

## Short Term Outcomes of Using Fecal Immunochemical Test for a Pilot Colorectal Cancer Screening Program. A Single Center Study on 3024 Consecutive Patients

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### Abbreviations:

CRC - colorectal cancer;  
FIT - faecal immunochemical test;  
CCE - colon capsule endoscopy;  
gFOBT - guaiac based faecal occult blood test;  
CTC - computed tomographic colonography;  
FS - flexible sigmoidoscopy;  
CRC-SP - colorectal cancer screening program;  
PAH - Ponderas Academic Hospital;  
PPV - positive predictive values;  
UR - uptake rate;  
PR - positivity rate;  
FPR - false positive rate;  
CCR - colonoscopy compliance rate.

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### Rezumat

**Rezultate precoce ale utilizării testelor fecale imunochimice (FIT) într-un program pilot de depistare a cancerului colorectal.**

**Studiu monocentric care include 3024 pacienți consecutivi asimptomatici**

**Introducere:** În România, cancerul colorectal nu beneficiază încă de un program național de screening. Pentru a reduce morbiditatea și mortalitatea cancerului colorectal (CRC), au fost adoptate programe oportuniste bazate pe endoscopie, în funcție de capacitatea fiecărui centru. Ponderas Academic Hospital (PAH) a lansat în 2019 un program pilot de screening al cancerului colorectal (CRC) bazat pe teste imunochimice fecale (FIT).

**Scop:** Studiul actual analizează rezultatele după primele 1500 de teste oferite gratuit prin programul de screening PAH-FIT-CRC. De asemenea, ne-am propus să comparăm eficiența programului de testare FIT cu colonoscopiile de screening efectuate în centrul nostru, în același interval de timp (2019).

**Metodă:** Testul a fost recomandat pacienților asimptomatici peste 45 de ani și a fost urmat de o colonoscopie atunci când rezultatele testului au fost pozitive. Mai mult, am efectuat un studiu observațional retrospectiv, colectând date de la toți pacienții

consecutivi incluși prospectiv în bazele de date ale spitalului, comparând eficacitatea celor două metode de screening al cancerului colorectal (FIT versus colonoscopie).

*Rezultate:* Între 01.01.2019 și 01.01.2020 s-au efectuat 1524 colonoscopii de screening, iar datele rezultate au fost comparate cu cele obținute în grupul FIT (1500 teste FIT distribuite gratuit). În grupul de colonoscopie de screening, rata de detecție a polipilor a fost de 38,98% și au fost identificate 22 (1,44%) adenocarcinoame. În grupul FIT, complianța pentru FIT a fost de 71%, cu o rată de pozitivitate de 21,7%. Rata de complianță pentru colonoscopie la pacienții cu FIT pozitivă a fost de 29,4%, cu doar 2 adenocarcinoame detectate.

*Concluzii:* În urma analizei datelor, este necesară îmbunătățirea complianței pacienților pentru metodele de screening, datorită acceptării relativ mici a testelor FIT și a colonoscoپیilor, în special în rândul bărbaților. Mai mult, ar trebui depuse eforturi speciale pentru a îmbunătăți indicatorii de calitate pentru screening-ul colonoscoپیilor (în special rata de detecție a polipilor și adenoamelor) în scopul scăderii proporției de pacienți identificați cu cancer de interval.

**Cuvinte cheie:** cancer colorectal, program de depistare precoce, testare imunochimică din fecale, (FIT), colonoscopie, rata de detectare a polipilor, rata de detectare a adenoamelor

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## Abstract

*Background:* In Romania, colorectal cancer does not benefit yet from a national screening program. In order to decrease the harm and burden of colorectal cancer (CRC), opportunistic programs relying on endoscopy has been adopted by each centre according to its capacity. A colorectal cancer (CRC) screening programme based on faecal immunochemical test (FIT) was launched at Ponderas Academic Hospital (PAH) in 2019.

*Aim:* The present study analyses the outcomes after the first 1500 tests in the PAH-FIT-CRC Screening Program. We have also aimed to compare the efficiency of the FIT testing program with the screening colonoscopies performed in our Center, withing the same time interval (2019).

*Methods:* The test was recommended in asymptomatic patients over 45 years, and it was followed by a colonoscopy when the test results were positive. Furthermore, we performed a retrospective observational study gathering data from all the consecutive patients prospectively included in the respective databases of our hospital, comparing the efficacy of the two colorectal cancer screening methods (FIT versus colonoscopy).

*Results:* Between 01.01.2019 and 01.01.2020, 1524 screening colonoscopies were performed, and the resulting data were compared with those obtained in the FIT group (1500 FIT tests freely distributed). In the screening colonoscopy group, the polyp detection rate was 38.98% and 22 (1.44%) adenocarcinomas were identified. In the FIT group, the FIT uptake rate was 71% with a positivity rate of 21.7%. The colonoscopy compliance rate for positive FIT patients was 29.4%, with only 2 adenocarcinomas detected.

*Conclusions:* Following data analysis, the need for improvement of uptake rate and colonoscopy compliance rate was suggested, due to the lower acceptance of FIT tests and colonoscopies, especially among men. Moreover, special efforts should be made in order to improve quality indicators for screening colonoscopies (especially adenoma detection rate) with the purpose of decreasing interval CRC.

**Key words:** colorectal cancer screening, faecal immunochemical testing (FIT), colonoscopy, adenoma detection rate (ADR)

## Introduction

Colorectal cancer (CRC) carries a high morbidity and mortality, ranking third among all types of cancers in terms of incidence (1). However, over the last decade incidence and mortality has been declining steadily in countries with effective screening programs. In contrast, in developing countries mortality and incidence continue to rise due to poor health infrastructure or lifestyle changes such as westernized diet (2). Thus, CRC screening for age group 50-75 has received a grade A recommendation (meaning a service that is highly recommended due to its major benefit) from the US Preventive Services Task Force (USPSTF) (3). Furthermore, according to Wilson and Jungner's criteria, colorectal cancer qualifies for screening due to increased incidence rate, its recognizable and curable precursors, long latent disease and the link between mortality and tumour stage (4). Nevertheless, the screening method's effectiveness is determined by various factors such as cost, the adherence to the test, the type of the test regarding its sensitivity and specificity. Also, in order to complete the screening process, retesting is necessary for both normal and abnormal tests, thus compliance with the follow-up is essential (5).

### *Stool tests*

Stool tests such as faecal immunochemical test (FIT), guaiac based faecal occult blood test (gFOBT) and faecal DNA testing represent non-invasive screening methods, being followed by a colonoscopy if the results are positive. The principle of these tests is based on the likelihood of CRC to bleed so, the blood presence in the stool represents a feasible target. Therefore, gFOBT detects occult blood in stool binding to haem. Although gFOBT is cheap and widely available, it requires dietary restrictions due to the lack of specificity to human haemoglobin. In addition, more than one sample is required in most screening programs. Currently, an increasing criticism has been noticed regarding gFOBT, due to its slow sensitivity and positivity rate for CRC

detection. Thus, a new test has been introduced to counteract gFOBT drawbacks (5). Therefore, the faecal immunochemical test (FIT) detects globin not haem, being specific for human blood and, consequently, the dietary restrictions are not being required. One sample is sufficient in most screening programs thereby, FIT is easier to be used, thus supporting an increased participation rate. In addition, quantitative results are provided (Og Hb per gram faeces) and the cut-off value for Hb detected may be predetermined in order to obtain different specificity and sensitivity rates. Above all, nowadays FIT is replacing gFOBT in CRC screening programs due to its major benefit-higher sensitivity rate for CRC detection (61% vs 23,8 %, respectively) (6).

### *DNA*

Faecal DNA tests are also available, identifying abnormal DNA in polyps or CRC cells (7). In one multicentre study including nearly 10.000 patients, faecal DNA test was compared with FIT and it showed to have higher sensitivity regarding CRC detection (92% vs 74%, respectively), but lower specificity (88% vs 95%, respectively) (7). Thereby, its role in CRC prevention is limited by the low capacity to detect large advanced adenomas (only 42%) (8, 9). Furthermore, faecal DNA test was found to be less cost-effective than FIT or colonoscopy in another study from Stanford University, thus making it underused for screening programs (10).

### *Colon capsule endoscopy*

Colon capsule endoscopy (CCE) can provide a minimally invasive assessment of the colon, although it still requires bowel cleansing. Despite its improved uptake, CCE usage is limited due to high cost, availability and the need for colonoscopy if lesions are found (11).

### *Computed tomographic colonography*

Virtual colonoscopy (computed tomographic colonography - CTC) may be considered as an alternative regarding the evaluation of the colon for CRC. It requires bowel cleansing and the use of a rectal catheter for the CO<sub>2</sub>

insufflation. Detection rate of large polyps or cancer showed to be similar compared to colonoscopy, but CTC appeared to have a lower detection rate for the lesions smaller than 1 cm (12). Moreover, the presence of any abnormality imposes a standard colonoscopy for either biopsy or polypectomy.

### *Flexible sigmoidoscopy or colonoscopy*

Flexible sigmoidoscopy (FS) or colonoscopy are considered minimal invasive techniques, extremely useful to reduce the risk and the mortality of CRC. FS has the advantage of a limited bowel preparation but, it should be always followed by a colonoscopy when distal polyps are identified(13). FS was shown to decrease mortality from CRC in several randomized controlled trials but the benefit resumes to left colon cancer. Thereby, colonoscopy has been lately preferred in screening programs rather than FS due to increased prevention results (14). By far, the most important drawbacks of the procedure are the potential for associated complications and the procedure's tolerance. The most frequent complications described include bleeding, bowel perforation, adverse events related to cleansing preparations as well complications of sedation. However, colonoscopy appears to be a safe procedure considering the low overall rate of serious complications (0.06%) reported by in some screening programs (15). Sedation can strongly influence the patient tolerance of the procedure, mild-to-moderate or deep sedation offering an increased comfort level compared with no sedation (16).

Colonoscopy, as the initial screening test, is offered mainly in countries where screening is opportunistic such as USA where colonoscopy is recommended to patients after 45-50 years through various healthcare providers (17). On the other hand, Poland has managed since 2012 to organize a national program in which all patients aged 55-64 are invited to a screening colonoscopy (18) and, besides the population low adherence to the program, a significant cancer prevention efficiency was demonstrated (19).

To our knowledge, besides few initiatives to retrospectively evaluate the outcomes of screening colonoscopies (20,21), no screening program for CRC has been organized or yet has published its results for the Romanian population (22).

As Ponderas Academic Hospital (PAH) recently focussed more on colorectal patients' care, becoming a high-volume centre on the related pathology (more than 4000 diagnostic and therapeutic colorectal procedures/year), further succeeding to be designated Centre of Excellence in Colorectal Surgery by Surgical Review Corporation (US) in 2017 (23), we have decided to initiate and run an opportunistic colorectal cancer screening program (CRC-SP).

The design of our CRC-SP was considering the limited compliance of healthy individuals to accept endoscopic or radiologic investigation, the procedure's cost, the test's efficiency as well, while aiming to include a large cohort of patients in the study. As a consequence, we have finally chosen the faecal immunochemical test (FIT).

A private institutional support group committed to this project, entitled PAH-FIT-CRC Screening Program, was set up in 2018. At its' launching, in 2019, the program covered the logistics and the free access of the patients to 3000 FITs and their evaluation, the access to free colonoscopy if positive testing, as well to colorectal surgery (24).

The main objective of the present study is to analyse the outcomes after running the first 1500 tests of the PAH-FIT-CRC Screening Program. We have also aimed to compare the efficiency of the FIT testing program with the screening colonoscopies performed in our Center, within the same time interval (2019).

### **Methodology**

We have retrospectively analysed all the patients included in the prospectively maintained data base of the PAH-FIT-CRC Screening Program, enrolling patients over 45 years old with no gastrointestinal symptoms and without a colonoscopy performed in the last 5 years. As for the present study, we have

included the first 1500 consecutive patients enrolled for FIT testing (Group A).

We have also retrospectively analysed all the consecutive patients who had screening colonoscopy between January 1<sup>st</sup>, 2019 and January 1<sup>st</sup>, 2020, in the Gastroenterology Department of Ponderas Academic Hospital. The same criteria were applied to enrol the patients (over 45 years with no gastrointestinal symptoms and without a colonoscopy performed in the past 5 years) and the information was introduced into a prospectively maintained database (MedPractice) (Group B).

The data was compared to evaluate the efficiency of the two CRC screening methods in our Center. The study was approved by the PAH institutional Review Board while all the patients have signed a specific informed consent.

### *FIT Testing*

FIT kits (SentiFIT<sup>®</sup>, Sentinel Diagnostic, Sentinel CH. SpA, Italy) were freely offered to the enrolled individuals (asymptomatic patients and visitors) within 6 months, following an active informative campaign on colorectal cancer prevention and the FIT testing methodology (24). Analysis has been performed on one sample of stool brought by the patient to the hospital in a dedicated envelope. When the test was negative patients received the recommendation to repeat the test in 2 years. If the test was positive, they were scheduled for colonoscopy. Participants with a non-assessable sample benefited from a new test. Individuals who did not return the test sample received reminder calls. Colonoscopy was the standard exam after a positive FIT test, while data from the examination and pathology reports were centralized into a prospectively maintained data base (MedPractice).

### *Colonoscopy*

Patients over 45 years with no gastrointestinal symptoms were referred to screening colonoscopy by general practitioners or specialists. CO<sub>2</sub> insufflation and intravenous sedation

(either midazolam or propofol sedation) were used in all the endoscopic investigations. Data from colonoscopy and pathology reports were centralized into a prospectively maintained data base (MedPractice).

### *Outcomes and Analyses*

Data has been collected and centralized to assess participation and positivity rates for FIT and colonoscopy groups. Furthermore, in the FIT group we evaluated the colonoscopy participation rate, positive predictive values (PPV) and detection rates. Likewise, positive predictive values and detection rates were also calculated in the colonoscopy group.

The FIT uptake rate (UR) has been defined as the number of individuals performing and returning the test divided by the number of tests offered minus the excluded population. The positivity rate (PR) means the number of participants with a positive test divided by the number of individuals with a valid test. Colonoscopy compliance rate (CCR) has been defined by the number of colonoscopies performed in FIT positive patients divided by the number of patients with a positive FIT.

Colorectal lesions described were polyps (adenomatous and hyperplastic) and CRC. Advanced adenomas were described to be larger than 10 mm, with high grade dysplasia or villous component on histology.

The detection rate represents the proportion of individuals with colorectal lesions seen on colonoscopy per 1000 screened persons. The polyp/adenoma detection rate (PDR/ADR) represents the number of patients with polyps/adenomas seen on colonoscopy divided by the number of screening colonoscopies performed. PPV was defined as the number of participants with colorectal lesions divided by the number of individuals who underwent colonoscopy. The false positive rate (FPR) was calculated as the number of patients with normal colonoscopies divided by the number of FIT positive patients. The resulting data were compared between the FIT and colonoscopy group.

## Statistical Analysis

The generated data was analysed with the Data Analysis ToolPak of Microsoft Office Excel® (Microsoft, Redmond, Washington, USA). The results from every parameter were defined as average and t-test was performed with statistical significance achieved at a p value of <0.05.

## Results

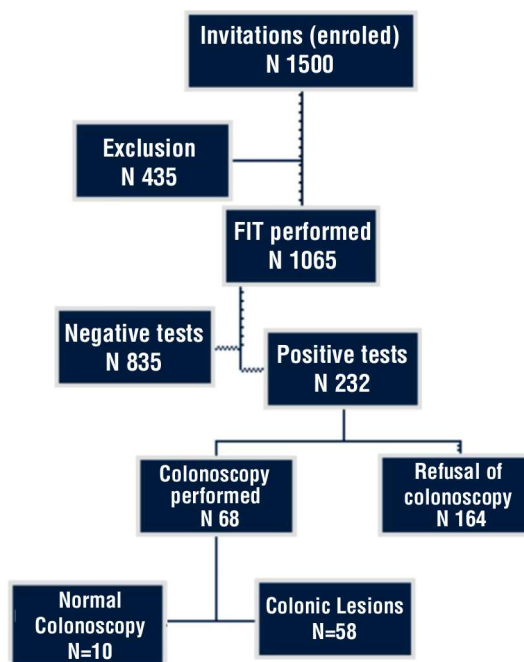
A total of 3024 patients were included in the present comparative study: 1524 screening colonoscopies performed in our endoscopy department between 01.01.2019 and 01.01.2020 compared with 1500 patients enrolled in the PAH-FIT-CRC Screening Program during the same period.

### Results in the FIT testing, followed by colonoscopy (Group A)

Out of the 1500 receivers of FIT, there were more female patients than male patients (61.4% vs. 38.6%). There were 435 participants excluded (either non-returned tests or not assessable tests) (Fig. 1). A total of 1065 tests were performed resulting in a FIT uptake rate of 71%. There were 232 positive and 833 negative tests with a positivity rate of 21.7%. The cut-off value for FIT test was 2.55 µg/g. The proportion of positive patients was slightly higher in females than in males (52.6% vs. 47.4%).

After a positive test, the patients were called to be informed of the result and to be scheduled for a colonoscopy. The colonoscopy compliance rate was 29.4% (68 out of 232 participants). The other 164 participants (70.6%) refused to perform a colonoscopy after a positive test. The CCR of females was higher than that of males (41.2% vs. 58.8%).

Despite of a positive test, 10 out of 68 patients had a normal colonoscopy (PPV 14%) and they were further referred to gastroscopy. The false positive rate (FPR) was 0,04%. A total of 58 lesions were found, including 23 adenomas (PPV 33.9%), 11



**Figure 1.** Flow chart of PAH FIT CRC screening programme (Group A)

advanced adenomas (PPV 16.2%) and 2 CRC (PPV 2.9%) (Table 1).

### Results in the screening colonoscopy (Group B)

Out of the 1524 screening colonoscopies none was excluded from the study and 594 pre-cancerous or cancerous lesions were revealed. Thus, the polyp detection rate (PDR) was 38.98%. A total of 256 adenomas were found, including 168 low risk adenomas and 92 advanced adenomas (adenoma detection rate of 17.06%). Furthermore, in histopathological reports 22 adenocarcinomas were described (1.44%) (Table 2).

Overall, for the 1592 colonoscopies, the rate of cecal intubation was 98% with no significant difference between the group A and Group B. No major complications were encountered during the colonoscopies, biopsies or polypectomies.

All the 24 patients identified with CRC underwent surgery in our Center (18 pts, 75%) or in other medical institutions.

**Table 1.** Detection rates and PPV values for FIT patients (Group A)

| Type of lesions  | Number | PPV  | Detection rate |
|--|--------|------|----------------|
| Hyperplastic polyps  | 4      | 5.9  |                |
| Low risk adenomas  | 23     | 33.9 | ADR 21.5%      |
| Advanced adenomas  | 11     | 16.2 | AADR 10.3%     |
| CRC  | 2      | 2.9  | CRC 1.8%       |
| IBD  | 1      | 1.4  |                |
| Other lesions (including haemorrhoids, diverticula, angioma) | 17     | 25   |                |
| Normal colonoscopy   | 10     | 14.7 |                |
| Total  | 68     | 100  |                |

ADR/PDR: adenoma/polyp detection rate

PPV: positive predictive value; IBD: inflammatory bowel disease; CRC: colorectal cancer.

The detection rate was defined as the proportion of individuals with colorectal lesions seen on colonoscopy per 1000 screened persons with a valid FIT (1065 in our study), whilst PPV was defined the number of participants with colorectal lesions divided by the number of individuals who performed colonoscopy

**Table 2.** Detections rates and PPV values for screening colonoscopy patients (Group B)

| Type of lesions  | Number   | PPV        | Detection rate          |
|--|----------|------------|-------------------------|
| Hyperplastic polyps  | 109      | 7,1        |                         |
| Low risk adenomas  | 168      | 11         | ADR 17.06%              |
| Advanced adenomas  | 92       | 6          | AADR 6.04%              |
| CRC  | 22       | 1.4        | CRC detection rate 1.4% |
| Other lesions (including inflammatory polyps, anal canal squamous papilloma, leiomyoma, juvenile polyps) | 10       | 0.6        |                         |
| Polyps with no pathology report  | 193      | 12.6       |                         |
| Total  | 594/1524 | PDR 38.98% |                         |

ADR/PDR: adenoma/polyp detection rate

PPV: the number of participants with colorectal lesions divided by the number of individuals who performed colonoscopy

The polyp/adenoma detection rate: the number of patients with polyps/adenomas seen on colonoscopy divided by the number of screening colonoscopies performed

## Discussion

The uptake rate (UR) in the FIT group was 71%, higher than the expected 45% defined by recent guidelines. Distributing tests inside the hospital without having to visit the GP might have biased the results, as some of the patients may be, most probably, already symptomatic. On other hand, being a single-centre cohort, the entire process was easier to organize and monitor. Surprisingly, colonoscopy compliance rate in our FIT cohort was very low (29.4%) in comparison with other screening programs, for e.g. the ones developed in France (70.5%) (25) or Netherlands (74.3%) (26). This fact might be due to the lack of confidence in an invasive procedure such as colonoscopy or the patient desire to choose

another center in order to perform this procedure.

In our FIT group (Group A) a higher UR was seen in females as compared to males which is in line with data obtained in other screening programs, for e.g. in Scotland (27) or United Kingdom (28). Although the male gender is considered a risk factor of CRC, our study revealed a higher participation rate in women than in men. Furthermore, females agreed to perform colonoscopy in higher numbers as compared to males. This results highlight the urgent need of raising up the UR and CCR of males. A telephone consultation with a health care professional has been suggested to be a valid counter-measure in order to increase UR and CCR in males (29), we have actively applied it, but it seems not to

work enough for our study.

The marketing campaign promoting the PAH FIT CRC Screening Program was included extended information on the method's need and efficiency and about the safety and the condition of the free-of-charge evaluation colonoscopy [www.treabamea.ro]. All the authors were involved in an adequate communication to the population, via accessed media (24). However, the compliance remained below 30%.

The positivity rate (PR) in our study was 21.7%, higher than in Netherlands (12,2%) due to the low cut-off value for FIT test of 2.55  $\mu\text{g/g}$  compared with 15  $\mu\text{g/g}$ . PPV values for advanced adenoma (16%) and CRC (2.9%) were comparable with data from Czech Republic (AA PPV 16.8%, CRC PPV 4.5%) or Ireland (AA PPV 5%, CRC PPV 4%) (26).

During colonoscopy, the entire colon is examined with the objective not only to detect CRC but also to identify and remove adenomatous polyps. Polypectomy was shown to have a protective effect on a long-term follow-up. Thus, CRC incidence decreased by 80% after a follow up of 10 years among colonoscopies with polypectomy (adenoma more than 5 mm) (30).

The introduction of countrywide CRC screening programs led to identification of several quality indicators for colonoscopy. The European Society of Gastrointestinal Endoscopy (ESGE) has introduced measures of quality in order to combat variation in performance among examiners. Thus several studies have shown that measures such as adequate bowel preparation, cecal intubation rate, polyp detection rate (PDR), adenoma detection rate (ADR), withdrawal time or complication rate represent major impact factors that influence clinical outcomes (31) Therefore a post-colonoscopy CRC (PCCRC) diagnosed within 3 years after a negative colonoscopy, is suggesting that a premalignant lesion or a cancer might have been missed represents an unwanted event related to non-compliance or poor compliance with quality standards (32,33). Taking into consideration that endoscopists

with higher PCCRC rates have lower ADR, in England for example, only screening-accredited colonoscopists with high key performance indicators (ADR being the most valuable) are enrolled in national screening program (34).

In the screening colonoscopy group (Group B), the values of ADR and PDR were slightly lower than those suggested by the European guidelines (31). Hence, a frequent strategy of resect and discard for low-risk diminutive left-sided colon polyps, correlated with a large number of polyps with no pathology report seen in our analysis and may thus explains the lower ADR (35). Consequently, improving quality indicators in colonoscopy should be a goal for the near future.

Comparing the outcomes of the two groups, A and B, ADR in colonoscopies for FIT positive was much higher (48.5%) than ADR in screening colonoscopies (17.06%). Our data are in line with the results from other international multicentre cohort studies and support the premise that higher ADR target for colonoscopies should represent a standard quality indicator (36). Nevertheless, the absolute numbers of patients with adenomatous polyps and CRC were much higher in the colonoscopy arm as compared with the FIT arm, indicating a possible selection bias and inclusion of possible symptomatic patients in the screening colonoscopy group.

Our study indicated potential advantages and disadvantages for the usage of FIT testing versus screening colonoscopy, both used to establish opportunistic CRC screening programs. Moreover, hybrid programs combining sequentially the two modalities of screening to individual patients might enhance the compliance to any modality of screening. We thus included 3024 consecutive asymptomatic patients over 45 years old, examined over a period of one-year (2019) in a tertiary referral centre, as the first pilot study on opportunistic CRC screening in Romania, which is been continued with the inclusion of a similar number of patients in 2020. This led to the depiction of a significant number of patients with advanced adenomas, as well as CRC.



Further prospective studies with randomisation of patients between the two modalities should be further pursued.

## Conclusion

PAH FIT CRC Screening Program, as the first opportunistic colorectal cancer screening pilot programme based on FIT run in Romania proved its efficiency. However, it still needs an improvement in UR and CCR, especially in men. Although colonoscopy screening looks more appropriate, this is hampered by the adherence of the target population and the availability of endoscopy services in a particular setting (37). Furthermore, quality indicators for screening colonoscopies or colonoscopies in FIT positive patients should be improved prior to the launch of organized population-based screening programs, mainly through leadership training, aiming to decrease interval CRC.

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## Conflict of Interest

The authors declare no conflict of interest.

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