de 50anys) a la població d'entre 40 i 49 anys, amb l'objectiu de valorar el seu impacte en la detecció precoç i la disminució de la mortalitat per càncer de colon i recte.

Quants centres hi participen?

Aquest estudi inclourà un total de 20.236 participants i es realitzarà a nivell de la Província de Girona.

Hi participaran els Centres d'Atenció Primària corresponents a les 7 comarques (*Alt Empordà, Baix Empordà, Garrotxa, Gironès, Pla de l'Estany, Ripollès I La Selva*) i els 10 municipis (*Calella, Canet de Mar, Malgrat de Mar, Palafolls, Pineda de Mar, Sant Cebrià de Vallalta, Sant Iscle de Vallalta, Sant Pol de Mar, Santa Susanna and Tordera*) englobats dins la Regió Sanitària de Girona.

I també hi participaran els següents Hospitals de referència: *Hospital Universitari Doctor Josep Trueta, Hospital Santa Caterina, Hospital d'Olot i Comarcal de la Garrotxa, Hospital de Figueres, Hospital de Palamós, Hospital de Campdevànol, Hospital de Sant Jaume de Calella, Hospital Comarcal de Blanes.*

Quines característiques han de reunir els/les pacients per participar en l'estudi?

Pot participar a l'estudi qualsevol persona entre 40 i 49 anys en possessió d'una targeta sanitària i amb domicili en el territori on està implementat l'estudi.

No podran participar a l'estudi aquelles persones que no compleixin els criteris mencionats anteriorment, o que presentin algun dels següents **criteris d'exclusió:**

- Colonoscòpia realitzada en els últims 5 anys
- Antecedent personal de càncer de colon i recte i/o adenomes colorectals
- Antecedent personal de malaltia inflamatòria intestinal (malaltia de Crohn, colitis ulcerosa)
- Malaltia terminal o invalidesa greu que contraindiqui l'estudi del còlon.
- Antecedent personal de colectomia total
- Història familiar de poliposi adenomatosa familiar o altres síndromes polipòsiques, o càncer colorectal hereditari no associat a poliposi.

- Antecedents familiars de càncer colorectal: 2 o més familiars de primer grau diagnosticats amb càncer colorectal (independentment de l'edat del diagnòstic), o 1 familiar de primer grau diagnosticat de càncer colorectal abans dels 60 anys.
- Símptomes o signes digestius baixos: sagnat a través de l'anus o amb les defecacions, canvis en els hàbits intestinals, dolor abdominal, pèrdua de pes acompanyada de cansament i pèrdua de pes inexplicables, presència d'una massa abdominal.
- Embaràs

En què consisteix la meva participació?

Un cop el participant accepti unir-se a l'estudi, serà distribuït de forma totalment aleatòria a un dels següents grups: 1) Grup que rebrà cribratge, o 2) Grup que no rebrà cribratge. Els participants no sabran a quin grup pertanyen.

A tots els participants se'ls facilitarà un "kit" per recollir una mostra de femtes i se'ls demanarà entregar-la al seu Centre d'Atenció Primària. A part de la mostra en femtes es requerirà, també, que tots els participants contestin una sèrie de preguntes sobre els seus hàbits de vida i estat de salut, formulades per un dels membres de l'estudi i se'ls i prendrà les dades de pes i talla.

- La mostra dels individus que no formin part del cribratge, no serà analitzada i per tant serà directament eliminada.
- La mostra dels individus que formin part del grup de cribratge, serà analitzada per detectar la presència de sang oculta en femtes. En cas d'obtenir un resultat positiu el participant serà contactat i se li recomanarà realitzar-se una colonoscòpia, i en funció dels seus resultats serà derivat a un especialista o podrà seguir amb l'estudi. En cas d'obtenir un resultat negatiu el participant no serà contactat.

Volem recalcar, que el participant no sabrà en quin dels dos grups pertany, i que tot i entregar una mostra de femtes aquesta pot ser no analitzada, per tan el fet que no contactem amb vostè no implica un resultat negatiu de l'anàlisi de la seva mostra, ja que podria formar part d'aquest grup en el qual no s'aplicarà l'anàlisi.

Aquest procés es repetirà una segona vegada al cap de 2 anys, pel que s'enviarà una mail recordatori a tots els participants.

A tots els individus se'ls demanarà que en cas de ser diagnosticats de càncer colorectal de forma aliena a l'estudi abans de completar totes les rondes de cribratge, contactin amb un dels membres de l'equip per informar-los del diagnòstic.

Al acabar totes les rondes de cribratge, es seguiran tots aquells participants que hagin estat diagnosticats de càncer colorectal fins als 5 anys dels seus respectius diagnòstics, moment en el qual se'ls valorarà la qualitat de vida a través d'un qüestionari que es farà per trucada telefònica.

Quina és la compensació econòmica?

L'estudi no ofereix cap remuneració econòmica en els seus participants, i tampoc suposarà cap cost addicional pel pacient.

Puc consultar amb altres professionals?

Sempre que ho desitgi pot consultar amb altres professionals i demanar una segona opinió abans d'accedir a participar en l'estudi.

3. BENEFICIS I RISCS DERIVATS DE LA PARTICIPACIÓ EN L'ESTUDI

Quins riscs assumeixo si participo a l'estudi?

Es corresponen amb els possibles efectes secundaris derivats de la colonoscòpia i la sedació utilitzada per realitzar-la.

- Colonoscopia: Perforació intestinal 0,1%, Hemorràgia 0,5-7%, infecció 0,5-7%, Riscos greus 0,1%.
- Sedació: Dessaturació d'oxigen (<80%) 0,46%, Bradicàrdia 0,21%, Broncoaspiracions 0,03%, Laringoespasme 0,03%, Convulsions 0,035%, Trastorns neurològics 0,0002%, complicacions totals 0,8%.

Li recordem que només a aquells participants del grup de cribratge amb un anàlisis de sang oculta en femtes positiu se'ls recomanarà realitzar una colonoscòpia.

Quins beneficis obtindré de la meva participació a l'estudi?

La seva participació contribuirà a un millor coneixement del càncer colorectal en adults per sota dels 50 anys i a saber quin impacte podria tenir el cribratge en el pronòstic de la malaltia. Aquest coneixement contribuirà a proporcionar futurs beneficis a persones

com vostè i a considerar si seria d'utilitat implementar aquesta mesura a nivell poblacional.

4. PARTICIPACIÓ VOLUNTÀRIA

Si està d'acord en participar a l'estudi, se li entregarà una còpia d'aquest document i el Consentiment informat, que haurà de signar d'acord amb les normatives vigents.

És obligatòria la participació?

La participació de l'estudi és totalment voluntària. A més, en cas d'acceptar participar, vostè té el dret de revocar el consentiment en qualsevol moment en cas que desitgi finalitzar la seva participació, sense donar cap explicació i sense que això ocasioni cap mena de perjudici en el seu tracte assistencial.

Si decideix retirar el consentiment de participar a l'estudi, no s'afegirà cap nova dada a la base de dades, tot i així els responsables de l'estudi podran continuar utilitzant la informació recollida fins aquell moment, tret que s'hi oposi expressament.

5. PRIVACITAT I CONFIDENCIALITAT

Com es protegirà la meva confidencialitat?

Les dades obtingudes seran totalment confidencials, recollides i analitzades de forma anònima, tal i com ho estableix la *Llei Orgànica de Protecció de Dades de Caràcter Personal i Garantia de Drets Digitals (3/2018)* i el *Reglaments 2016/679* del Parlament i Consell Europeu. Cal afegir, que d'acords a la LO15/1999, vostè pot exercir els drets a accés rectificació, oposició i cancel·lació de les dades; en cas de desitjar-ho haurà de contactar amb l'Investigador Principal de l'estudi.

Per garantir la seva privacitat, les seves mostres de femta tindran un codi numèric per tal que no es puguin identificar a partir del nom. A més, les seves dades i informació personal seran identificades mitjançant un codi per tal d'assegurar i mantenir la confidencialitat de les mateixes. L'accés a la seva informació personal quedarà restringit als investigadors de l'estudi, però sempre mantenint-ne la confidencialitat amb la legislació vigent, i seran sempre utilitzades amb finalitats d'investigació.

Què se'n farà de la informació obtinguda de l'estudi?

La publicació de resultats pot ser necessària per tal que altres centres i individus es beneficiïn de les troballes del nostre estudi. En cas de publicar els resultats a través de publicacions i/o congressos, qualsevol dada de caràcter personal serà tractada de forma anònima sense que el participant sigui identificable.

6. DUBTES I AGRAÏMENTS

Amb qui puc contactar per qualsevol dubte o problema que sorgeixi?

En cas de necessitar informació o comunicar qualsevol esdeveniment que succeeixi durant la realització de l'estudi, podrà posar-se en contacte amb algun dels membres del nostre estudi a través del correu electrònic_____ o amb el seu Centre d'Atenció Primària de referencia:_____
a través del número de telèfon _____.

Sigui quina sigui la seva decisió, l'equip d'investigació vol agrair-li el seu temps i atenció.

17.19. ANNEX 15- Colonoscopy Informed Consent

CONSENTIMENT INFORMAT COLONOSCÒPIA

Dades del pacient:

Primer cognom:.....

Segon cognom:.....

Nom:.....

Data de naixement:.....

NHC:.....**DNI:**.....

CIP: .....**Episodi d'origen:**.....

Nom del procediment: Colonoscòpia.

Descripció del procediment

L'endoscòpia digestiva baixa (colonoscòpia) és un examen visual de la mucosa del còlon (intestí gros). Per a realitzar-la s'ha d'introduir a través de l'anus una sonda òptica i flexible nomenada colonoscopi. Si és necessari durant l'exploració s'agafaran petites mostres de teixit (biòpsies) per analitzar-les amb un microscopi. S'administraran sedants perquè tingui poques molèsties durant el procediment.

Aquesta exploració es realitza sota sedació moderada-profunda per endoscòpia digestiva o terapèutica.

Riscos generals:

Qualsevol exploració, tractament o intervenció quirúrgica presenta uns riscs generals. El més greu és la possibilitat d'una parada cardíaca. Altres complicacions són les hemorràgies i les infeccions. En cas d'urgència vital caldrà actuar sobre aquestes complicacions amb els mitjans oportuns per al bé del pacient, dels quals s'informarà (sempre que les circumstàncies ho permetin) el malalt o la persona que en sigui responsable.

Riscs específics

Colonoscòpia:

- Perforació intestinal 0,1%
- Hemorràgia 0,5-7%
- infecció 0,5-7%
- Riscos greus 0,1%.

Sedació:

- Dessaturació d'oxigen (<80%) 0,46%

- Bradicàrdia 0,21%
- Broncoaspiracions 0,03%
- Laringoespasme 0,03%
- Convulsions 0,035%
- Trastorns neurològics 0,0002%
- Complicacions totals 0,8%.

Riscs Personalitzats:

Atesa la meva situació clínica i les meves circumstàncies personals, els meus riscos, que m'han explicat i he entès perfectament, poden dur a alguna complicació durant el procediment. Si així fos, dono el meu consentiment perquè es modifiqui el procediment previst i es pugui resoldre el meu problema.

Alternatives a l'intervenció:

Suggeriments del pacient:

Autorització:

He rebut la suficient informació verbal i/o escrita i he llegit el full informatiu sobre l'exploració, sedació, tractament i/o intervenció quirúrgica que em realitzaran. He pogut fer preguntes sobre aquest procediment. Puc canviar d'opinió en qualsevol moment, abans de la realització del procediment, si així ho crec convenient. He comprès la informació que m'ha estat donada, i per això conscientment autoritzo que es porti a terme el procediment. Aquest consentiment es formula d'acord amb el que estableix la Llei 16/2010, de 3 de juny, de modificació de la Llei 21/2000, de 29 de desembre, sobre els drets d'informació concernent la salut i l'autonomia del pacient i la documentació clínica, publicada al DOGC núm. 5647 del 10 de juny 2010.

Servei sol·licitant_____

Sol·licitant que informa_____

Número o identificació_____

Signatura i DNI del/la pacient _____**DATA**_____

☐ **Accepta**

☐ **No accepta**

Signatura del /la professional responsable_____**DATA**_____

17.20.ANNEX 16– Colonoscopy Report (78)

INFORME DE LA COLONOSCÒPIA

Dades administratives del pacient

- Nom i cognoms.
- Data de naixement.
- Número d'història clínica.
- Procedència o metge sol·licitant.

Informació del procediment

- Data del procediment.
- Número de prova.
- Confirmació que s'ha signat el consentiment informat.
- Indicacions de l'exploració.
- Professionals implicats en l'exploració (nom de l'endoscopista i dels assistents).
- Dades dels aparells i els materials emprats.
- Medicació administrada (analgèsia, anestesia, sedació).
- Qualitat de la preparació. És recomanable utilitzar una escala de neteja validada.
- Tram explorat: cal indicar el punt d'inserció i els centímetres des de l'anus (endoscopi rectificat).
- Cal especificar el lloc anatòmic d'inserció màxima sempre que es pugui (recte, sigma, angle hepàtic, cec). S'ha d'especificar si l'exploració ha estat completa.
- Per intubació cecal s'entén la inserció de la punta de l'endoscopi fins a un punt proximal a la vàlvula ileocecal, de manera que tot el pol cecal, inclosa la paret medial (localitzada entre la vàlvula ileocecal i l'orifici apendicular), sigui visualitzat i explorat. Documentació fotogràfica del cec sempre que sigui possible
- Limitacions de l'exploració (cal especificar-les).

Troballes

- Descripció individualitzada de cada pòlip: morfologia (mitjançant la classificació de París), mida (aproximada, en mil·límetres), localització (distància des de l'anus i probable zona —recte, sigma, colon, cec—, relació amb la vàlvula ileocecal) i aspecte (signes de malignitat, component vellós).

- Tècniques de resecció. Cal descriure si ha estat assistida i especificar si ha estat una resecció en bloc o fragmentada.
- En cas de resecció mucosa endoscòpica fragmentada, cal especificar si a criteri de l'endoscopista la resecció ha estat completa (això és important per establir la vigilància).
- Aspecte de l'escara resultant.
- Tècniques auxiliars: profilàctica per evitar complicacions.
- Marcatge mitjançant tatuatge i, si s'ha fet, si ha estat proximal o distal a la lesió.
- Recuperació dels pòlips per a l'estudi histològic.
- Cal especificar el número del pot on s'ha dipositat cada mostra.
- Temps de retirada de l'endoscopi (a partir que s'ha arribat al cec i fins a l'extracció de l'endoscopi per l'orifici anal, sense comptar el temps passat per fer terapèutica).
- Si s'han identificat pòlips i no s'ha realitzat la polipectomia, cal especificar la raó.
- S'ha d'especificar si la lesió és extirpable endoscòpicament o quirúrgicament.

Diagnòstics

- Es recomana utilitzar terminologia estandarditzada.
- En cas de múltiples pòlips, cal especificar el nombre exacte si són menys de 20 i per desenes si resulta difícil comptar-los tots.
- Complicacions durant l'exploració o immediates.
- Recomanacions posterior