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Introducing Colorectal Cancer Screening in Romania – Preliminary Results from the Regional Pilot Programs (ROCCAS)

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ABSTRACT

Background & Aims: Colorectal cancer (CRC) is the third cause of cancer-related death worldwide. Screening programs can reduce CRC mortality rates by up to 60%. In line with the European Union recommendations, Romania started the first four regional pilot screening programs in 2020 (the ROCCAS II projects). This study reports the interim screening performance indicators.

Methods: People aged 50 to 74 years were invited to the screening program. General practitioners (GPs) evaluated CRC risk based on a survey. High-risk or symptomatic individuals were referred directly to colonoscopy. The average risk participants received a fecal immunochemical test (FIT). Positive cases were invited to colonoscopy. Three regions were screened using the OC-SENSOR® (South-Muntenia, Bucharest-Ilfov, South-East) and one region (South-West) used the FOB GOLD®. The data was collected in the ROCCAS screening electronic registry. The following FIT parameters were evaluated: rates of return, invalidity, positivity, and colonoscopy acceptance rate according to age group, gender, region of provenience, and vulnerability status.

Results: We included all cases screened between January 1, 2022 and September 30, 2023. In total, 168,958 people received the FIT test within the projects. The global FIT return rate was 90%. Factors associated with a higher return rate were female gender (90.77% vs 88.83%, p<0.0001), vulnerable status (91.23% vs 88.83%; p<0.00001), and rural residence (91.84% vs 88.42%, p<0.00001). The overall positivity rate was 5.75%. It was higher in males (7.64% vs 4.57% in females, p<0.00001) and progressively increased with the age group. The total invalid FIT rate was 5.87%, significantly lower for OC-SENSOR® (2.24%) than for the FOB GOLD® (13.6%). The overall acceptability rate for colonoscopy was 51.3%.

Conclusions: According to our preliminary data, GP's participation in the pilot programs ensured adequate adherence to screening through FIT. The rate for FIT return and positivity were acceptable for both tests, while the invalid rate was much higher in FOB GOLD® compared to the OC-SENSOR®. Moreover, colonoscopy acceptance needs to be improved. Our preliminary analysis revealed the screening performance indicators meet the EU recommendations and fulfill the premises for national-level expansion of the program starting in 2024.

Key words: colorectal cancer – Romania – screening – ROCCAS – FIT – colonoscopy acceptance.

Abbreviations: CRC: colorectal cancer; EU: European Union; FIT: fecal immunochemical test; gFOBT: guaiac-based fecal occult blood test; GP: general practitioner; ROCCAS: Romanian Colorectal Cancer Screening.

INTRODUCTION

Colorectal cancer (CRC) is a major public health problem worldwide. GLOBOCAN statistics from 2020 revealed it as a major contributor to cancer incidence (3rd place: 2.4 million new cases) and mortality (2nd place: 1.2 million deaths annually). In Romania, more than 12,000 new cases are diagnosed yearly, and CRC mortality has been increasing in the past decade, accounting for 12.4% of the cancer-related deaths [1].

Nevertheless, CRC is to a large extent preventable. In 2003, the European Union (EU) recommended the member states implement national-level CRC screening programs based on fecal testing [2]. Screening can reduce CRC fatalities by diagnosis at early stages and the possibility of detecting and removing precursor lesions [3]. Since they are detected at earlier stages (I-II), screening found lesions are more likely to be treated by local excision [4]. Moreover, when compared to incidental cases, screening detected stage III – IV CRC cases have a less severe course and better survival [5].

The first non-invasive test used for CRC screening was the guaiac-based fecal occult blood test (gFOBT) and although it led to a decrease in CRC mortality it has low sensitivity and specificity for colonic neoplasms [6]. The use of a quantitative fecal immunochemical test (FIT) followed by a colonoscopy in positives was recently endorsed by the newest EU Council recommendations [7]. The screening participation rates were higher in countries adopting FIT (range: 22.8–71.3%) than in those using gFOBT (range: 4.5–66.6%) [8].

Until 2020, Romania did not have a national CRC screening program. However, in 2019 owing to the European Social Funding programs, several screening projects were concurrently initiated in our country (breast and cervical cancer, chronic hepatitis B and C infection, tuberculosis, and cardiovascular diseases). On CRC, the program started with the ROCCAS I project (Romanian Colorectal Cancer Screening). This project was responsible for the development of a national methodology in CRC screening, the national CRC screening registry, the formula for the whole screening process, and the training of the personnel involved (GPs, endoscopists, pathologists). Consecutively, the pilot programs were started in four administrative regions of Romania (the ROCCAS II programs). The goal of these programs was to generate the infrastructure for subsequent CRC screening implementation at a national level. To fully achieve the benefits of CRC screening, every aspect of the process must be monitored, reported and maximized, including target population identification and outreach, test performance and availability, colonoscopy quality, treatment, surveillance, and aftercare protocols [9].

This study aimed to evaluate several performance indicators of the ROCCAS programs and to reveal any opportunity for further optimization of the program before national-level roll-out.

METHODS

Study Settings and Design

We performed a cohort analysis of the cases screened for CRC within ROCCAS II between January 1, 2022 and September 30, 2023. The pilot programs were initiated in four administrative regions of Romania: South-East, South-Muntenia, South-West Oltenia, and Bucharest-Ilfov respectively. One screening center was developed in each region. General practitioners (GPs) were involved in the program. They conducted the screening invitation of the target population, the risk questionnaire, and provided the FIT. They were also responsible for communicating the FIT result and explained the colonoscopy recommendation in FIT-positive cases. In each center, non-governmental organizations (NGOs) with expertise in screening were involved in carrying out informative campaigns and reaching out to vulnerable communities. The design off the study is presented in Fig. 1.

Study Participants

The target population was defined as individuals between 50 and 74 years. The risk for CRC was established by the GPs using a predetermined survey (Supplementary file, Table I). High-risk individuals were referred directly to colonoscopy. The average risk population was offered a FIT. FIT-positive persons (≥20 μg hemoglobin/g feces) were further referred to colonoscopy. The testing was done using FIT, either OC-SENSOR® (South-Muntenia, Bucharest-Ilfov, South-East) or FOB GOLD® (South-West). If the FIT test was invalid, a second FIT was provided. Among the ROCCAS II targets were: offering 200,000 FITs to the eligible population (50,000 per region) and having at least 50% of the beneficiaries belonging to a vulnerable group (according to the EU Social funding applications – Supplementary Table II). NGOs assisted with active recruitment of vulnerable individuals and transportation was provided for FIT-positive cases.

Data Sources

All screening-related data was systematically recorded in the ROCCAS electronic registry and included: information about the patient, informed consent, GDPR, demographics, vulnerability status, risk questionnaire, FIT providing, FIT return, initial FIT result, subsequently FIT result in a person with a previous invalid test, acceptance for colonoscopy, if FIT positive. Colonoscopy data and histopathology results were also collected in a standardized manner but are not the subject of this article.

Outcomes and Data Analysis

Our outcomes included the following screening performance indicators related to FIT: rate of return, invalidity,

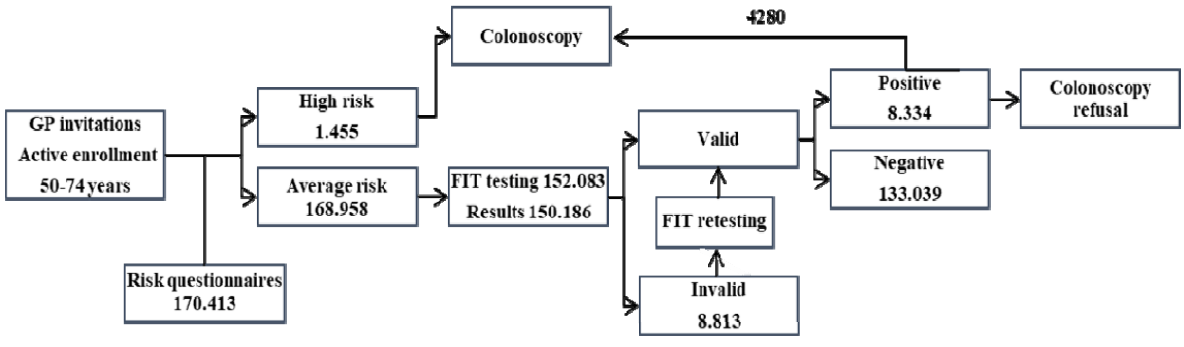

Fig. 1. Study design of the reported data from ROCCAS registry. FIT: fecal immunochemical test.

positivity, and colonoscopy acceptance. A statistical analysis was performed with SPSS. Continuous variables are reported as mean ± standard deviations (SD) and the differences between groups were examined using a 2-tailed t-test. Categorical variables are reported as numbers (percentage) and were analyzed using a 2-tailed chi-squared test. We assessed the association of the screening performance indicators with age, gender, rural/urban residence, and vulnerability status. Two-tailed alpha of 0.05 defined statistical significance.

RESULTS

Between the 1st of January 2022 and the 30th of September 2023, a total of 170,413 risk questionnaires were applied by the GPs. As a result, 1,455 individuals were identified as having high risk for CRC and sent directly to colonoscopy. The other 168,958 accepted the FIT test and 152,083 people returned it, resulting in a return rate of 90.01%. The sociodemographic parameters of the cohort involved in screening are reported in Table I.

Table I. Socio-demographic characteristics of tthe screened persons

	South Muntenia 49,705	South West 50,187	South East 29,110	Bucharest-Ilfov 39,956	All regions 168,958
Age, y, (Mean ± SD)	61.13 ± 7.10	61.12 ± 7.02	61.78 ± 7.00	61.46 ± 7.08	61.32 ± 7.06
Females, n, %	61.63	58.50	63.70	60.78	60.86
Residence area urban, %	39.24	42.71	48.96	88.20	53.63
Vulnerable, %	62.21	57.60	57.19	18.33	49.51
High risk, %	0.59	0.15	1.23	1.77	0.85

SD: standard deviation.

The results for each region and return rates are summarized in Fig. 2. As observed, one region reached 50,000 screened persons target (South West), while the others, South Muntenia, South East, and Bucharest-Ilfov, covered 99.41%, 58.22%, and 79.91%, respectively.

Data related to FIT return rates is summarized in Table II. The overall return rate was higher in females (90.77%) compared to males (88.83%) ($p<0.0001$, $\chi^2=169.6276$) and for individuals aged above 65 years compared to the younger participants ($p<0.0001$, $\chi^2=31.7344$). The lowest return rate was observed in the Bucharest-Ilfov region (80.91%), while the highest was in South West (95.44%). Among the 168,958

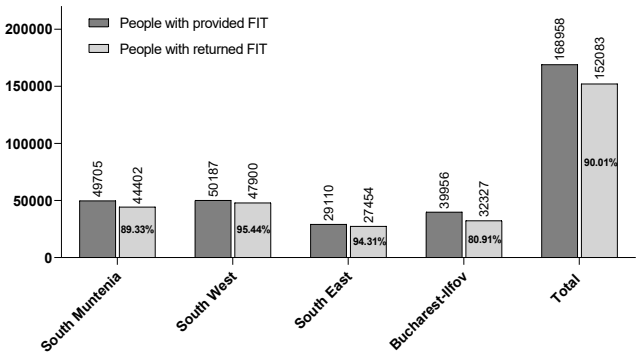

Fig. 2. Number of provided and returned fecal immunochemical test (FIT).

people who were handed out the FIT, 83,102 (49.19%) belonged to the vulnerable group. The return rate was significantly higher in the vulnerable group compared to the non-vulnerable one (91.23% vs 88.83%; $p<0.00001$, $\chi^2=271.3537$).

We also analyzed the return rate according to residence area. Overall, 90,212 tests were distributed to people residing in urban areas, compared to 78,746 tests given to people in rural areas. We obtained a statistically significant difference regarding the return rate in the rural segment (91.84%) versus the urban segment (88.42%) ($p<0.00001$, $\chi^2=548.5133$). Similar results were found across the four regional subgroups.

From the 152,083 returned tests, only 150,186 results were available in the registry at the time of the study. The results from the lacking 1,897 tests had not yet been submitted to the platform due to a gap between FIT return and the final laboratory result. The data for the first test provided are reported in Table III. For 8,813 people, the result of the first test was invalid, generating an overall invalid rate of 5.87%. Among the invalid tests, 2,300 were OC-SENSOR, generating an invalid rate of 2.24%, and 6,513 were FOB GOLD generating an invalid rate of 13.60% for this type of FIT. The difference in invalid FIT rates between OC-SENSOR and FOB GOLD was statistically significant. $p<0.00001$, $\chi^2=1561.5617$).

For each invalid test, a new test was provided to the screening participant if he/she agreed to repeat the FIT. After adding the subsequent FIT retesting results, the number of valid tests increased from 141,373 to 144,837 at the end of the study. The results are presented in Table IV.

A total number of 8,334 tests were positive. The FIT positivity rates are presented in Table IV. At the moment of the analysis, the

Table II. Fecal immunochemical test return rate

	South Muntenia 49,705	South East 29,110	Bucharest-Ilfov 39,956	South West 50,187	All regions 168,958
Total %	89.33	94.31	80.91	95.44	90.01
Male, %	87.47	93.66	79.05	94.96	88.83
Female, %	90.49	94.68	82.1	95.78	90.77
Age <65, %	88.92	94.33	79.75	95.50	89.69
Age ≥65, %	90.03	94.29	82.72	95.34	90.54
Vulnerable, %	88.48	94.56	79.02	95.5	91.23
Non-vulnerable, %	90.74	93.97	81.33	95.37	88.83
Urban %	90.54	93.81	81.05	95.03	88.42
Rural %	88.55	94.78	79.83	95.75	91.84

Table III. Invalid fecal immunochemical test rates

Region	Type of test	Number of tests returned	Number of tests with results	FIT invalid tests and rate (%)
South Muntenia	OC-SENSOR	44,402	44,197	982 (2.22)
South East		27,454	26,959	498 (1.85)
Ilfov-Bucharest		32,327	31,130	820 (2.63)
Total OC-SENSOR		104,183	102,286	2300 (2.24)
South West	FOB GOLD	47,900	47,900	6.513 (13.60)
All regions		152,083	150,186	8.813 (5.87)

Table IV. Positive fecal immunochemical test rates

	South Muntenia	South East	Bucharest-Ilfov	South West	All regions
Valid FIT, n	43,569	26,606	30,582	44,080	144,837
Total, %	5.92	5.28	5.18	6.28	5.75
Male, %	7.90	6.84	7.05	8.21	7.64
Female, %	4.74	4.40	4.01	4.90	4.57
Age <65, %	4.86	4.45	6.42	5.52	5.32
Age ≥65, %	7.75	6.49	6.87	7.65	7.28
Vulnerable, %	5.98	5.40	5.40	6.28	5.91
Non-vulnerable, %	5.83	5.11	5.13	6.28	5.60
Urban, %	5.73	5.27	5.12	6.14	5.54
Rural, %	6.05	5.28	5.62	6.38	5.99

overall FIT positivity rate was 5.75%. The highest FIT positivity rate was recorded in the South West region (6.28%). Overall, there was a higher positivity rate in males compared to females ($p<0.00001$, $\chi^2=597.9126$) (Table IV). Participants aged under 65 years had lower positivity rates scores compared to older individuals ($p<0.0001$, $\chi^2=328.1736$) (Fig. 3).

Moreover, when analyzing the positivity rate considering the 5 age categories, again a significantly higher positivity rate was observed in the older age groups ($p<0.0001$, $\chi^2=455.1104$) (Fig. 3).

From the 8,334 FIT positives, 7,993 were informed of the result and 4,280 already accepted to be scheduled for colonoscopy resulting in a preliminary colonoscopy acceptance rate of 51.3%. Not all individuals have undergone the procedure yet since there is a delay in scheduling (at least 1 month). In Table V we present the interim results for the colonoscopy acceptance rate in the four regions. There was no statistical difference regarding the type of test and the colonoscopy acceptance rate ($p=0.89$), but the region Bucharest Ilfov has a higher rate of acceptability compared to the other three regions ($p<0.0001$).

DISCUSSION

This is the first CRC screening program in Romania that uses quantitative FIT and colonoscopy in a targeted population. Piloting was preferred not only in order to test the adherence of the population to such preventive activities but also in order to assess the colonoscopy acceptance rate and the type of endoscopic lesions identified. This data should help prepare for the infrastructure of an organized screening program based on quantitative FIT.

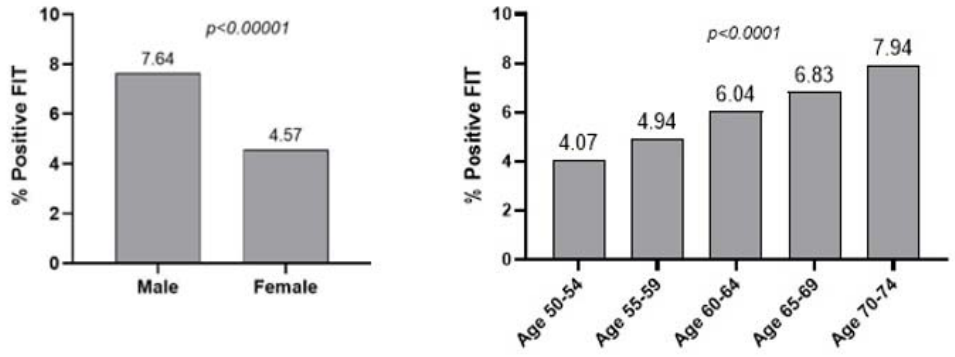

Fig. 3. Rate of fecal immunochemical test (FIT) positivity according to gender and age category.

Table V. Colonoscopy acceptance

Region	Type of test	Nr positive FITs	Informed positive FITs	Colonoscopy Acceptance Rate (%)
South Muntenia	OC-SENSOR	2,579	2,545	1,208 (47.5)
South East		1,404	1,263	610 (48.3)
Ilfov-Bucharest		1,583	1,446	1,001 (69.2)
Total OC-SENSOR		5,566	5,254	2,819 (53.7)
South West	FOB GOLD	2,768	2,739	1,461 (53.3)
All regions		8,334	7,993	4,280 (53.6)

FIT: fecal immunochemical test

The projects were designed according to a 4-year schedule but encountered a significant time reduction due to the COVID pandemic, a phenomenon observed in screening programs all over the world. After an aggregated effort, two regions (South and Southwest) currently surpass the 50,000 screened threshold based on the risk questionnaires completed. The other two regions have achieved 90% (Bucharest-Ilfov) and 75% (South-East) of the target. This level of performance within a 2-year implementation period is quite surprising, particularly when taking into consideration the lack of any precedent and the particular barriers.

The FIT return rate is higher than any predetermined number for this type of preventive measure in Romania, especially considering the high proportion of vulnerable groups. It is important to realize that this target was achieved in the population who accepted to complete the risk questionnaire. For the pilots, an active enrollment was accepted especially in vulnerable groups, therefore this is quite a selected population. Despite these encouraging numbers, it is essential to emphasize that this is only the first population response and not the real adherence to the screening program, which is closely linked to its effectiveness [10]. Similarly high rates have been encountered in smaller colorectal cancer screening programs and it is highly possible that this rate will get lower with the rollout as in other reports [11].

Strikingly or not, the lowest return rate obtained was in the Bucharest-Ilfov area, where there was the lowest percentage of vulnerable population. One hypothesis can be that visits to the GPs are less frequent in favor of specialist consultations. This trend is also supported by the fact that the return rate was significantly higher in rural areas. This contrasts with other countries reporting lower rates in rural areas [12]. There are many factors that might have contributed to this, such as the GP's significant authority in the smaller rural communities or the growing interest in getting medical investigations in areas that have less access. Other aspects to consider before designing a national screening program are the level of health literacy, life conditions, and the infrastructure. These are particularly important since cancer rates can be higher in rural compared to urban populations [13].

The invalidity rate must be discussed separately for the two tests we used. We obtained a 2.24% invalidity rate for the OC-SENSOR, a slightly lower value to the recommended 3% threshold, particularly in the setting of a national program [14]. The surprising element was the elevated number of invalid tests in the region tested with FOB GOLD. According to previous studies, error rates can be higher in FOB GOLD compared to OC-SENSOR [15]. The probable explanation is the misuse of the test, which will require improving the instructions for FIT completion. More importantly, the use of the FOB GOLD test did not affect the return rate, making it a suitable test for screening purposes, especially since it shows higher detection incidence rates [16].

The FIT positivity rate was similar regardless of the test used or the region. The value between 5% and 6.5% was chosen at the beginning of the project, and it has otherwise been proven acceptable; therefore, the cut-off value of 20 μg Hb/g feces was used for the entire project. Other screening programs have used different thresholds. However, recent studies have underlined the importance of adjusting the value of FIT depending on age and gender [17, 18].

We also obtained a higher rate of positivity as the age increased. This could either suggest that a higher percentage of neoplastic lesions can be found in older populations or that other causes can lead to an elevated FIT value, and therefore these individuals should not be directed to colonoscopy [19]. Additionally, the higher positivity rates in males suggest a higher prevalence of lesions, consequently requiring a high acceptance rate for colonoscopies. In 2022, a Dutch study suggested a stratifying strategy with higher FIT values to be used for the younger age groups and lower values for the 70-74 age group in order to increase detection rates and reduce the number of colonoscopies [20].

The preliminary colonoscopy acceptance rate is lower than expected but around the general 50%. We reckon this percentage will increase after all data is centralized and all the colonoscopies pooled. However, this is a strong signal that the population should be sensitized towards the importance of early colonoscopy. Increasing general awareness of the importance of timely detection and the potential benefits of screening must be prioritized. This is probably one of the most important barriers to the pilot program and will be specifically targeted in the 2024 national CRC screening action plan.

There are many factors that can be incriminated, such as a long distance from the endoscopic center, which can prove troublesome in the setting of a colonoscopy preparation, fear of colonoscopy, physician behavior, and delays in scheduling that might prompt the preference for another colonoscopy center. For this initial pilot study, all the centers involved were equipped for advanced endoscopy, and all the operators had ample experience in therapeutic colonoscopy. Transportation was provided only for the vulnerable groups, which could explain the higher adherence from this group.

There are limitations to this study arising mainly from the registry reporting and the use of two types of FIT. These

are partial results that, due to the geographic and population differences between the rest of the Romanian provinces, may not be extrapolated to all of them. Also, absence of follow-up information for the patients regarding the decision of colonoscopy could artificially lower the colonoscopy acceptance rate. These limitations will be addressed in the future after the registry is completed and all the information will be available.

This was the first centralized CRC screening study in our country. The results for colonoscopies and pathological reports will provide the data for detection rates and positive predictive values (PPVs) for CRC and advanced adenomas. Our results support the feasibility of an organized CRC screening through the existing healthcare system in Romania. Future studies should explore the means to optimize the capacity of the healthcare system for adequate colonoscopy services across the regions and to improve the colonoscopy acceptance rate in certain populations. Furthermore, follow-up rates for FIT testing should be another key element in designing a national screening program to which the population can adhere in the long term.

CONCLUSIONS

Overall, FIT performed well in the colorectal screening regional pilot projects (ROCCAS II). Individuals who accepted the risk questionnaire, accepted FIT and the overall return rate was higher than previously expected. In the Romanian particular setting, the GPs played a pivotal role in the screening process as the return rate for FIT was so high. Their implication in the first step, establishing individual CRC risk and providing FIT seems to be the best way of implementing this type of screening in our country.

The invalid rate for the OC SENSOR test was good (less than 3%). However, FOB GOLD generated a much higher rate for the same performance indicators, which could limit its use in future programs without any specific measures. The rate of positivity was acceptable, and no changes in the cut-off value were needed during the pilots. The colonoscopy acceptance rate was not as high as anticipated, which requires additional assessment and recommendations.

Data from the ROCCAS registry will allow the expansion of the design and further development of the 8 regional CRC screening programs in Romania starting in 2024. A FIT-based screening for age and risk-appropriate patients is practical in this environment, where the capacity and acceptability of colonoscopy are limited.

Conflicts of interest: None to declare.

Authors' contribution: M. M. and D.M. contributed significantly to the conception of the manuscript, E.D, DI.G, M.J., B.C, F. I.R. supervised the regional registry and collected data. C.U. supervised the registry, D.M., M.U. and I.S. had full access to the registry, ensuring data accuracy. T.M., E.M., and M.D. conducted the research with analysis and data interpretation. T.M. and E.M. drafted the manuscript. S.S., M.M., C.G., and M.D. critically revised the draft and approved the final version of the manuscript. All authors approved the final version to be published and agreed to be accountable for all aspects of the work.

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