National Pilot Program:

Colorectal Cancer Screening in Bulgaria

(March-June 2024)

2024

Contents

I. Summary

Colorectal cancer (CRC) is a serious malignancy affecting the colon and rectum. Globally, it is the third most common cancer, with an estimated 1.9 million new cases and 903,859 deaths in 2022. In Bulgaria, CRC is the most frequently diagnosed cancer, comprising 15.5% of new cases and resulting in 2,759 deaths annually.

Key risk factors include age, genetic predisposition, polyps, and unhealthy lifestyle choices. Early detection is critical for successful treatment, with a five-year survival rate of around 90% when diagnosed early.

Bulgaria currently lacks an organized colorectal cancer (CRC) screening program, thus posing a significant public health challenge. Unlike many European countries that have implemented systematic CRC screening to detect the disease at an early, more treatable stage, Bulgaria has yet to establish such an initiative on a national scale. This absence results in delayed diagnoses, often when the disease has already progressed to advanced stages, leading to poorer survival rates and increased treatment costs. As such, Bulgaria is the only EU country which has increased levels of mortality due to cancer. It is important to note, that it wasn't until 2023 that Bulgaria adopted a national anti-cancer plan- one of the last European countries to do so . A pilot CRC screening campaign launched in Bulgaria in 2024 aimed to enhance early diagnosis. This programme marks a significant step forward as the first CRC screening initiative in Bulgaria. The initial target was to screen 50,000 individuals, providing access to free tests. Expected outcomes of the pilot programme include increased early CRC diagnosis and a 30% reduction in mortality by 2030.

The national CRC screening campaign represents strategic initiative aimed at preventing the disease and improving public health in Bulgaria. Through targeted efforts for early diagnosis and active public awareness, the campaign has the potential to extend the lives of CRC patients, as well as increase their quality-adjusted life years. Through a systematic analysis of the collected data, the

results of the pilot campaign will inform future health policies and strategies, demonstrating the potential for implementing a national CRC screening program.

The pilot screening campaign for colorectal cancer was conducted from March 28 to June 30, 2024, with an option for extension until July to accommodate participants. The campaign is a private initiative, led by the Lachezar Tsotsorkov Foundation, which has a network of subcontractors and partners.. The campaign used multiple communication channels, including the Internet, television, radio stations, social media and printed materials, to raise awareness.

Free testing kits were provided through laboratories, pharmacies, and other channels, with patients returning the samples to partnering laboratories for analysis. Results were sent to patients, with routine screening recommended in the case of a negative result and additional tests, including colonoscopy, recommended in the case of a positive result.

The campaign primarily targeted individuals aged 50-74 but was also open to those over 18 at high risk or showing symptoms. As a result, 16.2% of participants were under 50 years of age. This aligns with the most recent recommendations from the Centers for Disease Control and Prevention (CDC), which advise screening for individuals aged 45 and older due to the increasing incidence of CRC in younger populations. This flexible approach underscores the importance of individualized screening that takes into account not only age but also other risk factors.

The colon cancer screening pilot campaign registered 93,381 tests performed. Of these, 85.75% were negative, 14.22% were positive, and 0.03% were indeterminate. 63.28% of the participants were female, and 36.64% were male. The rate of positive results was 11.93% in females and 18.19% in males. The mean age of the participants was 61.3 years. The number of positive results increased with age: 8.5% (18-49 years), 14.4% (50-74 years) and 20.2% (75+ years). Sofia accounted for the largest share of participants (17.2%). Television was the most effective outreach method (45.1%), followed by personal recommendations (24.6%). Moreover, 7.7% of the participants had a previous diagnosis of cancer,

and 16.2% had a family history. Continued participation from the population, especially males and older patient groups, remains critically important.

The colorectal cancer (CRC) screening program in Bulgaria demonstrated substantial health and economic benefits. The total budget by 31 August 2024 was EUR 731,340.27(BGN 1,430,376.91), with the cost per participant being EUR 7.84 (BGN 15.34), covering tests and public awareness efforts. According to the analysis, the cost of six months of treatment per patient with stage III-IV colorectal cancer (CRC) amounts to EUR 6 417,85 (BGN 12,552.23; including pharmacotherapy and hospitalizations for treatment administration).

The cost of this pilot screening program is justified, as it results in cost savings and improved health benefits for CRC patients. Early screening facilitates timely diagnosis and treatment of asymptomatic patients, thereby avoiding the more expensive later stages of treatment. Health utility modelling indicates that the screening program results in treatment cost savings for late-stage CRC and improves health benefits for patients, expressed as an increase in quality-adjusted life years (QALYs).

The CRC screening program saves EUR 67.07 (BGN 131.18) and gains +1.58 QALYs per CRC patient over a modelled lifetime time horizon of 50 years. For the estimated 747 patients expected to be identified through the pilot program, this translates to total savings due to earlier diagnosis of EUR 50 101.61 (BGN 97,990.21) and utilities of +1,179.59 QALYs gained. This improvement in health utilities also has a direct economic impact on the country. Approximately 56% of the program participants are of working age, meaning their improved health contributes an estimated EUR 15,947,405.22 (BGN 31,190,406.30) to GDP, equivalent to 0.017% of Bulgaria's total GDP in 2023.

Based on data from the pilot screening program, it can be concluded that the introduction of a national CRC screening program would yield even greater health and economic benefits, provided that the high efficiency of participant outreach and test performance seen in the pilot program is maintained. Furthermore, successful referral of participants for follow-up colonoscopy after positive results is

essential. The national implementation of the program is expected to yield significant cost savings by preventing advanced-stage colorectal cancer (CRC) cases through early diagnosis. For the target population aged 50–74 years, projected savings amount to EUR 13,848,917.98 (BGN 27,086,122.96) for the period 2025–2029, and EUR 33,111,796.21 (BGN 64,761,029.33) for individuals aged 18 years and older during the same period. Additionally, between 2033–2037, further savings of EUR 16 837 337.24 (BGN 32,930,961.64) are anticipated for the 50–74 age group, and EUR 40 256 898.07 (BGN 78,735,630.65) for the 18+ population, due to a reduced incidence of CRC. These savings stem from the preventive impact of widespread early detection, expected to materialize eight years after the program's introduction.

The pilot CRC screening program demonstrates clear advantages over the screening initiative outlined in Bulgaria's National Cancer Control Plan for 2027. The National Cancer Control Plan aims to screen 100,000 participants by 2027, allocating EUR 76,69,380.00 (BGN 15,000,000) for this purpose (EUR 76,69 [BGN 150] per participant). In contrast, the pilot program screened 93,218 participants over three months (March 28 to June 30, 2024) at a cost of EUR 731,340.27 (BGN 1,430,376.91),EUR 7.84 BGN 15.34) per participant). Expanding the program's reach could lead to the detection of significantly more CRC cases, including an estimated 366 additional early-stage patients each year who might otherwise go undiagnosed under limited screening coverage.

The pilot program identifies more early-stage CRC cases than the National Cancer Control Plan, delivering considerable incremental health utilities (+863.77 QALYs per year) and economic contribution to GDP (+EUR 11,68 [+BGN 22.84] million per year).

These results highlight the pilot screening program's dual success: improving health outcomes and delivering significant economic advantages for the healthcare system and society. Additionally, it establishes a strong foundation for how a

national CRC screening campaign, modelled after the pilot's success, could deliver even greater health and economic benefits.

The pilot CRC screening program achieved notable success, screening over 90,000 people in just three months, identifying the most effective channels for participant outreach, and analysing demographic characteristics. In contrast, the current National Cancer Plan aims to screen 100,000 individuals over 4 years, reflecting a substantially limited population coverage compared to the pilot program.

To enhance outcomes and expand coverage, three key recommendations are proposed: 1. Strengthen the referral and follow-up system: Ensure the timely referral of patients with positive results to specialists. 2. Expand the network of laboratories: Maintain and extend facilities, including the use of mobile screening units in remote areas. 3. Use the program as a model for other health initiatives, integrating educational efforts to encourage lifestyle and dietary changes. The 2024 campaign employed a multi-channel communication approach and included individuals aged 18 and older, increasing accessibility to screening services.

II. Introduction

Colorectal carcinoma (CRC) is a type of cancer that develops in the colon or rectum. It represents a major public health problem, as it is one of the most common types of cancer worldwide and is characterized by significantly high mortality rates. Colorectal cancer usually begins as noncancerous polyps – small clusters of cells located on the inner lining of the colon or rectum. Although most polyps are benign, some types, such as adenomas, can become cancerous if left untreated (Figure 1).[1] CRC can be classified based on its location: colon cancer, which originates in the colon, and rectal cancer, which begins in the rectum. These two types are often collectively referred to as colorectal cancer due to their anatomical and pathological similarities.[2]

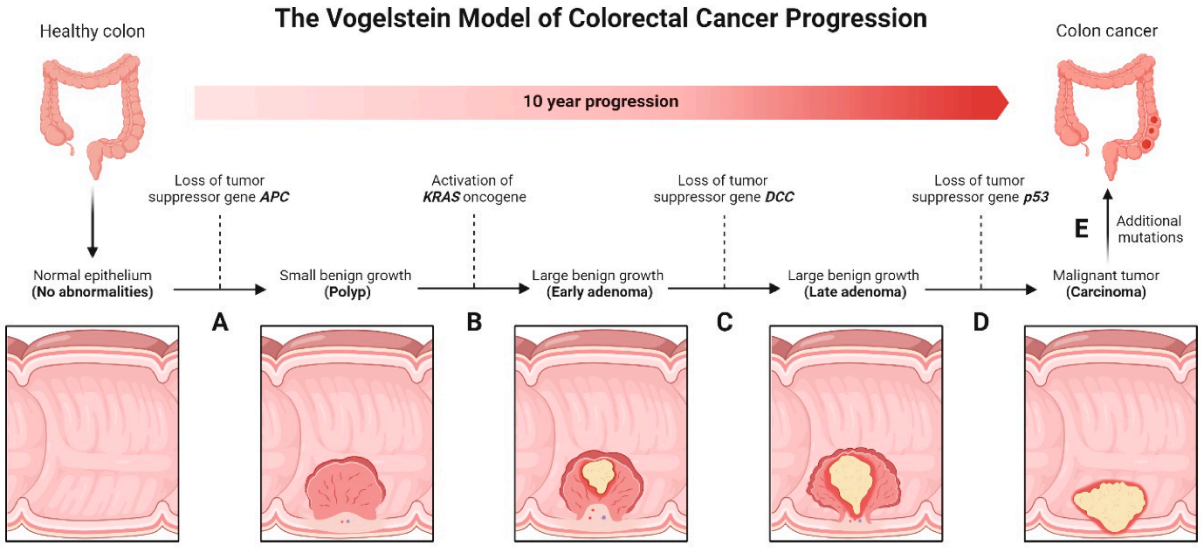

Figure 1. Progression of CRC

Reference: [1]

(**A**) The initial genetic event leads to the formation of a small, benign polyp. This occurs due to the inactivation of the APC gene, a critical tumor suppressor. (**B**) The next stage involves the transition from a small polyp to a large benign early adenoma. Activation of the *KRAS* oncogene, a key driver of cell proliferation, facilitates the growth and expansion of the adenomatous polyp. (**C**) Subsequently, the loss of the tumor suppressor gene DCC contributes to the development of a late adenoma, resulting in large benign growth. (**D**) The next stage is the progression from a late adenoma to an invasive malignant tumor or carcinoma which is a result of the loss of the tumor suppressor gene *TP53*. (**E**) In the final stage, an advanced, invasive malignant tumor mass forms. This stage may also involve additional genetic alterations beyond the primary events.

In 2022, CRC was reported as the third most common cancer worldwide, with approximately 1,926,118 new cases reported. The highest age-standardized incidence rates (ASRs) were recorded in Europe, followed by Australia/New Zealand and North America.[3] Conversely, the lowest ASRs were observed in

Africa and the Eastern Mediterranean region. CRC is also the second leading cause of cancer-related deaths globally, with approximately 903,859 deaths registered in 2022. Europe accounted for the highest age-standardized mortality rate (ASMR).[3]

According to GLOBOCAN data, colorectal cancer was the most common cancer type in Bulgaria in 2022, representing 15.5% of all newly diagnosed cancer cases. That same year, 2,759 people died from CRC, making it the second leading cause of cancer-related death in the country. Bulgaria is the only country in the European Union (EU) to report an increase in cancer mortality – 8% in males and 5% in females – compared to the EU average decrease of 10% for males and 5% for females.[4]

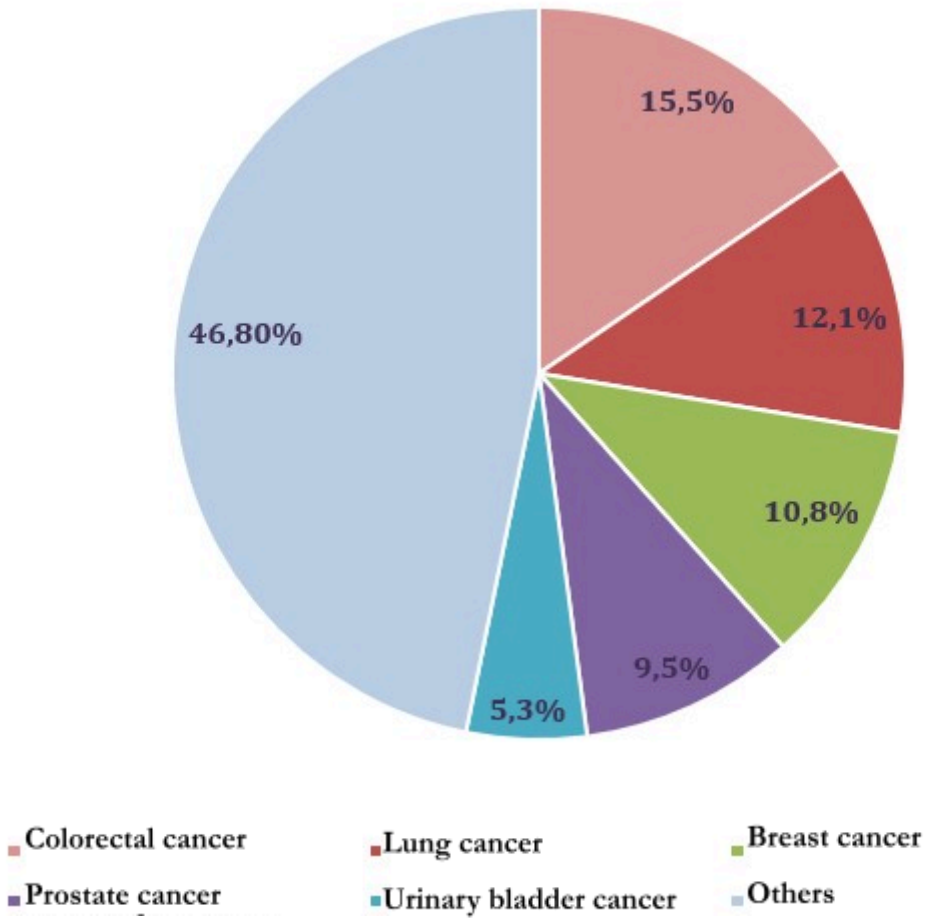

Figure 2. Cancer Incidence in Bulgaria, 2022 (Both Sexes)
Reference: [5]

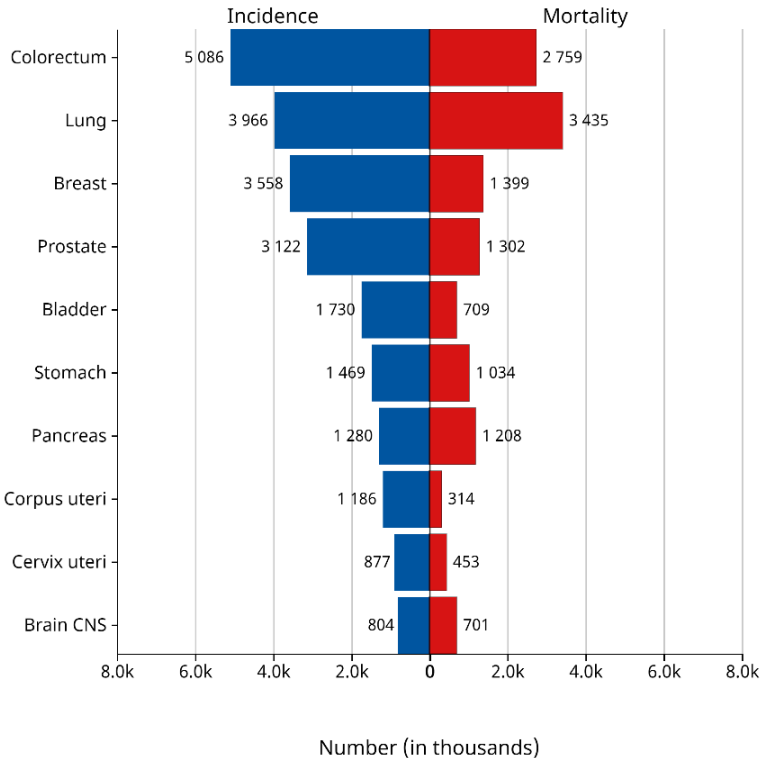

Figure 3. Incidence and Mortality of the Top 10 Cancer Sites, 2022 (Both Sexes)

Reference: [5]

The global burden of CRC is projected to rise substantially in the next decades. By 2040, the annual number of new CRC cases is expected to increase by 63.3%, growing from 1,931,590 in 2020 to 3,154,674.[6] This alarming growth highlights the urgent need for implementing effective, widespread screening programs. Timely intervention through such programs can significantly improve prognosis and patient outcomes. Although current guidelines recommend routine screening for individuals aged 50 to 74 years, the identification of additional risk factors may warrant an expansion of these criteria.[7] Effective screening programs hold immense potential to substantially reduce both the incidence and mortality of CRC.

The etiology of CRC is complex and multifactorial. Age is a significant risk factor, with incidence rising notably among individuals aged 40 to 50 and continuing to increase with each subsequent decade.[8]

Approximately 20% of CRC cases are associated with genetic predispositions, including Lynch syndrome and familial adenomatous polyposis

(FAP), which increase the risk of developing the disease threefold in first-degree relatives of CRC patients.[9] Non-cancerous conditions such as colorectal polyps and inflammatory diseases like ulcerative colitis and Crohn's disease also predispose individuals to developing CRC, particularly in the presence of long-standing inflammation. Studies indicate that 3–5% of patients with ulcerative colitis develop CRC, with the risk increasing to over 10% after 20 years with the disease.[10,11] Additionally, 15–40% of colorectal cancer (CRC) cases arise from colon polyps, with the likelihood of malignancy increasing with adenoma size.[12]

Lifestyle factors significantly influence CRC risk.[13,14] A diet high in red and processed meats, low fiber intake, smoking, excessive alcohol consumption, physical inactivity, and obesity are associated with heightened CRC risk. Conversely, regular physical activity and a diet rich in fruits, vegetables, and fiber are associated with a reduced risk of CRC. The use of aspirin, non-steroidal anti-inflammatory drugs (NSAIDs), hormone replacement therapy, and statins has shown an inverse relationship with CRC risk; however, some, such as aspirin, carry potential side effects, including bleeding, warranting further investigation.[15]

CRC is a multifactorial disease that develops through the adenoma-carcinoma sequence – a multistep process involving the accumulation of mutations in genes regulating cell growth and proliferation. This progression begins with hyperplasia of epithelial cells lining the colon, advancing through stages of atypical hyperplasia and adenomas, and culmination in cancer may occur.[16] Approximately 75–80% of CRC cases are sporadic, resulting from the gradual accumulation of genetic mutations, while hereditary forms, comprising 15–30%, are linked to specific gene abnormalities.[17]

The clinical presentation of CRC varies based on tumour location, stage, and complications, such as obstruction or metastases.[18] Early stages are often asymptomatic, underscoring the critical importance of screening. As the disease progresses, symptoms like changes in bowel habits, rectal bleeding, abdominal discomfort, unexplained weight loss, fatigue, and weakness may emerge.[8] These non-specific symptoms often delay diagnosis, complicate treatment, and worsen

survival rates. Given the asymptomatic nature of early-stage CRC, screening is essential for early detection and effective treatment, ultimately reducing CRC mortality.

CRC prevention can be categorized into primary and secondary approaches. Primary prevention focuses on mitigating risk factors and enhancing protective behaviors (diet, physical activity, specific medications/supplements).[19] Lifestyle changes, including smoking cessation, reduced fat intake, and increased physical activity, can reduce CRC risk. Regular physical activity decreases CRC risk by 25–30%, with optimal results from moderate to vigorous aerobic exercise.[19–22] Diets rich in fruits and vegetables have been shown to lower CRC risk by up to 50%.[23,24] Secondary prevention includes CRC screening to detect and remove precancerous polyps, significantly reducing CRC incidence. Studies have shown that screening methods such as the fecal occult blood test (FOBT) and lower gastrointestinal endoscopy (sigmoidoscopy/colonoscopy) play a pivotal role in reducing CRC mortality.[19] These preventive measures are crucial for combating CRC, particularly in light of the growing global burden of the disease. Studies show primary prevention reduces CRC mortality by 35%, while secondary prevention via early screening decreases mortality by 53%.[25–27] Early CRC detection significantly improves treatment outcomes. Therefore, routine screening is recommended for individuals aged 50 and older or earlier for high-risk groups.

Early diagnosis of CRC is vital for both patients and the healthcare system, as it significantly enhances the likelihood of successful treatment and improves patient survival rates. The five-year survival rate for early-stage CRC (stage I) is approximately 90%, compared to 10–14% for late-stage CRC (stage IV).[28] Treatment of early-stage CRC often involves surgery, avoiding costly therapies like chemotherapy, targeted therapy, or immunotherapy required for advanced stages.[29] Treating early-stage CRC often leads to fewer side effects, shorter recovery periods, and a better quality of life compared to the aggressive treatments required for advanced cancer.

From an economic perspective, early diagnosis minimizes healthcare costs associated with advanced cancer treatments, hospitalizations, and palliative care.[28] Early-stage CRC treatment is also considerably more cost-effective for healthcare systems, involving fewer medical procedures and shorter therapy durations. In addition, early detection also reduces productivity losses, as patients more frequently recover and return to work, alleviating the economic impact of CRC-related disability and mortality.[28]

Early CRC screening and diagnosis significantly improve the chances of successful treatment, prolong patients' lives, as well as quality-adjusted life years, while alleviating the economic burden on healthcare systems and society.

Bulgaria currently lacks an organized colorectal cancer (CRC) screening program, thus posing a significant public health challenge. Unlike many European countries that have implemented systematic CRC screening to detect the disease at an early, more treatable stage, Bulgaria has yet to establish such an initiative on a national scale. This absence results in delayed diagnoses, often when the disease has already progressed to advanced stages, leading to poorer survival rates and increased treatment costs.

In 2024, a pilot CRC screening campaign was conducted to assess its effectiveness and scope. The campaign is a private initiative, led by the Lachezar Tsotsorkov Foundation, which has a network of subcontractors and partners, with institutional support from the Ministry of Health. This institutional support involved assistance through the Regional Health Inspectorates who distributed testing kits to local businesses and general practitioners.

The pilot CRC screening programme marks a significant step forward as the first CRC screening initiative in Bulgaria. This pilot program aims to address the urgent need for early detection by testing the feasibility and impact of organised screening.. The lack of a nationwide comprehensive CRC screening program underscores the need for coordinated policy action, improved healthcare infrastructure, and greater public awareness to reduce the burden of colorectal cancer in the country.

Employing a multi-channel approach, the campaign aimed to screen 50,000 individuals aged 18 and older, targeting a broad range of risk groups to enhance access. The key objective of the campaign was early CRC detection when the disease is most manageable. Another objective of the program was establishing a network of laboratories providing free testing in regional cities, ensuring national coverage and accessibility. A long-term objective of the program was analyzing collected data to inform future CRC prevention initiatives and health policies in Bulgaria.

The campaign was conducted between March 28 and June 30, 2024, with some tests accepted in July to allow the participation of people who experienced delays in participation.

The analysis encompassed several key aspects aimed at evaluating the campaign's effectiveness, accessibility, and overall impact. The program included males and females, and primarily targeted individuals aged 50–74 years, who are at the highest risk of developing CRC. Younger individuals with a family history or relevant medical conditions were also included. Screening was performed using the immunochemical fecal occult blood test (iFOBT or FIT test), with positive results referred for diagnostic colonoscopy.

The analysis focused on data collected through registration forms included patient information such as sex, age, place of residence, family history, and previous medical conditions. Expected outcomes include increased early CRC diagnosis and a 30% reduction in mortality by 2030. Additionally, the analysis examined the cost-effectiveness of the campaign by conducting a comprehensive review of the budget and project implementation expenses.

The anonymized and systematized data serve as a strong basis for shaping future health strategies in Bulgaria, rooted in real-world outcomes and proven effectiveness. Furthermore, the communication strategy—encompassing media campaigns, social media, influencer collaborations, and educational initiatives—was evaluated for its role in the campaign's success.

III. Methods

The campaign utilized multiple communication channels. Information was shared via platforms such as the Internet, television (32-second clips), national radio stations (32-second spots), healthcare professionals, medical laboratories, social media (Facebook), print media, and other outlets. To ensure accessibility, free testing kits were distributed via laboratories and pharmacies.

Patients prepared the material for the FIT test at home according to the provided instructions. The test samples were then returned to designated laboratories for analysis. The laboratories processed the samples, and the results were communicated to the patients. For individuals with negative results, routine screening was recommended at appropriate intervals. For individuals with positive results, additional diagnostic tests, including colonoscopy, were advised.

During registration, patients provided demographic and medical information, including: age, sex, place of residence, family history, and history of malignancy.

The campaign's official communication channels targeted males and females aged 50 to 74, as recommended by national and international guidelines for colorectal cancer screening. However, to address broader risk factors beyond age, the campaign was also open to individuals over 18 years of age. This inclusive approach allowed high-risk individuals or those with symptoms indicative of early disease to participate.

This strategic flexibility proved crucial, with individuals under 50 years accounting for 16.2% of all campaign participants. This highlights the value of an individualized approach to colorectal cancer screening, taking into account both age and other clinical or personal risk factors.

IV. Results and Impact of the Screening Program

Proportion of positive and negative results

A total of **93,381** tests were conducted. For analysis purposes, the number of tests was assumed to equal the number of participants, as data differentiating between individual participants was unavailable.

Negative results: (80,075/93,381) 85.75% of participants tested negative.

Positive results: (13,281/93,381) 14.22% of participants tested positive.

0.03% (25/93,381) of participants fell into the category "suspicious/uncertain results".

Notably, the relatively high percentage of positive results highlights the necessity for additional diagnostic testing in these individuals. This percentage was higher compared to prior analyses.

1. Sex distribution of participants

Females: (59,092/93,381) 63.28% of the participants were females.

Males: (34,219/93,381) 36.64% of the participants were males.

Unspecified sex: (70/93,381) 0.07% of all participants were unspecified sex.

Distribution of positive results by sex

Females: (7,047/13,281) 53.06% of all positive results were in females.

Males: (6,225/13,281) 46.87% of all positive results were in males.

Unspecified sex: (9/13,281) 0.07% of all positive results were in people with unspecified sex.

Although females had a higher absolute number of positive cases, males exhibited a higher percentage of positive results. Among females, 11.93% (7,047of 59,092) tested positive. Among males, 18.19% (6,225 of 34,219) tested positive. Nearly 1 in 5 males tested positive.

Key findings:

- **Nearly 1 in 5 males tested positive.**

2. Age analysis

(The following data points were excluded: 722, 157,155, 123, 114, and participants aged 0 to 17 years. This adjustment slightly altered the mean age: overall: from 61.26 to 61.28 years; males: from 60.49 to 60.54 years; females: from 61.70 to 61.72 years)

Age data was missing for 163 participants. The mean age of the participants was 61.3 ± 12.4 years. The mean age of males was 60.5 years and that of females – 61.7 years.

Table 1. Age Distribution into 4 groups and positive results

Age group	Number	%	Number of positive results	% (+) results
18-49 years old	15,121	16.2%	1,280	8.5%
50-60 years old	26,163	28.1%	3,081	11.8%
61-74 years old	39,061	41.9%	6,299	16.1%
75+ years old	12,873	13.8%	2,603	20.2%

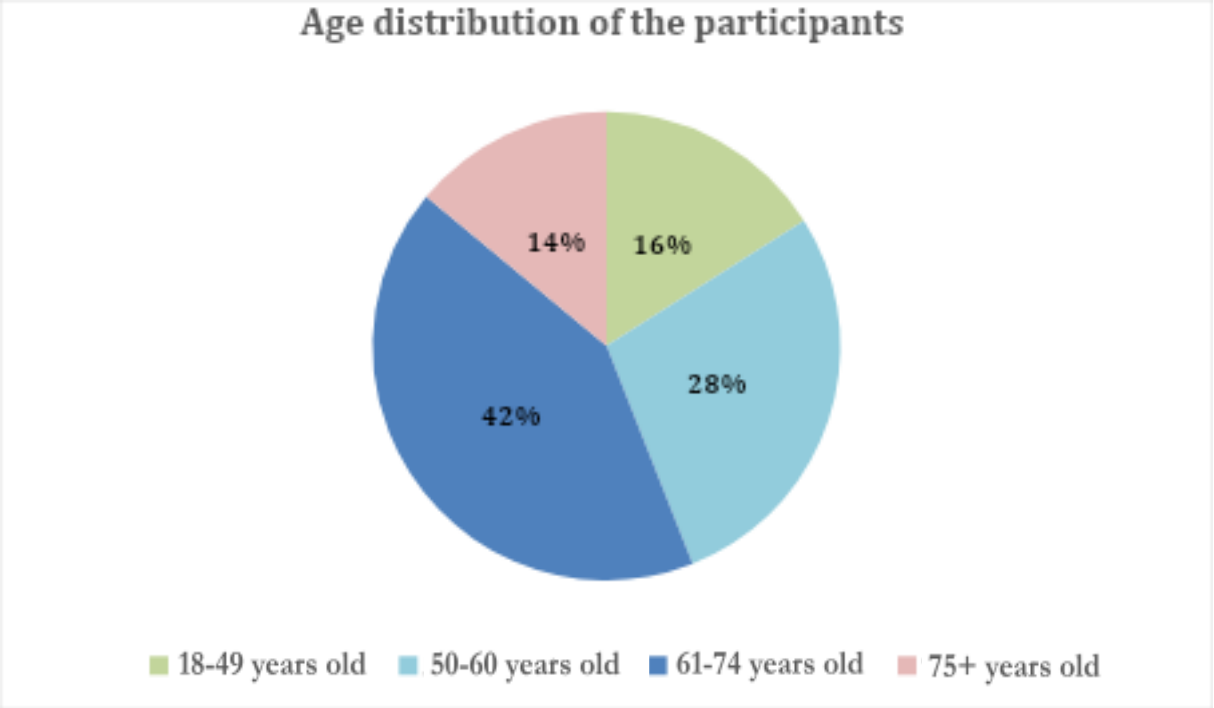

Figure 4. Diagram of age distribution into 4 groups

Table 2. Age Distribution into 3 groups and positive results

Age group	Number	%	Number of positive results	% (+) results
18-49 years old	15,121	16.2%	1,280	8.5%
50-74 years old	65,224	70.0%	9,380	14.4%
75+ years old	12,873	13.8%	2,603	20.2%

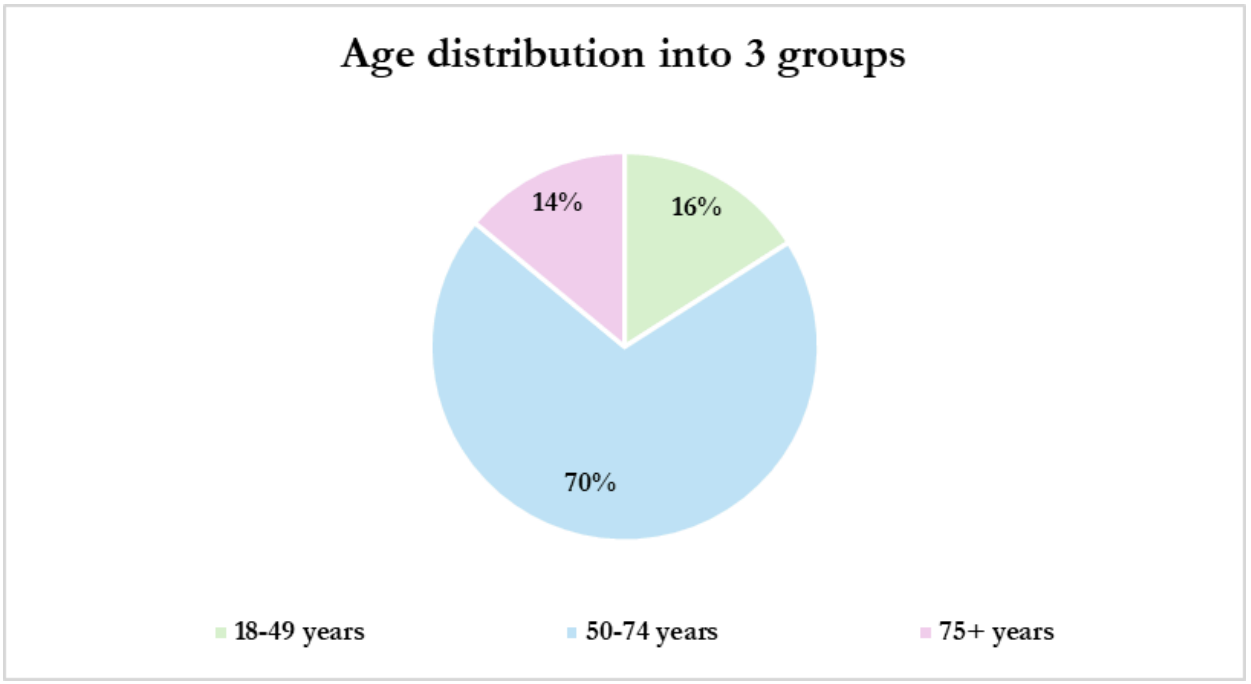

Figure 5. Diagram of Age Distribution into 3 Groups

Distribution of positive results by age

The frequency of positive results increases with age. Data from this analysis can be compared to the previous pilot screening program conducted in late 2022 and early 2023, which included 5,717 participants. In the **18–49 age group**, 8.5% tested positive (1,280/15,131), an increase from the 2022-2023 previous pilot program's rate of 6.29% (58/922). According to the guidelines, the target group for CRC screening is **50-74 years**. In this group, 14.4% tested positive (9,380/65,224), which again shows an increase compared to 12.17% (520/4,274) in the earlier program. For participants **over 74 years**, the positive rate was 20.2% (2,603/12,873), showing a slight decrease from 21.07% (114/541) in the previous analysis. (Figure 6, Figure 7).

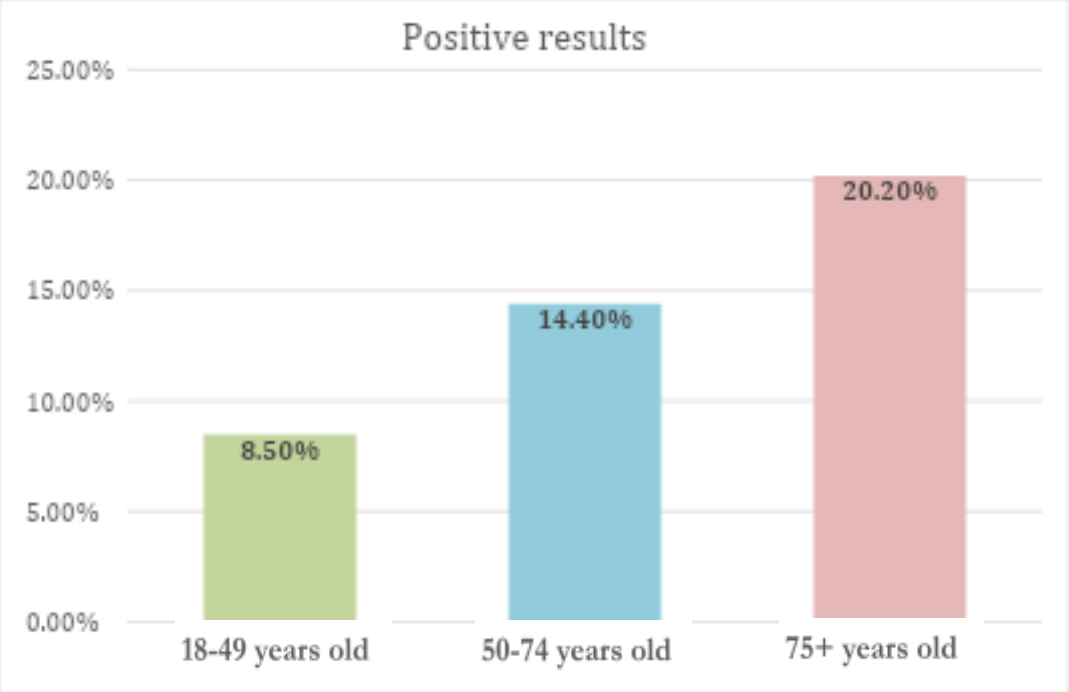

Figure 6. Positive results by age (3 groups)

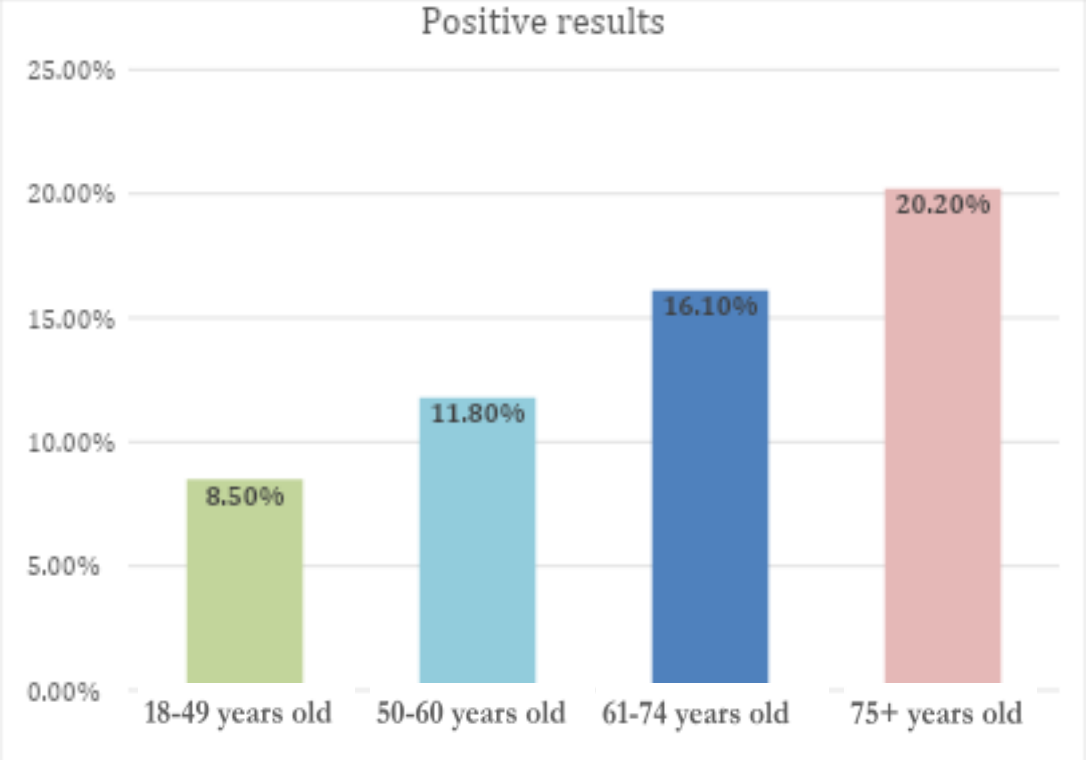

Figure 7. Positive results by age (4 Groups)

Key findings:

- **Increase in positive results with age: Positive results rise notably with age. While only 8.5% of participants aged 18-49 years tested positive, this percentage reached 14.4% in the 50-74 group and 20.2% in the group of participants over 75 years of age. This trend highlights the critical importance of regular screening for individuals over 50, which is in accordance with the guidelines.**
- **Screening target group (50-74 years): The screening target group (ages 50–74) comprised the largest proportion of participants (70%) and exhibited a significant rate of positive results (14.4%). Given the increasing rates of positive results, this finding emphasizes the importance of sustained efforts in cancer screening for this age group.**

3. Place of residence

The largest share of participants (15,680/90,963, 17.2%) lives in Sofia, making it the primary city represented in the sample. The next largest city is Plovdiv with 6,440 participants (7.1%), Varna with 5,773 (6.3%), Burgas with 4,160 (4.6%) and Stara Zagora with 2,441 (2.7%). Other significant cities include Pleven (2,185 participants), Yambol (1,944), Sliven (1,827), Dobrich (1,507) and Kardzhali (1,483), Shumen (1,476), Ruse (1,390), Dimitrovgrad (1,195) and Asenovgrad (1,169). Information for the place of residence was unavailable for 2,418 participants. This broad geographical distribution highlights the campaign's representative nature, ensuring extensive coverage and engagement across different regions of Bulgaria.

Table 3. Age, sex and positive results by place of residence

	Number	%	Number of positive results	% (+) results	Mean age	% males
Sofia	15,680	17.2%	2,100	13.4%	60.2	37.8%
Plovdiv	6,440	7.1%	928	14.4%	60.8	35.2%
Varna	5,773	6.3%	1,095	19.0%	60.9	36.0%
Burgas	4,160	4.6%	508	12.2%	62.0	35.0%
Stara Zagora	2,441	2.7%	250	10.2%	62.3	35.9%
Pleven	2,185	2.4%	294	13.5%	63.3	35.2%
Yambol	1,944	2.1%	266	13.7%	62.8	37.6%
Sliven	1,827	2.0%	207	11.3%	60.7	34.8%
Dobrich	1,507	1.7%	136	9.0%	62.5	37.2%
Kardzhali	1,483	1.6%	177	11.9%	56.7	33.2%
Shumen	1,476	1.6%	178	12.1%	60.5	38.2%
Ruse	1,390	1.5%	120	8.6%	62.8	35.0%
Dimitrovgrad	1,195	1.3%	94	7.9%	62.4	30.2%
Asenovgrad	1,169	1.3%	137	11.7%	61.0	35.8%
Others	44,711	49.2%	6,791	15.2%	61.6	37.1%

Key findings:

- **This study is representative of the entire country.**

4. Communication Channels

Figure 8 illustrates the communication channels through which the participants learned about the campaign, as indicated in their registration forms. Data was unavailable for 2,126 participants.

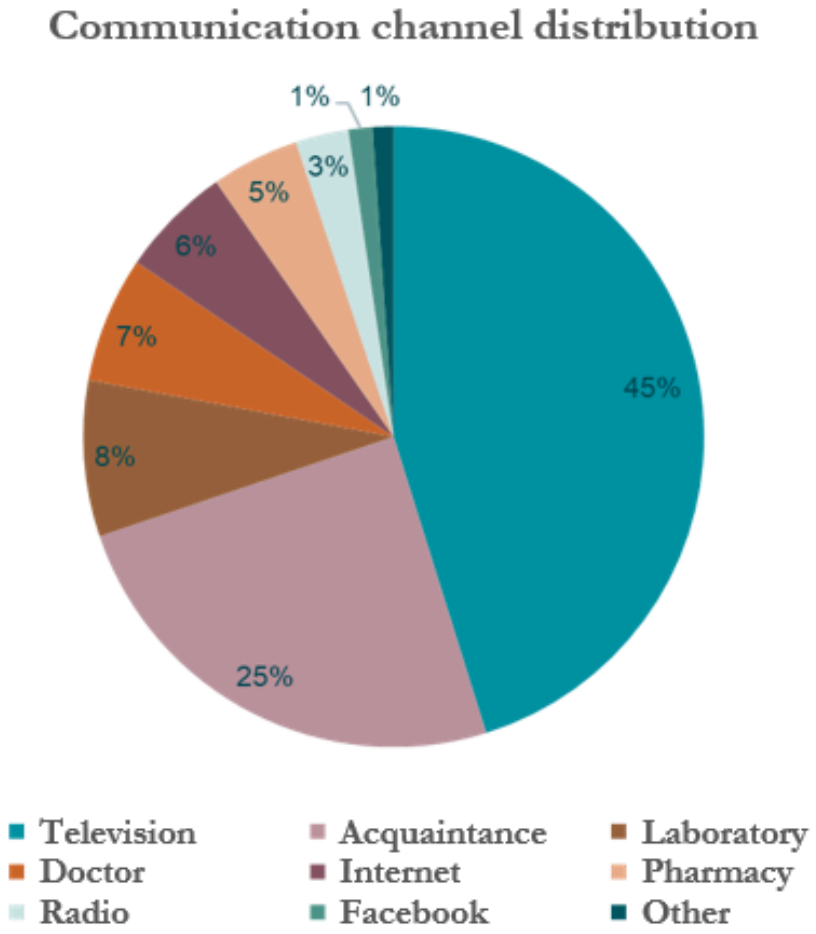

Figure 8. Communication channels in the campaign

The largest proportion of participants (45.1%, 41,192/91,255) reported learning about the campaign through **television**, underscoring the significant role of mass media as a powerful communication tool. 24.6% (22,443/91,255) of participants were informed about the campaign through **acquaintances or family members**, highlighting the effectiveness of personal references in distribution of information. **Laboratories** accounted for 8.1% (7,417/91,255) of the communication channels, emphasizing the importance of healthcare facilities in reaching the target audience. **Doctors** (predominantly general practitioners) informed 6.6% (5,989/91,255) of the participants, which is considered a direct medical recommendation. The **internet** served as an information source for 5.8% (5,299/91,255) of participants, demonstrating the growing influence of online platforms. **Pharmacies**, where the campaign materials were distributed, informed

4.6% (4,183/91,255) of participants. **Radio** informed 2.8% (2,528/91,255) of participants, while **Facebook** informed 1.2% (1,132/91,255). The "**Other**" category, representing less popular or individual methods, accounted for 1% (989/91,255). A small group (0.1%, 83/91,255) reported learning about the campaign through multiple channels, categorized under the "**Multiple Sources**" segment.

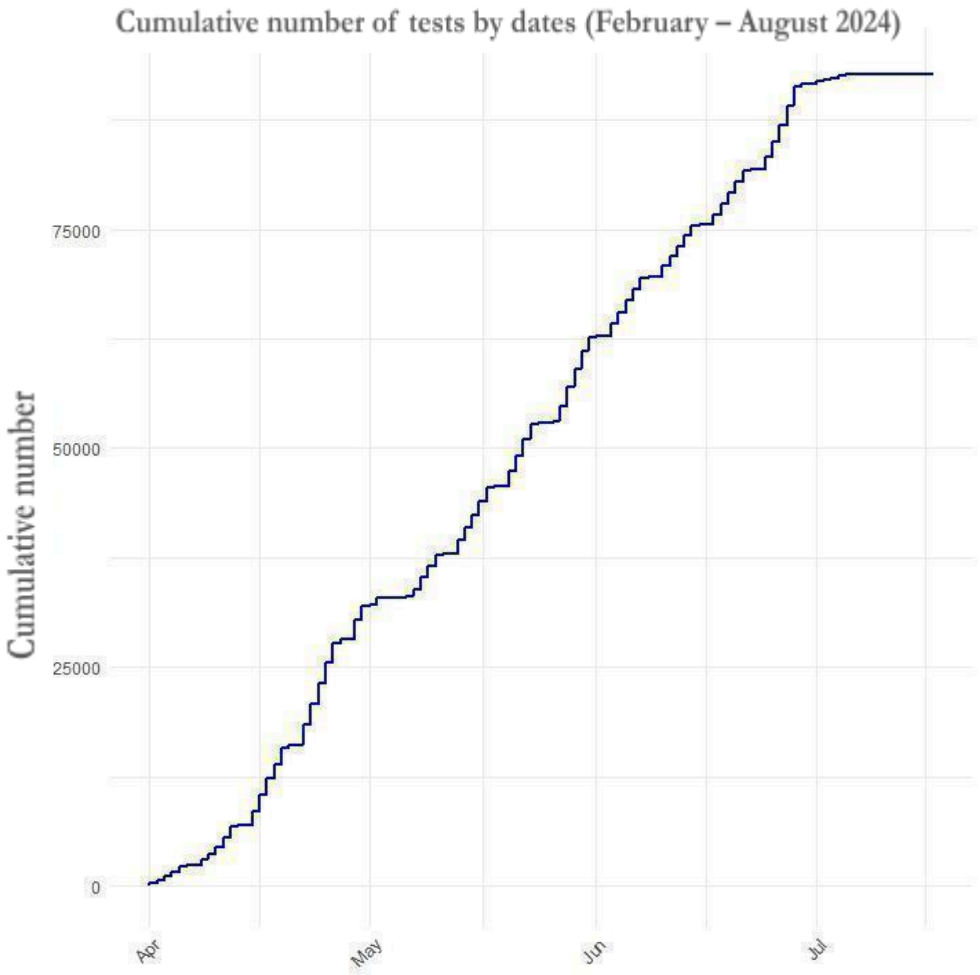

Figure 9. Total number of tests conducted during the campaign

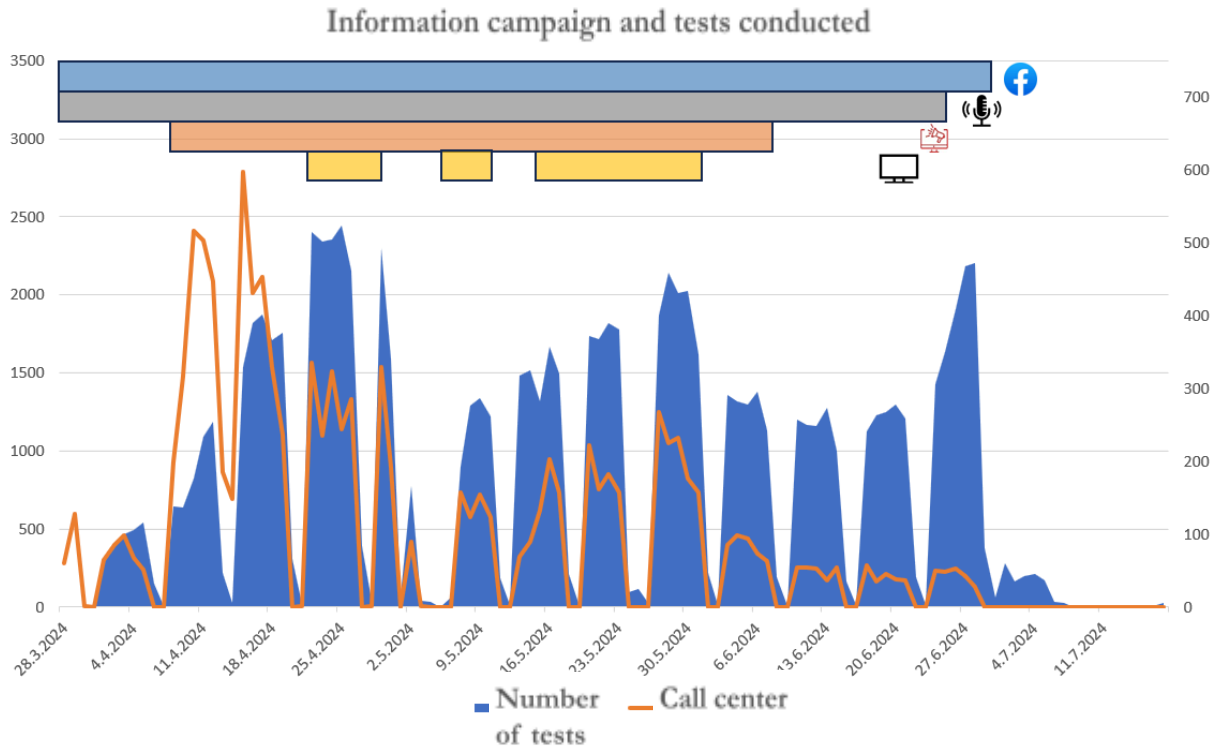

Figure 10. The timeline of tests conducted, with communication channels

Key (at the top of the figure): blue bar - Facebook; gray bar - radio; orange bar – a digital channel; yellow bar – television

Table 4. Tests Conducted by Month

Month	Number
April	32,114
May	30,812
June	29,226
July	1,226

As illustrated in Figure 10, call center activity (orange bar) peaked in early April and again in May. These peaks suggest that the call center played an important role in campaign communication during the initial stages, likely driven by heightened advertising or increased activity in other communication channels at the times. Despite the clear peaks in call volume, there is no consistent correlation between the spikes in calls and the number of tests conducted (blue bar). This could indicate that calls do not directly translate into immediate test completion but may serve other purposes, such as providing information or addressing participant inquiries. After the May peaks, call activity declined in June, potentially signaling waning interest in the campaign or reduced call center efficiency during the later

months. However, even as call volume dropped in June and July, the number of tests performed continued to rise, with noticeable peaks, implying that other factors or communication channels might have driven the sustained testing activity.

The upper section of Figure 10 illustrates the timeline for specific communication channels, including Facebook, radio, digital channel, and television. Among these, Facebook (blue bar) maintained the longest active period, running throughout the entire campaign. Radio (gray bar) ceased broadcasting shortly before the campaign concluded, while the digital channel (orange bar) operated from early April to early June. Television (yellow bar) broadcasted for short periods of activity in April and May.

With 45.1% of participants attributing their awareness to television, it stands out as the campaign's most effective communication medium. Personal contact and digital channels also played an important role (Figure 8). Personal recommendations from acquaintances accounted for 24.6% of participants' awareness, and the Internet accounted for 5.8%, demonstrating significant effectiveness in spreading information about colon cancer screening. Laboratories (8.1%) and pharmacies (4.6%) played significant roles in campaign outreach, highlighting the need for a multi-channel approach in the health campaigns that combines traditional and digital media, as well as direct medical recommendations. Although the call center played a role in maintaining communication with campaign participants, its effect on the number of immediate tests performed is not clear.

Key findings:

- **Television as the most influential channel:** With 45.1% of participants learning about the campaign through television, television remains the cornerstone of awareness-building. This finding highlights the broad reach and influence of traditional media, particularly for engaging diverse

audiences. Improved airtime positioning compared to previous campaigns contributed to its much higher success.

- **Personal recommendations have a substantial role:** Personal recommendations from acquaintances come in second place with 24.6%, highlighting the enduring importance of direct communication. This finding emphasizes the need to incorporate social engagement strategies and direct connections into health campaigns to maximize impact.
- **Healthcare facilities as key intermediaries:** Laboratories (8.1%) and general practitioners (6.6%) also play significant roles, likely serving as trusted sources of information during routine visits. Medical recommendations clearly influence participation. Leveraging healthcare professionals, particularly general practitioners, as proactive referrers to screening programs is crucial for future campaigns. They should play a leading role in referring patients to screening programs by providing proactive and personalized information. Strengthening doctor-patient relationships can further enhance campaign participation and effectiveness.
- **The internet and online platforms:** While not as dominant as traditional media, the internet (5.8%) and Facebook (1.2%) demonstrated their value, especially for engaging younger or tech-savvy audiences. These channels should continue to evolve alongside traditional media.

Patients diagnosed with cancer and family history

Column "Patients diagnosed with cancer"

2,261 participants did not provide data for the column "Patients Diagnosed with Cancer". Of the remaining 6,979/91,120 (7.7%) reported "Yes", while 84,141/91,120 (92.3%) reported "No".

Table 5. Patients diagnosed with cancer by age, sex and place of residence

	Number	%	Patients Diagnosed with Cancer	Patients Diagnosed with Cancer, %
Sofia	15,680	17.2%	1,271	8.1%
Plovdiv	6,440	7.1%	478	7.4%
Varna	5,773	6.3%	452	7.8%
Burgas	4,160	4.6%	350	8.4%
Stara Zagora	2,441	2.7%	181	7.4%
Pleven	2,185	2.4%	207	9.5%
Yambol	1,944	2.1%	140	7.2%
Sliven	1,827	2.0%	143	7.8%
Dobrich	1,507	1.7%	118	7.8%
Kardzhali	1,483	1.6%	81	5.5%
Shumen	1,476	1.6%	89	6.0%
Ruse	1,390	1.5%	121	8.7%
Dimitrovgrad	1,195	1.3%	82	6.9%
Asenovgrad	1,169	1.3%	91	7.8%
Others	44,711	49.2%	3,175	7.1%
Sex, males	34,219	36.6%	2,034	5.9%
Sex, females	59,092	63.3%	4,942	8.4%
18-49 years old	15,121	16.2%	462	3.1%
50-60 years old	26,163	28.1%	1,330	5.1%
61-74 years old	39,061	41.9%	3,486	8.9%
75+ years old	12,873	13.8%	1,695	13.2%

"Family History" column

2,345 participants did not provide data for the column "Family History". Of the remaining 14,770/91,036 (16.2%) reported "Yes", while 76,266/91,036 (83.8%) reported "No".

Table 6. Family history by age, sex and place of residence

	Number	%	Family history (FH)	FH, %
Sofia	15,680	17.2%	3,195	20.4%
Plovdiv	6,440	7.1%	1,091	16.9%
Varna	5,773	6.3%	984	17.0%
Burgas	4,160	4.6%	647	15.6%
Stara Zagora	2,441	2.7%	360	14.7%
Pleven	2,185	2.4%	345	15.8%
Yambol	1,944	2.1%	254	13.1%
Sliven	1,827	2.0%	259	14.2%
Dobrich	1,507	1.7%	190	12.6%
Kardzhali	1,483	1.6%	134	9.0%
Shumen	1,476	1.6%	223	15.1%
Ruse	1,390	1.5%	283	20.4%
Dimitrovgrad	1,195	1.3%	179	15.0%
Asenovgrad	1,169	1.3%	180	15.4%
Others	44,711	49.2%	6,446	14.4%
Sex, males	34,219	36.6%	4,794	14.0%
Sex, females	59,092	63.3%	9,968	16.9%
18-49 years old	15,121	16.2%	3,121	20.6%
50-60 years old	26,163	28.1%	4,509	17.2%
61-74 years old	39,061	41.9%	5,558	14.2%
75+ years old	12,873	13.8%	1,560	12.1%

Key findings:

Some participants had a family history, which increases the risk of developing CRC. It is essential to emphasize that family history is one of the factors that can increase risk, but early detection through screening is critical for all groups, regardless of family history. By ensuring regular and timely screening for all individuals, including those with a family history, the frequency of early diagnosis can be increased, and clinical outcomes can be improved. Screening remains an essential strategy for reducing morbidity and mortality in the general population, regardless of the presence of familial risk factors.

V. Economic Analysis of a Colorectal Cancer Screening Program

a. Examples from Other Countries

Economic burden of CRC

Colorectal cancer (CRC) is the third most commonly diagnosed malignancy, accounting for approximately 1.9 million cases annually – 10% of all new cancer cases worldwide. Its incidence increases substantially with age and has traditionally been highest in Western, developed nations. However, developing countries are now experiencing significantly rising rates. With the ageing population, CRC is becoming a rapidly growing challenge for many societies, highlighting the need for major prevention efforts. A number of effective screening options are available, and the implementation of well-organized screening programs could have a significant impact in reducing the future burden of the disease. The total economic burden of CRC is estimated at around EUR 19 billion per year in Europe alone. This figure is expected to rise in the coming years.[30,31]

Screening programmes as a method to reduce the economic burden of CRC: decrease in morbidity and mortality

A recently published guideline from WHO Europe identifies CRC screening as one of the most cost-effective public health interventions, frequently described as the "best investment" in cancer prevention strategies. The guideline urges countries to implement organized screening programs with at least 70% coverage of the eligible population to maximize their impact. This approach aims to achieve earlier detection, better outcomes, and significant reductions in CRC burden across Europe.[32]

Evidence from countries with established screening programs demonstrates substantial reductions in CRC incidence. Initially, countries with high-coverage screening often observe a short-term rise in diagnosed cases. Over time, these programs lead to a higher proportion of stage I diagnoses. Conversely, countries without widespread screening experience stable or increasing incidence rates.[33] Screening also reduces CRC mortality by detecting malignancies at an earlier, more

treatable stage and by identifying and removing precancerous lesions before they progress to cancer.[33]

Indeed, international population-based studies have shown that CRC incidence reduction has been observed with screening programs based on flexible sigmoidoscopy (18–26% in intention-to-screen analyses and 31–35% in per-protocol analyses in a randomized clinical trial [RCT]), colonoscopy (68% in a meta-analysis of observational studies), and FIT (10–22% in observational studies). Evidence for the effectiveness of gFOBT in reducing incidence is limited, but one Minnesota study reported a 17% reduction.[33–40]

Studies have shown significant reductions in mortality with different screening methods: gFOBT demonstrated a 15% reduction in intention-to-screen analyses and 25% in per-protocol analyses; FIT resulted in a 10–50% reduction in observational studies; flexible sigmoidoscopy yields an 18–30% reduction in intention-to-screen analyses and 38–41% in per-protocol analyses; and colonoscopy achieves an approximately 70% reduction in observational studies.[34–39,41,42]

Examples of screening programs in other countries

The Netherlands launched its national CRC screening program in 2014 with the objective of reducing CRC mortality. Its focus is detecting precancerous advanced adenomas and early-stage cancers through stool-based tests. Between 2018 and 2021, 72% of targeted participants returned FIT samples. Of those with positive FIT results (270,547), 85% underwent colonoscopy. Screening led to the detection of 12,156 CRC cases and 70,526 advanced adenomas. These results underscore the effectiveness of well-organized screening programs in achieving early diagnosis.[43]

The Colorectal Cancer Screening Program in Paris, launched in 2016 and running until June 30, 2017, targeted individuals aged 50–74 years. Participants underwent the OC Sensor® FIT test, which detects hemoglobin in stool. Data were collected over 18 months. Of the 620,227 eligible individuals, 409,340 were invited

to participate, and 88,796 completed the test, yielding a participation rate of nearly 22%. Among participants, 4.3% tested positive in FIT. Of those, 70.5% underwent colonoscopy, leading to the detection of 2,401 colorectal lesions, including 205 cases of colorectal cancer. While participation was lower than anticipated, the program effectively identified advanced adenomas and colorectal cancer. The Colorectal Cancer Screening Program in Paris highlighted the effectiveness of the FIT in identifying advanced adenomas and colorectal cancer.[44]

The national colorectal cancer screening program in Slovenia began in 2015, targeting individuals aged 50–74 years and also utilizing FIT. Over two years, 303,343 individuals participated out of 536,709 invited. Among those screened, 6.2% tested positive (15,310 individuals), resulting in 13,919 colonoscopies. The program detected 862 cases of colorectal cancer and 5,159 advanced adenomas.[45] 5.63% of individuals with a positive FIT were diagnosed with CRC based on data from the Slovenian screening program (862 out of 15,310 people).

b. Purpose of the Analysis

This analysis aims to evaluate the costs associated with the pilot colorectal cancer screening program using FIT in Bulgaria, conducted between March and July 2024. Additionally, the analysis assesses the program's potential economic impact and its health utilities for patients through early CRC detection and treatment. Based on these findings, the cost-effectiveness of the program and its economic implications for Bulgaria can be determined.

c. Applied Analysis

A cost-utility analysis (CUA) was performed to compare the outcomes of a CRC screening program versus no program. This included calculating the costs of screening and treatment per CRC patient, along with health utilities in the form of quality-adjusted life years (QALYs) gained. An economic impact analysis of implementing a CRC screening program in Bulgaria was also conducted.

d. Campaign Costs

The first stage of the pilot CRC screening program in Bulgaria used immunochemical tests for occult blood (FIT or iFOBT). Consumables, specially purchased by the Foundation, were provided to laboratories for qualitative testing of participant samples. Participants collected their samples using customized test kits, each containing a feces container, information brochure, and laboratory registration form. These kits were pre-distributed in 225 physical locations of SOpharmacy pharmacies, as well as to laboratories, the Regional Health Inspectorate (RHI), general practitioners (GPs) and other partners. Online distribution via SOpharmacy was also carried out (Figure 11). While the use of special testing kits was optional, as participants could collect samples in any container, the kits significantly facilitated the process. This was especially important, as collecting fecal samples can be an uncomfortable experience for participants.

The first stage of collecting and testing samples from participants lasted from March 28 to June 30, 2024, but tests were performed until July 16-17, 2024. A total of 93,218 tests were performed.

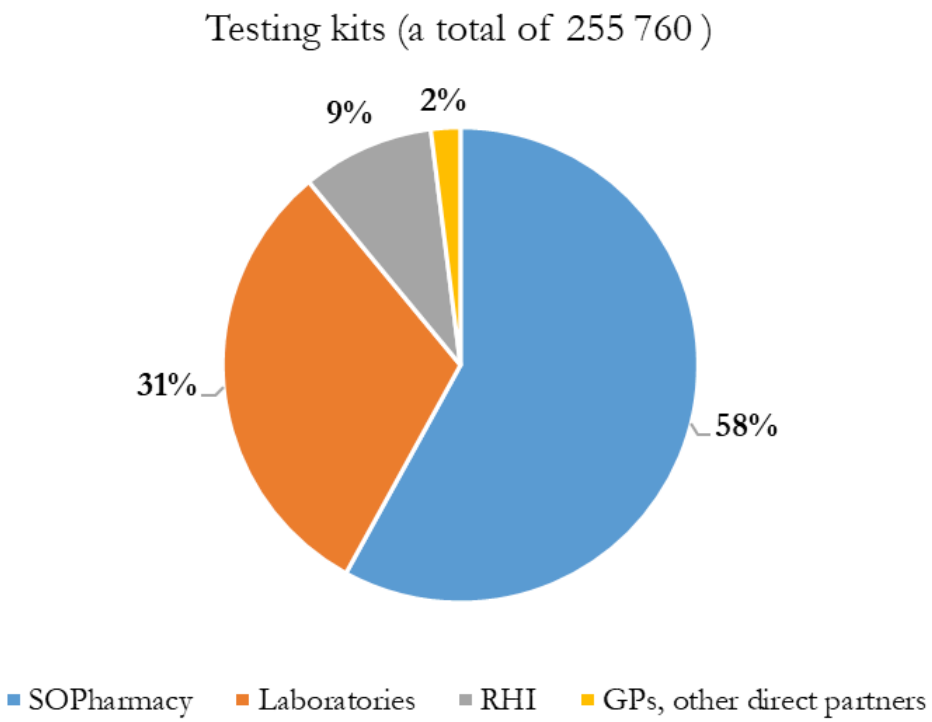

Figure 11. Distribution of Testing Kits

The budget for the pilot screening program also accounted for creating an educational campaign targeting general practitioners and disseminating information through national media channels (television, radio, and digital advertising), social networks, and influencers. Additionally, it included the development of an informational website to support the initiative.[46,47] The costs of procuring and distributing tests, conducting laboratory analyses, and managing logistics such as shipping, coordination, project management, and demand planning were also included. **By August 31, 2024, the total expenditure for the National Campaign amounted to EUR 731,340.27 (BGN 1,430,376.91).**

Based on the allocated budget and the number of participants, the cost per participant was calculated at EUR 7.84 (BGN 15.34). This figure encompasses not only the cost of the tests but also the expenses related to the information campaigns promoting the screening program.

e. Structure of the Applied Analysis: Markov Model

To evaluate the cost-effectiveness of the CRC screening program (SP) compared to no program, a Markov model was constructed using TreeAge Pro

2023 software. The model includes four health states (undiagnosed patient with CRC, diagnosed patient with stage I-II CRC, diagnosed patient with stage III-IV CRC, and death). The structure of the model is summarized in Figure 12, illustrating transitions between health states.

Two arms were analyzed: the assessed arm "With screening" and the comparator arm "Without screening". The structure of the model is consistent across both arms and is detailed in Figure 13.

The analysis was conducted over a lifetime horizon (50 years) to comprehensively capture the life span of the modeled patients. Each model cycle represents one year, and an annual discount rate of 3.5% was applied to both costs and utilities after the first year. The analysis was conducted from the perspectives of the National Health Insurance Fund (NHIF) and the payer of the screening program. Only CRC patients were modeled. The model assumes that all CRC patients, whether screened or unscreened, will eventually be diagnosed. The primary distinction between the two arms lies in the timing of diagnosis – patients in the "With screening" arm are more likely to be diagnosed at earlier stages (I–II), whereas those in the "Without screening" arm are more likely to be diagnosed at later stages (III–IV).

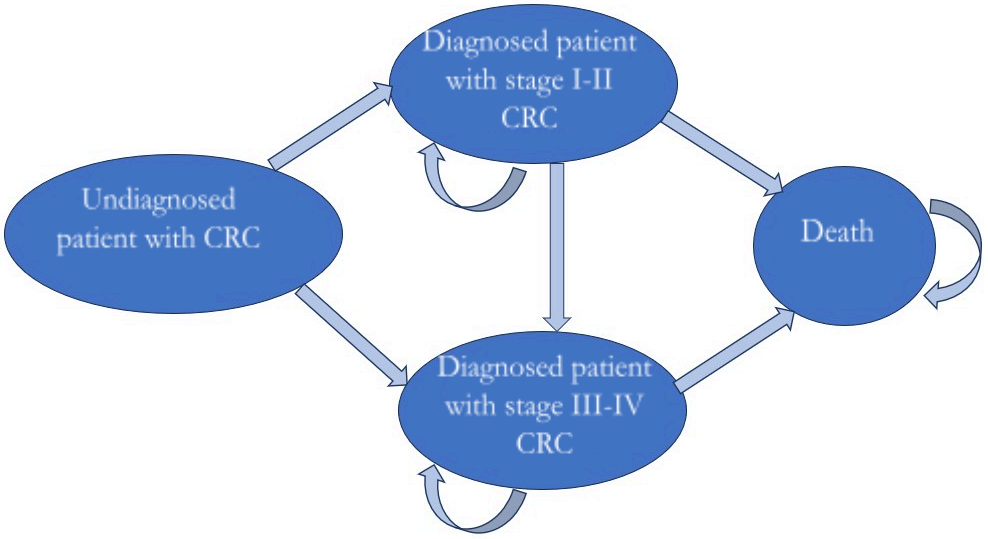

Figure 12. Markov Model Structure by Health States

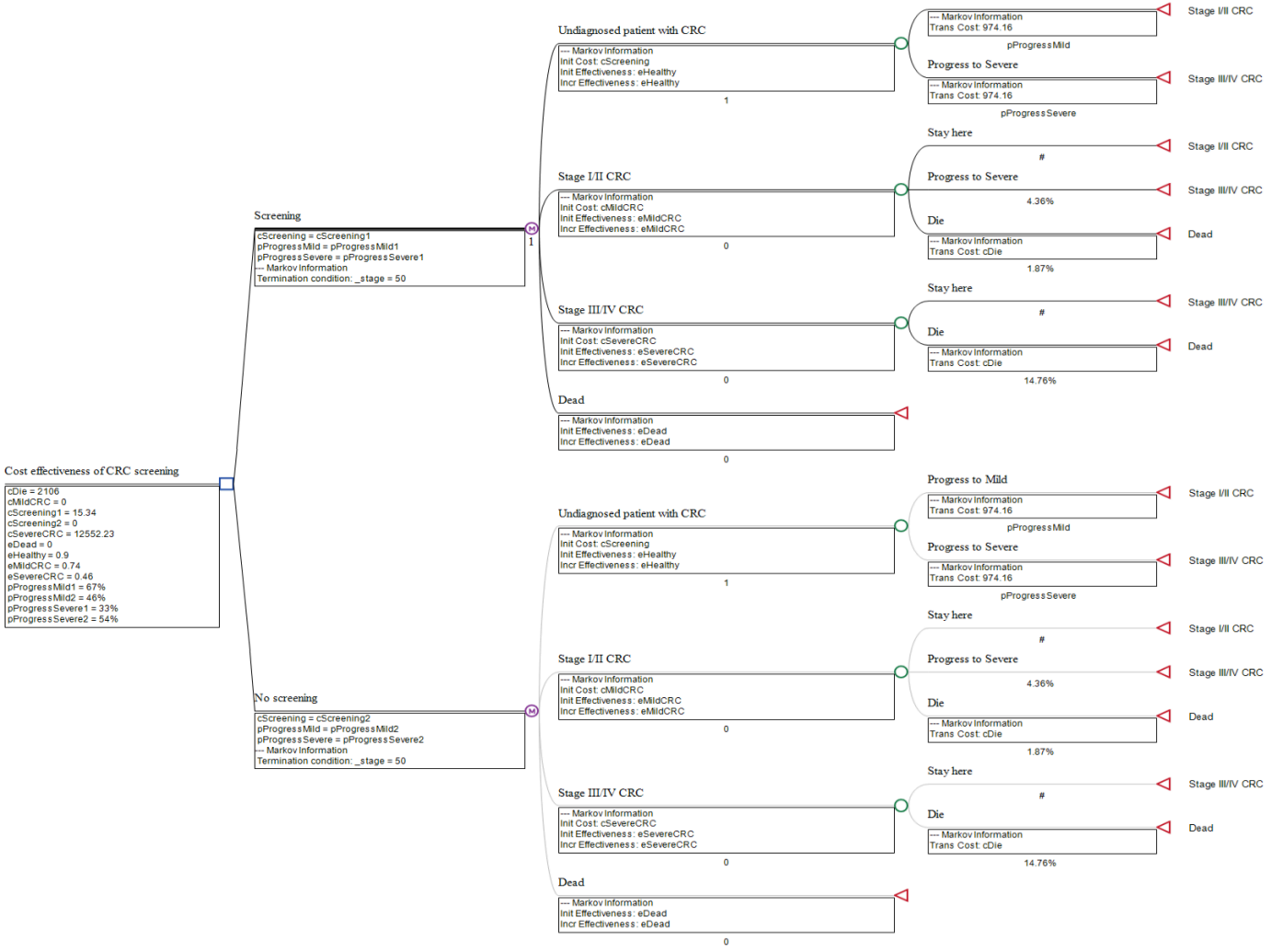

Figure 13. Detailed Diagram of the Markov Model (Showing the Two Evaluated Arms)

Input Data for Transition Probabilities Between Health States

Screening programs enable a higher percentage of patients to be diagnosed at earlier stages of colorectal cancer, improving survival rates and quality of life.

The probabilities for transitioning to "diagnosed patient with stage I-II CRC" or "diagnosed patient with stage III-IV CRC" are derived from data collected through a screening program in the Netherlands and are summarized in Table 7.[48]

Table 7. Input Data for Diagnosis Probabilities in Stage I-II and Stage III-IV CRC

Strategy	Stage I-II CRC	Stage III-IV CRC
Detected within the screening program	67.00%	33.00%
Detected outside the screening program	46.00%	54.00%

The model incorporates stage-specific CRC mortality probabilities. According to SEER data, the 5-year survival rates for patients with stage I-II CRC and stage III-IV CRC are 91% and 45%, respectively. (This corresponds to 5-year mortality probabilities of 9% for stage I-II and 55% for stage III-IV CRC).[49]

Because the model uses annual probabilities, the 5-year survival rates were converted to annual mortality probabilities using the formula shown in Equation 1. Based on this conversion, the following annual mortality probabilities were calculated: stage I-II: 1.87%; stage III-IV: 14.76%.

Equation 1. Formula for Converting 5-Year Survival Probability to Annual Mortality Probability

$$\textit{Annual mortality probability} = 1 - (\textit{5-year survival probability})^{\wedge}(1/5)$$

The model also accounts for the annual probability of disease progression from stage I-II to stage III-IV (the natural course of the disease). Due to limited data on progression probabilities, the model assumes a conservative approach:

relapse is associated with subsequent progression. A recent Danish study reported 5-year cumulative incidence functions (CIF) of recurrence for stage I and stage II CRC:

stage I CRC: 6.80% for colon cancer and 9.50% for rectal cancer (mean: 8.15%); stage II CRC: 11.60% for colon cancer and 18.40% for rectal cancer (mean: 15.00%).

For cancers detected via screening, recurrence rates are even lower.[50] Based on this data, a mean 5-year CIF of recurrence for stage I-II CRC was calculated as 11.58% (or 2.43% annual incidence after conversion) was calculated.

The model defines "death" as an absorbing health state (patients cannot transition to another state beyond death). No costs or health utilities are accumulated in this state.

Cost Inputs

Patients enter the model in the state "undiagnosed patient with CRC". Depending on the evaluated arm, the modeled patients either undergo screening or do not. A one-time cost of EUR 7.84 (BGN 15.34) per patient is incurred in the "With screening" arm, calculated as the total campaign cost (EUR 731 340,27 [BGN 1,430,376.91]) divided by the total number of screened individuals (93,218). Patients in the "Without screening" arm do not incur screening costs.

Patients diagnosed with CRC also incur colonoscopy costs, reported as the cost of one clinical pathway (CP) No. 69 "Highly specialized interventional procedures for gastrointestinal diseases for individuals aged 18 and older" (EUR 498.08 [BGN 974.16]).

Patients in stage I-II do not incur additional pharmacotherapy costs. According to the Pharmacotherapeutic Guideline (PTG) for Medical Oncology (Supplement to the State Gazette, No. 63 of July 26, 2024), stage I does not require pharmacotherapy, and stage II rarely involves neoadjuvant or adjuvant chemotherapy. Therefore, pharmacotherapy costs for stage I-II CRC are excluded based on PTG recommendations and local expert input.

Patients in stage III-IV CRC receive an average of 6 months of treatment, as estimated by experts. Based on average monthly data on drug sales for ICD C18, C19 and C20 provided by the NHIF, the estimated mean pharmacotherapy cost for 6-month treatment is EUR 2,031.53 (BGN 3,979.19) per patient. In real-world, when applying pharmacotherapy for the treatment of CRC, it is possible to report two CPs No. 240 "Long-term systemic parenteral drug treatment for malignant solid tumors and its associated complications" per month (a total of 12 CPs No. 240 for 6 months of treatment). Since the unit value of CP No. 240 is EUR 365.28 (BGN 714.42), the administration cost totals EUR 4,383.33 (BGN 8,573.04). The cost of the 6-month treatment of a patient with stage III-IV CRC amounts to EUR 6,417.85 (BGN 12,552.23; including pharmacotherapy and hospitalizations for treatment administration).

The model also reports palliative care costs of EUR 1,076.78 (BGN 2,106.00; 10 days under CP No. 253 "Palliative care for oncological patients") for patients transitioning to the "death" state.

Health Utilities Inputs

The model incorporates health utilities based on patient health states as reported in the literature.[51] Average utilities are assumed for two conditions: a diagnosed patient with stage I-II CRC and a diagnosed patient with stage III-IV CRC.

Table 8. Mean Health Utilities by CRC Stage

Stage	Health utilities by stage (QALY)	Mean health utilities by stage (QALY)	Reference
Stage I	0.74	0.74	Ness *et al.* 1999[51]
Stage II	0.74		
Stage III	0.67	0.46	
Stage IV	0.25		

f. Results of the Analysis

Cost-Effectiveness of the CRC Screening Program Compared to No Screening Benefits of Early Diagnosis (Markov Model Results)

To evaluate the cost-effectiveness of the CRC screening program compared to no screening, a Markov model with four health states was developed. The model quantifies the impact of diagnosing patients at earlier disease stages, showing how this influences associated costs and health utilities.

Table 9 presents the cumulative costs and utilities per patient over the full-time horizon. Table 10 extends these results to the total estimated number of CRC patients. Since the total number of CRC patients diagnosed through the pilot screening program is not directly available, estimates were derived from literature, using data from similar programs employing the same type of tests that were used in this program – the FIT tests. To estimate the number of CRC patients, data from the Slovenian screening program were used.[45] It indicates that 5.63% of participants with a positive FIT test were diagnosed with CRC (862 out of 15,310 people).[45] Applying this rate to Bulgarian data, where 13,263 participants had positive FIT results, an estimated 747 CRC patients (5.63% of 13,263) were identified. These estimates allow predictions about cumulative utilities for patients diagnosed via the screening program.

Table 9. Results Per Patient (Markov Model): Discounted Final Results for Costs and Utilities

Evaluated arm/strategy	Costs, EUR (BGN)	Δ costs, EUR (BGN)	QALY	Δ QALY	ICUR, BGN/QALY
With screening	1,137.24 (2,224.24)	-	8.46	-	**The screening program dominates**
Without screening	1,204.31 (2,355.42)	**-67.07 (-131.18)**	6.88	**+1.58**	

Table 10. Results for All CRC Patients from the Screening Program: Discounted Final Results for Costs and Utilities

Evaluated arm/strategy	Costs, EUR (BGN)	Δ costs, EUR (BGN)	QALY	Δ QALY	ICUR, BGN/QALY
With screening	849,515.95 (1,661,508.39)	-	6,317.43	-	**The screening program dominates**
Without screening	899,617.56 (1,759,498.61)	-50,101.61 (**-97,990.21)**	5,137.84	**+1,179.59**	

The analysis indicates that **the CRC screening program dominates no screening**, offering both cost savings (-EUR 67.07 [-BGN 131.18 per patient]) and incremental utilities (+1.58 QALY per patient). For the total 747 CRC patients identified through the program, this equates to total cost savings: -EUR 50,101.61 (-BGN 97,990.2)1; total utilities gained: +1,179.59 QALYs.

Economic Impact of a CRC Screening Program

Pilot Program: Incremental GDP Contribution from QALYs Gained for CRC Patients

The estimated utilities from the Markov model presented above also allow to calculate the QALYs gained for patients of working age. According to the analysis, all assumed 747 CRC patients will gain a total of +1,179.59 QALYs as utility. As the mean age of the participants in the screening program is 61.3 years and 56% of the participants screened are of working age (52,321 out of 93,218), it can be assumed that 56% of the 747 CRC patients are also of working age, which means 419 working age CRC patients. This translates to +662.08 QALYs gained for patients of working age (+1.58 QALYs per patient, 419 patients in total). Assuming that QALYs represent full working capacity, the incremental GDP contribution is calculated by multiplying 668.08 QALYs by the GDP per capita of the working age population, which is EUR 24,087,00 (BGN 47,110.07) (Table 11, Table 12). According to the calculations, the potential incremental GDP contribution of patients who gained QALYs from the screening program is EUR 15,947,405.22 (BGN 31,190,406.30) or 0.017% of Bulgaria's GDP for 2023.

Table 11. Data on GDP per Capita in Bulgaria (2023)

GDP per capita in Bulgaria (2023) (NSI data)	
Gross Domestic Product (GDP), EUR (BGN)	93,946,530,472.80 (183,743,400,000.00)
Bulgarian working-age population, number	3,900,300
GDP per capita (working-age population), EUR (BGN)	24,087.00 (47,110.07)

Table 12. Total GDP Contribution Based on Data on QALYs Gained and GDP per Capita

Total GDP contribution based on data on QALYs gained and GDP per capita	
Total QALYs gained for all CRC patients	+1,179.59
Percentage of working-age participants, %	56%
QALYs gained for working-age patients	+662.08
GDP per capita (working-age population), EUR (BGN)	24,087.00 (47,110.07)
Total incremental GDP contribution, EUR (BGN)	15,947,405.22 (31,190,406.30)

Further Analysis: Cost Savings from Early Diagnosis

Based on data from the pilot screening program, it can be reasonably concluded that the introduction of a national CRC screening program would yield even greater health and economic utilities, provided the high efficiency of participant outreach and test conduction seen in the pilot program is maintained. Furthermore, successful referral of participants for follow-up colonoscopy after positive results is essential.

To estimate potential savings from reduced treatment costs for advanced CRC cases following the implementation of a screening program, data from the Netherlands were used to model the distribution of newly diagnosed cases by disease stage depending on whether the cases were detected within the screening program or not. Without a screening program, 54% of new CRC cases are diagnosed at stages III-IV. In contrast, with a screening program, only 33% of new

cases are diagnosed at these advanced stages.[43] Using this distribution, the number of avoided stage III-IV CRC diagnoses and the associated cost savings can be calculated (as outlined in Section 1.5, the cost of treating a patient with stage III-IV CRC is estimated at EUR 6,417.85 [BGN 12,552.23]). For projecting the population size during the analysis period, an annual population decline in Bulgaria of -1.147% was applied, based on NSI data. The CRC incidence rate was derived from GLOBOCAN 2022 estimates, averaging 5,086 cases annually or 95.22 cases per 100,000 adults.[52] The screening target group includes the population of Bulgaria between 50-74 years of age. As a result, cost savings of EUR 13,848,917.98 (BGN 27,086,122.96) are projected from avoided advanced CRC cases due to timely diagnosis during the period 2025–2029.

Table 13. Cost Savings from Avoided Newly Diagnosed Advanced CRC Cases in Screened Participants (Aged 50–74)

Year	2025	2026	2027	2028	2029	2025-2029
Population 50-74, number	2,208,353	2,183,023	2,157,984	2,133,232	2,108,764	-
Incidence rate (new cases)	2,103	2,079	2,055	2,031	2,008	10,276
Incidence rate (new cases with stage III-IV) without screening	1,136	1,122	1,110	1,097	1,084	5,549
Incidence rate (new cases with stage III-IV) with screening	694	686	678	670	663	3,391
Avoided cases of stage III-IV CRC with screening	442	437	432	427	422	2,158
Cost savings from avoided CRC cases in individuals aged 50-74, EUR (BGN)	**2,834,055.39 (5,542,929.27)**	**2,801,548.78 (5,479,351.87)**	**2,769,415.01 (5,416,503.70)**	**2,737,649.82 (5,354,376.41)**	**2,706,248.98 (5,292,961.71)**	**13,848,917.98 (27,086,122.9 6)**

To explore the potential impact of expanding the screening program to cover the entire adult population (mirroring the pilot program's inclusion of individuals aged 18 and older without restrictions), additional calculations were performed. These projections indicate that expanding the program could result in EUR 33,111,796.21 (BGN 64,761,029.33) in savings for the period 2025–2029, attributed to avoided advanced CRC treatment costs.

Table 14. Cost Savings from Avoided Newly Diagnosed Advanced CRC Cases in Screened Participants (Aged 18+)

Year	2025	2026	2027	2028	2029	2025-2029
Population, 18+, number	5,280,018	5,219,457	5,159,590	5,100,409	5,041,907	-
Incidence rate (new cases)	5,028	4,970	4,913	4,857	4,801	24,568
Incidence rate (new cases with stage III-IV) without screening	2,715	2,684	2,653	2,623	2,593	13,267
Incidence rate (new cases with stage III-IV) with screening	1,659	1,640	1,621	1,603	1,584	8,108
Avoided cases of stage III-IV CRC with screening	1,056	1,044	1,032	1,020	1,008	5,159
Cost savings from avoided CRC cases in individuals aged 18+, EUR (BGN)	**6,776,028.62 (13,252,756.97)**	**6,698,307.57 (13,100,747.85)**	**6,621,477.98 (12,950,482.27)**	**6,545,529.63 (12,801,940.24)**	**6,470,452.41 (12,655,101.99)**	**33,111,796.21 (64,761,029.33)**

Further Analysis: Cost Savings from Long-Term Reduction in Incidence Rate

Evidence from literature and international experience indicates that implementing colorectal cancer screening programs leads to a significant reduction in CRC incidence and mortality. Observational studies report that screening programs utilizing the FIT test can achieve a 10–22% decrease in incidence rates and a 10–50% reduction in mortality.[33–40,53] CRC incidence rate refers to the number of newly diagnosed cases within a specified period, typically one year. Following the introduction of a CRC screening program in the Netherlands, there was an initial increase in incidence due to the detection of asymptomatic cases.[43]

However, incidence rates subsequently decreased, dropping from 14,557 new cases in 2015 to 11,440 new cases in 2019, comparable to pre-program levels in 2013. Among males, the incidence rate decreased by 27% between 2015 and 2019, while females experienced a 14% reduction.[43]

Similarly, data from a successful FIT-based screening program in Italy demonstrate a substantial impact, with a 28% reduction in newly diagnosed CRC cases observed eight years after the program's introduction, attributable to early diagnosis and effective treatment of asymptomatic patients.[54] Based on these findings, it is reasonable to anticipate that a CRC screening program in Bulgaria could achieve a comparable 28% reduction in incidence rates within eight years of implementation.

While the exact dynamics of incidence rates during the initial eight years are uncertain – likely involving a temporary increase followed by a decline – the analysis projects the potential cost savings after this period. A 28% reduction in incidence rate is projected after 2032 (eight years after 2025), beginning from 2033 and analyzing a 5-year period thereafter until 2037. For this analysis, a conservative approach assumes treatment costs will remain constant, though they may increase due to the introduction of newer, more expensive therapies.

Under these assumptions, the CRC screening program is projected to save EUR 16,837,337.24 (BGN 32,930,961.64) in treatment costs between 2033 and 2037. These savings result from a reduced number of newly diagnosed CRC cases requiring treatment, reflecting a 28% decrease in incidence rates compared to current levels.

The cost savings were calculated by multiplying the number of avoided CRC cases by the average cost of treating a single patient, estimated at EUR 6,417.85 (BGN 12,552.23; including pharmacotherapy and hospitalizations for treatment administration). Population projections during the analysis period were adjusted for an annual decline of -1.147%, based on NSI data. The CRC incidence rate without

a screening program was derived from GLOBOCAN 2022 estimates (5,086 cases annually or 95.22 cases per 100,000 adults).[52] The incidence rate reduction was modeled using data from Bucchi *et al.* (2022), which supported a 28% reduction due to screening.[54] The difference in newly diagnosed cases (avoided CRC cases), multiplied by the per-patient treatment cost, estimated at EUR 6,417.85 (BGN 12,552.23; including pharmacotherapy and hospitalizations for treatment administration), results in total savings for treatment of EUR 16,837,337.24 (BGN 32,930,961.64) over the five-year period from 2033 to 2037.

Table 15. Avoided CRC Cases Through a Screening Program (Population 50-74 Years)

Year	2033	2034	2035	2036	2037	Total 2033-2037
Population 50-74, number	2,013,666	1,990,569	1,967,737	1,945,167	1,922,856	-
Incidence rate without screening	1,917	1,895	1,874	1,852	1,831	9,370
Incidence rate with screening	1,381	1,365	1,349	1,334	1,318	6,746
Avoided CRC cases with screening	537	531	525	519	513	2,624
Cost savings from avoided CRC cases in individuals aged 50-74, EUR (BGN)	**3,445,608.28 (6,739,022.47)**	**3,406,087.15 (6,661,725.88)**	**3,367,019.33 (6,585,315.88)**	**3,328,399.62 (6,509,782.31)**	**3,290,222.87 (6,435,115.11)**	**16,837,337.24 32,930,961.64**

To explore the potential impact of expanding the screening program to cover the entire adult population (mirroring the pilot program's inclusion of individuals aged 18 and older without restrictions), additional calculations were performed with a target population over 18 years of age and they are presented in the Table below. For the period 2033-2037, a total of EUR 40,256,898.07 (BGN 78,735,630.65) costs for treating CRC patients will be saved due to reduced incidence rate as a result of an effective CRC screening program.

Table 16. Avoided CRC Cases Through a Screening Program (Population Aged 18+ Years)

Year	2033	2034	2035	2036	2037	Total 2033- 2037
Population, 18+, number	4,814,534	4,759,311	4,704,722	4,650,759	4,597,415	-
Incidence rate without screening	4,584	4,532	4,480	4,428	4,378	22,402
Incidence rate with screening	3,301	3,263	3,226	3,189	3,152	16,130
Avoided CRC cases with screening	1,284	1,269	1,254	1,240	1,226	6,273
Cost savings from avoided CRC cases in individuals aged over 18, EUR (BGN)	**8,238,208.87 (16,112,532.32)**	**8,143,716.62 (15,927,721.58)**	**8,050,308.19 (15,745,030.61)**	**7,957,971.16 (15,564,435.11)**	**7,866,693.23 (15,385,911.04)**	**40,256,898.07 (78,735,630.65)**

The implementation of a screening program would significantly reduce colorectal cancer (CRC) mortality by detecting and removing malignant lesions at an early stage, as well as by identifying and eliminating precancerous lesions that could otherwise progress to cancer. This contributes to a decrease in CRC incidence rates and mortality.[33] According to the literature, successful CRC screening programs reduce mortality by over 50%, yielding significant health utilities for patients.[42]

Further Analysis: Comparison to the Screening Program Outlined in Bulgaria's National Cancer Control Plan for 2027

This analysis compares the screening program proposed in Bulgaria's National Cancer Control Plan for 2027 (hereafter referred to as the "National Cancer Control Plan") with the pilot screening program detailed in this report.

The National Cancer Control Plan aims to screen 100,000 participants by 2027, allocating EUR 76,69,380.00 (BGN 15,000,000) for this purpose (EUR 76,69

[BGN 150] per participant). In contrast, the pilot program screened 93,218 participants over three months (March 28 to June 30, 2024) at a cost of EUR 731,340.27 (BGN 1,430,376.91),EUR 7.84 BGN 15.34) per participant).

To facilitate a comparison, it is assumed that the National Cancer Control Plan would screen 25,000 participants annually, while the pilot program could reach 93,218 participants annually.

The pilot program would potentially detect a significantly larger number of CRC patients (+547 patients per year) (Table 17). A conservative estimate assumes that both screening programs would detect 33% of CRC cases at an advanced stage (based on data from the Netherlands' screening program).[43] Using this assumption, the pilot program is projected to identify 247 advanced-stage CRC patients per year, compared to 66 patients detected under the National Cancer Control Plan. This results in an incremental treatment cost of EUR 1,161,631.29 (BGN 2,271,952.80) for the additional advanced-stage cases detected by the pilot program (Table 17). However, the pilot program would also identify a significantly higher number of early-stage CRC patients annually – 500 compared to 134 under the National Cancer Control Plan (+366 patients), who would be missed by screening with a lower coverage per year, as set out in the National Cancer Control Plan (Table 17). Under the assumption that each year the pilot screening program identifies 500 early-stage patients compared to 134 with the screening program proposed in the National Cancer Control Plan (+366 patients per year), it can be inferred that by reaching 100,000 people screened in three years, as set out in the National Cancer Control Plan, a total of 964 early-stage patients would be missed. These missed early-stage patients are likely to progress to advanced stages, requiring more expensive treatments (Table 18).

It is important to note that the pilot screening program also delivers substantial incremental utilities for CRC patients. Based on the results of the Markov model presented above, CRC patients diagnosed within the screening

program gain an additional +1.58 quality-adjusted life years (QALYs). Therefore, the cumulative utilities for patients in the pilot program are projected to be significantly higher: 1,179.59 QALYs compared to 315.82 QALYs under the screening program based on the National Cancer Control Plan (a difference of +863.77 QALYs per year) (Table 17). Assuming that the pilot program continues to reach 93,218 people per year, over the entire 3-year period, the incremental utilities of the pilot program are projected to be +2,272.33 QALYs compared to the screening program based on the National Cancer Control Plan (Table 18).

To estimate the potential GDP contribution of CRC patients gaining quality-adjusted life years (QALYs) through a screening program, the percentage of working-age patients (56%, based on the pilot program) is used. The incremental GDP contribution of working-age CRC patients is projected to be EUR 15,947,405.22 (BGN 31,190,406.30) annually for the pilot program and EUR 4,269,720.27 (BGN 8,350,845.06) for the National Cancer Control Plan (+EUR 11,677,684.95 [+BGN 22,839,561.24] contribution to GDP per year). If the pilot program continues to screen 93,218 participants annually, the cumulative incremental GDP contribution over three years is estimated at EUR 47,820,867.05 (BGN 93,529,464.67), compared to EUR 17,100,229.69 (BGN 33,445,134.46) under the screening program based on the National Cancer Control Plan (a difference of +EUR 30,720,637.36 [+BGN 60,084,330.20] in incremental GDP contribution).

Table 17. Comparative Analysis of the National Cancer Control Plan Screening Program versus the Pilot Screening Program

Parameter	National Plan	Pilot Program	Difference
	Year 1	Year 1	Year 1
Number of individuals screened, total	25,000	93,218	68,218
% positive based on pilot program data	14.23%	14.23%	-
Number of positive, total	3,557	13,263	9,706
% individuals with CRC out of those who tested FIT positive based on a study from Slovenia	5.63%	5.63%	-
Estimated number of individuals with CRC out of those positive	200	747	547
CRC patients diagnosed at stage I-II	134	500	366
CRC patients diagnosed at stage III-IV	66	247	181
Incremental cost for treatment of patients diagnosed at stage III-IV, EUR (BGN)	**423,578.26 (828,446.88)**	**1,585,209.55 (3,100,399.68)**	**1,161,631.29 (2,271,952.80)**
Total QALYs gained for CRC patients due to a screening program	**315.82**	**1,179.59**	**863.77**
Number of QALYs for the working-age individuals (56%, based on the pilot program)	**177.26**	**662.08**	**484.81**
Incremental GDP contribution, EUR (BGN)	**4,269,720.27 (8,350,845.06)**	**15,947,405.22 (31,190,406.30)**	**11,677,684.95 (22,839,561.24)**

Table 18. Comparative Analysis of the National Cancer Control Plan Screening Program versus the Pilot Screening Program

Parameter	National Plan	Pilot Program	Difference
	Year 1-3	Year 1-3	Year 1-3
Number of individuals screened, total	100,000	279,654	179,654
% positive based on pilot program data	14.23%	14.23%	-
Number of positive, total	14,228	39,789	25,561
% individuals with CRC out of those who tested FIT positive based on a study from Slovenia	5.63%	5.63%	-
Number of individuals with CRC out of those positive	801	2,240	1,439
CRC patients diagnosed at stage I-II	537	1,501	964
CRC patients diagnosed at stage III-IV	264	739	475
Incremental cost for treatment of patients diagnosed at stage III-IV, EUR (BGN)	**1,694,313.04 (3,313,787.51)**	**4,742,792.95 (9,276,094.58)**	**3,048,479.91 (5,962,307.07)**
Total QALYs gained for CRC patients due to a screening program	1,264.86	3,537.19	2,272.33
Number of QALYs for the working-age individuals (56%, based on the pilot program)	**709.94**	**1,985.34**	**1,275.40**
Incremental GDP contribution, EUR (BGN)	**17,100,229.69 (33,445,134.46)**	**47,820,867.05 (93,529,464.67)**	**30,720,637.36 (60,084,330.20)**

VI. Recommendations and Suggestions for Future Programs and Initiatives

Following the success of the CRC screening program, which screened over 90,000 individuals in just three months, several key recommendations can be made to enhance and expand on this achievement. The program's comprehensive national coverage, supported by an extensive network of laboratories and an effective advertising campaign, significantly raised public awareness and participation. Building on this foundation, maintaining and expanding the program offer great potential to improve early CRC detection and long-term health outcomes.

1. Strengthening the Referral and Follow-Up System

An efficient referral and follow-up system is critical for maximizing the screening program's effectiveness. Patients with positive results must be promptly referred to specialists for confirmatory testing and diagnosis. A well-structured referral system should be implemented and closely monitored to minimize delays in diagnosis and treatment, as such delays can negatively impact patient outcomes. Introducing navigator services could enhance the referral process by offering personalized assistance to patients with positive results to guide them through all steps of the diagnostic and treatment process, ensuring they receive timely care and the necessary treatment. This would help streamline the diagnostic and treatment journey, reducing the risk of delays.

2. Maintaining and expanding the laboratory network

The extensive national network of laboratories provided free and easy access to colorectal cancer screening. Sustaining this network is vital to the program’s continued effectiveness. Efforts should also be made to expand the network, for example by introducing mobile screening units in remote areas. This approach

could further improve accessibility, ensuring equitable CRC screening services across the country.

3. Leveraging Success for Broader Prevention Initiatives

The CRC screening program's success provides an exemplary model for other preventive health efforts. Combining educational initiatives that promote lifestyle and dietary changes with screening activities could help address modifiable risk factors for CRC. This integrated approach would encourage healthy lifestyles, potentially reducing CRC incidence rates and reinforcing public health prevention strategies.

The effectiveness of the scope of a screening program for CRC is assessed. This pilot campaign, conducted in 2024, employed a multi-channel communication strategy and innovatively extended its target group to include individuals over 18 years of age, beyond the traditional age range. This adjustment accommodated specific risk profiles and expanded access to screening for a wider population. The current data highlights the need for regulatory amendments in Ordinance No. 8 of 3 November 2016 on Preventive Examinations and Periodic Monitoring (amended and supplemented, issue 3 of 9 January 2024, effective from 1 January 2024). These amendments would provide a stable legal foundation and sustainable mechanisms for supporting screening programs and other preventive public health initiatives.

VII. Conclusion

The 2024 national colorectal cancer (CRC) screening program yielded significant results, underscoring the critical role of early detection through organized efforts. With over 90,000 participants, 14.22% tested positive, affirming the need for sustained and expanded screening initiatives. Males exhibited a higher positivity rate (18.19%) compared to females (11.93%). The frequency of positive results increased with age, reaching 20.2% in participants over 75 years old. These findings highlight the importance of prioritizing older adults and males in future campaigns. Among the screened population, 16.2% reported a family history of CRC, a critical risk factor. This underscores the need for targeted and consistent screening for individuals with hereditary risk, improving early diagnosis and clinical outcomes. The communication strategy, encompassing media campaigns, social networks, influencer partnerships, and educational initiative, effectively engaged the target audience. Television emerged as the most influential medium, informing 45.1% of participants.

The pilot colorectal cancer screening program in Bulgaria demonstrated substantial health and economic benefit. The total budget by 31 Aug 2024 was EUR 731,340.27(BGN 1,430 ,376.91), with the cost per participant being EUR 7.84 (BGN 15.34)„ covering tests and public awareness efforts. The screening program facilitated early diagnosis and timely treatment of asymptomatic patients, thereby reducing the need for more expensive treatments at advanced stages. Screening saves EUR 131.18(BGN 131.18) and gains 1.58 QALYs per patient. For the estimated 747 patients expected to be identified through the pilot campaign, this translates to total savings due to earlier diagnosis of EUR 50,101.61 (BGN 97,990.21) and health benefit of 1,179.59 QALYs gained. Approximately 56% of the participants were of working age, resulting in a GDP contribution of EUR 15,947,405.22 (BGN 31,190,406.30).

Based on the data collected from the pilot screening program, it can be reasonably concluded that the introduction of a national colorectal cancer screening

program would lead to even greater health and economic benefits. The national implementation of the program in the population aged 50-74 is projected to save EUR 13,848,917.98 (BGN 27,086,122.96) from 2025 to 2029 by preventing advanced CRC cases. A further EUR 16,837,337.24 (BGN 32,930,961.64) is expected to be saved between 2033 and 2037 for the target group aged 50-74 due to the anticipated reduction in CRC incidence and associated treatment costs.

The pilot CRC screening program demonstrates clear advantages over the screening initiative outlined in Bulgaria's National Cancer Control Plan for 2027. The pilot program screened significantly more patients in one year (93,218 vs. 25,000) and achieved a much lower cost per participant (EUR 7,84 [BGN 15.34] vs. EUR 76,69 [BGN 150]). This broader reach could detect a higher number of CRC cases, including an estimated +366 additional early-stage patients annually, who might otherwise be missed under limited screening coverage.

The pilot program not only identifies more early-stage CRC cases than the National Cancer Control Plan, but also delivers considerable incremental benefit (+863.77 QALYs per year) and economic contribution to GDP (+EUR 11,68 [+BGN 22.84] million per year).

The successful implementation of the screening program underscores the critical role of early diagnosis in reducing the incidence of colorectal cancer and, indirectly, its associated mortality. The program highlights the need to sustain and expand screening initiatives, particularly targeting high-risk groups such as male patients, individuals over 50 years of age, and those with a family history of CRC. This campaign lays a robust foundation for future health policies and strategies. Systematic data collection plays a vital role in enhancing understanding of epidemiological trends and supports the development of targeted prevention and treatment interventions.

Regular screening campaigns, coupled with educational initiatives promoting healthy lifestyles, would contribute to improved long-term health outcomes and help alleviate the burden of CRC nationwide. Expanding the laboratory network,

particularly in underserved or remote areas, alongside optimizing referral systems and follow-up care for individuals with positive results, would enhance healthcare delivery and ensure timely treatment.

The analysis concludes that future screening programs should focus on tailoring screening criteria to specific risk factors and age groups to maximize coverage and improve effectiveness in the fight against colorectal cancer.

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VIII. References

1. Gharib E, Robichaud GA. From Crypts to Cancer: A Holistic Perspective on Colorectal Carcinogenesis and Therapeutic Strategies. *Int J Mol Sci 2024, Vol 25, Page 9463*. 2024;25(17):9463. doi:10.3390/IJMS25179463
2. World Health Organization. Colorectal cancer.
3. Bray Bsc F, Laversanne | Mathieu, Hyuna |, et al. Global cancer statistics 2022: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. *CA Cancer J Clin*. 2024;74(3):229-263. doi:10.3322/CAAC.21834
4. Профили на държавите по отношение на рака: България 2023. *Профили на държавите по отношение на рака България 2023*. February 2023. doi:10.1787/FA33BC55-BG
5. GLOBOCAN. Cancer Today. http://gco.iarc.fr/today. Published 2020. Accessed March 17, 2021.
6. Morgan E, Arnold M, Gini A, et al. Global burden of colorectal cancer in 2020 and 2040: incidence and mortality estimates from GLOBOCAN. *Gut*. 2023;72(2):338-344. doi:10.1136/GUTJNL-2022-327736
7. Bnard F, Brkun AN, Martel M, Von Renteln D. Systematic review of colorectal cancer screening guidelines for average-risk adults: Summarizing the current global recommendations. *World J Gastroenterol*. 2018;24(1):124-138. doi:10.3748/WJG.V24.I1.124
8. American Cancer Society. Colorectal Cancer Risk Factors | Hereditary Colorectal Risk Factors.
9. Maida M, Macaluso FS, Ianiro G, et al. Screening of colorectal cancer: present and future. *Expert Rev Anticancer Ther*. 2017;17(12):1131-1146. doi:10.1080/14737140.2017.1392243
10. Yashiro M. Ulcerative colitis-associated colorectal cancer. *World J Gastroenterol*. 2014;20(44):16389. doi:10.3748/WJG.V20.I44.16389
11. Roncucci L, Mariani F. Prevention of colorectal cancer: How many tools do

we have in our basket? *Eur J Intern Med.* 2015;26(10):752-756. doi:10.1016/J.EJIM.2015.08.019

12. García JP, Arribas J, Cañete Á, et al. Association of Polyps with Early-Onset Colorectal Cancer and Throughout Surveillance: Novel Clinical and Molecular Implications. *Cancers (Basel).* 2019;11(12). doi:10.3390/CANCERS11121900
13. Gupta S. Screening for Colorectal Cancer. *Hematol Oncol Clin North Am.* 2022;36(3):393-414. doi:10.1016/J.HOC.2022.02.001
14. Dekker E, Tanis PJ, Vleugels JLA, Kasi PM, Wallace MB. Colorectal cancer. *Lancet (London, England).* 2019;394(10207):1467-1480. doi:10.1016/S0140-6736(19)32319-0
15. Bailie L, Loughrey MB, Coleman HG. Lifestyle Risk Factors for Serrated Colorectal Polyps: A Systematic Review and Meta-analysis. *Gastroenterology.* 2017;152(1):92-104. doi:10.1053/J.GASTRO.2016.09.003
16. Sakorafas GH, Zouros E, Peros G. Applied vascular anatomy of the colon and rectum: clinical implications for the surgical oncologist. *Surg Oncol.* 2006;15(4):243-255. doi:10.1016/J.SURONC.2007.03.002
17. Young GP, Pedersen SK, Mansfield S, et al. A cross-sectional study comparing a blood test for methylated BCAT1 and IKZF1 tumor-derived DNA with CEA for detection of recurrent colorectal cancer. *Cancer Med.* 2016;5(10):2763-2772. doi:10.1002/CAM4.868
18. Recio-Boiles A, Cagir B, Alejandro Recio-Boiles. Colon Cancer. Stat Pearls. https://www.statpearls.com/ArticleLibrary/viewarticle/19739. Published 2021. Accessed April 20, 2021.
19. Roshandel G, Ghasemi-Kebria F, Malekzadeh R. Colorectal Cancer: Epidemiology, Risk Factors, and Prevention. *Cancers 2024, Vol 16, Page 1530.* 2024;16(8):1530. doi:10.3390/CANCERS16081530
20. Mazzilli KM, Matthews CE, Salerno EA, Moore SC. Weight Training and Risk of 10 Common Types of Cancer. *Med Sci Sports Exerc.*

2019;51(9):1845-1851. doi:10.1249/MSS.0000000000001987

21. Matthews CE, Moore SC, Arem H, et al. Amount and intensity of leisure-time physical activity and lower cancer risk. *J Clin Oncol*. 2020;38(7):686-698. doi:10.1200/JCO.19.02407/SUPPL_FILE/DS_JCO.19.02407.PDF
22. Mctiernan A, Friedenreich CM, Katzmarzyk PT, et al. Physical Activity in Cancer Prevention and Survival: A Systematic Review. *Med Sci Sports Exerc*. 2019;51(6):1252-1261. doi:10.1249/MSS.0000000000001937
23. Lee JE, Chan AT. Fruit, vegetables, and folate: cultivating the evidence for cancer prevention. *Gastroenterology*. 2011;141(1):16-20. doi:10.1053/J.GASTRO.2011.05.020
24. Sansbury LB, Wanke K, Albert PS, Kahle L, Schatzkin A, Lanza E. The Effect of Strict Adherence to a High-Fiber, High-Fruit and -Vegetable, and Low-Fat Eating Pattern on Adenoma Recurrence. *Am J Epidemiol*. 2009;170(5):576-584. doi:10.1093/AJE/KWP169
25. Kabat GC, Matthews CE, Kamensky V, Hollenbeck AR, Rohan TE. Adherence to cancer prevention guidelines and cancer incidence, cancer mortality, and total mortality: a prospective cohort study. *Am J Clin Nutr*. 2015;101(3):558-569. doi:10.3945/AJCN.114.094854
26. Song M, Giovannucci E. Preventable Incidence and Mortality of Carcinoma Associated With Lifestyle Factors Among White Adults in the United States. *JAMA Oncol*. 2016;2(9):1154-1161. doi:10.1001/JAMAONCOL.2016.0843
27. Aleksandrova K, Pischon T, Jenab M, et al. Combined impact of healthy lifestyle factors on colorectal cancer: a large European cohort study. *BMC Med*. 2014;12(1). doi:10.1186/S12916-014-0168-4
28. Goede SL, Kuntz KM, Van Ballegooijen M, et al. Cost-savings to Medicare from Pre-Medicare Colorectal Cancer Screening. *Med Care*. 2015;53(7):630. doi:10.1097/MLR.0000000000000380
29. Mariotto AB, Robin Yabroff K, Shao Y, Feuer EJ, Brown ML. Projections of

the Cost of Cancer Care in the United States: 2010–2020. *JNCI J Natl Cancer Inst*. 2011;103(2):117. doi:10.1093/JNCI/DJQ495

30. Klimeck L, Heisser T, Hoffmeister M, Brenner H. Colorectal cancer: A health and economic problem. *Best Pract Res Clin Gastroenterol*. 2023;66:101839. doi:10.1016/J.BPG.2023.101839
31. Henderson RH, French D, Maughan T, et al. The economic burden of colorectal cancer across Europe: a population-based cost-of-illness study. *Lancet Gastroenterol Hepatol*. 2021;6(9):709-722. doi:10.1016/S2468-1253(21)00147-3
32. WHO. When is screening for cancer the right course of action? https://www.who.int/europe/news/item/02-02-2022-when-is-screening-for-cancer-the-right-course-of-action. Published 2022. Accessed October 11, 2024.
33. Cardoso R, Guo F, Heisser T, et al. Colorectal cancer incidence, mortality, and stage distribution in European countries in the colorectal cancer screening era: an international population-based study. *Lancet Oncol*. 2021;22(7):1002-1013. doi:10.1016/S1470-2045(21)00199-6
34. Segnan N, Armaroli P, Bonelli L, et al. Once-only sigmoidoscopy in colorectal cancer screening: follow-up findings of the Italian Randomized Controlled Trial--SCORE. *J Natl Cancer Inst*. 2011;103(17):1310-1322. doi:10.1093/JNCI/DJR284
35. Brenner H, Stock C, Hoffmeister M. Effect of screening sigmoidoscopy and screening colonoscopy on colorectal cancer incidence and mortality: systematic review and meta-analysis of randomised controlled trials and observational studies. *BMJ*. 2014;348. doi:10.1136/bmj.g2467
36. Atkin W, Wooldrage K, Parkin DM, et al. Long term effects of once-only flexible sigmoidoscopy screening after 17 years of follow-up: the UK Flexible Sigmoidoscopy Screening randomised controlled trial. *Lancet*. 2017;389(10076):1299-1311. doi:10.1016/S0140-6736(17)30396-3

37. Holme Ø, Løberg M, Kalager M, et al. Long-Term Effectiveness of Sigmoidoscopy Screening on ColorectalCancer Incidence and Mortality in Women and Men: a randomizedtrial. *Ann Intern Med.* 2018;168(11):775. doi:10.7326/M17-1441

38. Miller EA, Pinsky PF, Schoen RE, Prorok PC, Church TR. Effect of flexible sigmoidoscopy screening on colorectal cancer incidence and mortality: long-term follow-up of the randomised US PLCO cancer screening trial. *Lancet Gastroenterol Hepatol.* 2019;4(2):101-110. doi:10.1016/S2468-1253(18)30358-3

39. Lauby-Secretan B, Vilahur N, Straif K. *IARC Handbook of Cancer Prevention Vol. 17 - Colorectal Cancer Screening*. Vol 4.; 2018. doi:10.1200/jgo.18.17700

40. Mandel JS, Church TR, Bond JH, et al. The effect of fecal occult-blood screening on the incidence of colorectal cancer. *N Engl J Med.* 2000;343(22):1603-1607. doi:10.1056/NEJM200011303432203

41. Hewitson P, Glasziou P, Watson E, Towler B, Irwig L. Cochrane systematic review of colorectal cancer screening using the fecal occult blood test (hemoccult): an update. *Am J Gastroenterol.* 2008;103(6):1541-1549. doi:10.1111/J.1572-0241.2008.01875.X

42. Chiu HM, Jen GHH, Wang YW, et al. Long-term effectiveness of faecal immunochemical test screening for proximal and distal colorectal cancers. *Gut*. 2021;70(12):2321-2329. doi:10.1136/GUTJNL-2020-322545

43. van Iersel C, Toes-Zoutendijk E, de Jonge L, et al. *National Evaluation of the Population-Based Colorectal Cancer Screening Programme in the Netherlands 2018-2021*.; 2023. https://www.rivm.nl/sites/default/files/2023-05/Evaluation of the Colorectal Cancer Screening Programme 2018-2021.pdf.

44. Pellat A, Deyra J, Coriat R, Chaussade S. Results of the national organised colorectal cancer screening program with FIT in Paris. *Sci Rep*. 2018;8(1):8-11. doi:10.1038/s41598-018-22481-9

45. Tepeš B, Bracko M, Novak Mlakar D, et al. Results of the FIT-based National Colorectal Cancer Screening Program in Slovenia. *J Clin Gastroenterol.* 2017;51(6):e52-e59. doi:10.1097/MCG.0000000000000662
46. ТЕСТВАЙ СЕ. https://testvai.bg/. Published 2024.
47. Национална кампания за скрининг на рак на дебелото черво 2024 | CredoWeb. https://www.credoweb.bg/course/136899/natsionalna-kampaniya-za-skrining-na-rak-na-debeloto-chervo-2024/course. Accessed October 11, 2024.
48. Evaluation Team for Colorectal Cancer N. National evaluation of the population-based colorectal cancer screening programm e 2018 till 2021. 2018. www.zoiets.com. Accessed October 9, 2024.
49. Colorectal Cancer — Cancer Stat Facts. https://seer.cancer.gov/statfacts/html/colorect.html. Accessed October 9, 2024.
50. Nors J, Iversen LH, Erichsen R, Gotschalck KA, Andersen CL. Incidence of Recurrence and Time to Recurrence in Stage I to III Colorectal Cancer: A Nationwide Danish Cohort Study. *JAMA Oncol.* 2024;10(1):54-62. doi:10.1001/JAMAONCOL.2023.5098
51. Ness RM, Holmes AM, Klein R, Dittus R. Utility valuations for outcome states of colorectal cancer. *Am J Gastroenterol.* 1999;94(6):1650-1657. doi:10.1111/J.1572-0241.1999.01157.X
52. WHO. Statistics at a glance: Bulgaria. 2022. https://gco.iarc.who.int/media/globocan/factsheets/populations/100-bulgaria-fact-sheet.pdf. Accessed October 15, 2024.
53. European Comission. Participation in colorectal cancer screening programmes. 2024. https://cancer-inequalities.jrc.ec.europa.eu/sites/default/files/ECIR-inequalities-factsheet-colorectal-cancer-screening-Mar2024.pdf. Accessed October 14, 2024.

54. Bucchi L, Mancini S, Baldacchini F, et al. How a faecal immunochemical test screening programme changes annual colorectal cancer incidence rates: an Italian intention-to-screen study. *Br J Cancer 2022 1273*. 2022;127(3):541-548. doi:10.1038/s41416-022-01813-7

55. Ferlay J, Colombet M, Soerjomataram I, et al. Cancer incidence and mortality patterns in Europe: Estimates for 40 countries and 25 major cancers in 2018. *Eur J Cancer*. 2018;103:356-387. doi:10.1016/J.EJCA.2018.07.005