

Research Article

Conflict of Clinical and Public Health Viewpoint in Colorectal Screening

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Summary

Mortality rates from colorectal cancer are dramatically high, therefore the reduction by population screening as a public health measure is considered as one of the priorities of national public health programmes worldwide. In Hungary, in the beginning a human-specific immunological test was applied in “model programmes” as a screening tool, to detect the occult blood in the stool; compliance was 32% on average. However, the objectives of the model programmes have not been achieved, because – among other reasons – debates on method of choice and the strategy to follow have divided the professional public opinion. In this paper, the debated issues are critically discussed, being convinced that – at present – population screening seems to be the most promising way to alleviate the burden of colorectal cancer.

Keywords: colorectal cancer, gFOBT, iFOBT, flexible sigmoidoscopy, colonoscopy

Colorectal cancer is a major health problem worldwide. It represents almost 10% of the global cancer incidence burden in 2012. It is the third most common cancer in men (an estimated 746 000 cases), the second most common in women (614 000 cases), and the fourth most common cause of death from cancer worldwide, with an estimated 694 000 deaths. Incidence varies 10-fold between countries worldwide. In the industrially developed countries, colorectal cancer is the second most common cancer and – behind lung cancer – the most common cause of cancer death in both sexes. More than 65% of new cases occurred in countries with high or very high levels of human development (HDI). Almost half of the estimated new cases occurred in Europe and the Americas [1]. The highest incidence rates are in men in central Europe: Slovakia, Hungary, and the Czech Republic [2]. The global burden of colorectal cancer is expected to increase by 60% to more than 2.2 million new cases and 1.1 million deaths by 2030 [3].

The majority of well operable tumours are discovered in an advanced, inoperable stage, the consequence of which is high disease specific mortality. Early detection and early treatment of this type of cancer would most likely alleviate the health burden caused by colorectal cancer. It is widely agreed that the reduction of mortality is indispensable and the most promising way for this is the organized screening of asymptomatic persons.

The Health Ministers of the European Union unanimously adopted a set of recommendations on cancer screening on 2 December 2003 [4]. The recommendation spelled out the fundamental principles of the best practices in cancer screening, and encouraged the Member States to take common action to implement cancer screening programmes, particularly, for colorectal cancer using faecal occult blood test as screening tool. The importance of colorectal screening is emphasized by the “Brussels Declaration” that was signed by the representatives of a number of scientific societies, cancer leagues, patient organizations, foundations, health insurance companies, and several members of the European Parliament. The Declaration urged the European Council to prepare a plan of action to alleviate the burden of colorectal cancer on the societies (“Europe against Colorectal Cancer”), and to support by all means the governments of the Member Countries to establish call-and-recall based, organized screening programmes for colorectal cancer [5]. Similarly, the urgency of the implementation of colorectal screening was emphasized by the “Budapest Declaration” by the European Association of Gastroenterologists [6]. In 2011, the European Commission – in collaboration with the International Agency for Research on Cancer (WHO/IARC) – published a detailed guideline on quality assurance in colorectal screening [7].

In Hungary, the National Public Health Programme set up in 2002, like numerous other countries, proposed the reduction of mortality from colorectal cancer in up to 20% in 8-10 years’ time by the implementation of organized screening programmes for early detection of the disease and its premalignant lesions using human-specific faecal occult blood tests [8]. However, in 2008, an investigation by the National Audit Office on the utilization of public money spent for organized colorectal screening had stated that “the goals set were not met” [9]. One of the reasons for the failure was a sharp debate, and divided the professional public on the strategy and screening methods of colorectal screening. The debated issues were: whether the “two-step strategy” in which the faecal occult blood test is the “first step”, and in case of non-negative blood test colonoscopy should follow, or, the “one step” strategy: colonoscopy alone is the method of choice.

This paper intends to explore this debate in depth, and to arrive at a clear recommendation: which of the two “strategies” is to be implemented in organized population screening.

Pathway to malignancy (natural history)

Due to its biological and pathological characteristics, colorectal cancer is particularly suitable for screening, as benign adenomatous polyps, or inflammatory bowel diseases regularly precede the development of colorectal cancer. The prevalence of colorectal polyps widely varies. Among asymptomatic, average-risk population, the prevalence of adenoma of colon and rectum is approximately 5-10%. In a study offering total colonoscopy screening to individuals without any lower gastrointestinal symptoms, the prevalence of colorectal polyps, including potentially premalignant lesions in asymptomatic persons aged 40-59 years, was somewhat higher (12-16%) [10]. A meta-analysis resulted in much higher prevalence for non-advanced and advanced adenoma (30% or above) [11]. In first-degree relatives of those having family occurrence of adenomas, the prevalence of adenoma is four-times higher as compared to the average-risk population [12].

The aetiology of colorectal cancer involves the complex interaction of environmental carcinogen exposure and genetic factors in the population. Indeed, most colorectal cancer cases are *sporadic*, occurring in individuals without any known familial predisposition. Approximately 10–30% of cases have a positive family history of this neoplasm [13].

Transformation of normal colorectal epithelium to an adenoma and ultimately to an invasive and metastatic tumour has been well known for a long time as “*adenoma-carcinoma sequence*” [14]. Today, the genetic alterations taking place during the malignant transformation are also described in detail [15]. The correlation is supported by the observation that following the colonoscopic removal of adenomatous polyps the incidence of colorectal cancer decreases [16]. There is a correlation between the size of the polyp and the likelihood of malignant transformation. [17].

Screening methods

In 1968, the WHO drew up the criteria of a population screening; they are valid up to the present day. (18) The most important criteria are the following:

- the target disease should be of public health importance;
- the natural history of the target disease is known, and it has a rather long preclinical detectable phase (PCDP);
- the detected target disease should have an established treatment, and the referral routes should be well determined;
- The screening tool should be cost-effective.

The expectations from screening methods suitable for early detection of asymptomatic polyps and colorectal cancers are: that they should be inexpensive, simple to perform and reliable. Furthermore, the methods should be sensitive, specific, and have appropriate predictive values. Further expectations are that the screening method should be harmless, it should not cause any complication, and only acceptable burden and discomfort for the persons under investigation. The provider should do his/her best to optimise the social acceptance of the offered screening (“compliance”). It is an advantage if the

method is not invasive. In order to ease the avoidable psychological side effects, the quick disclosure of test results is desirable.

Methods of colorectal screening

The primary aim of colorectal screening is the detection, removal and early treatment of adenomatous polyps of 10 mm in diameter which develops in average risk persons, and are considered as premalignant lesion of colorectal cancer (removal of a premalignant polyp may be seen as primary prevention of colorectal cancer), and those of non-invasive colorectal cancers. A secondary aim is to detect and treat the sources of bleeding in bowels.

Although the methodological arsenal of colorectal seems to be plentiful, the fact is that to this very day we do not have such a screening method which would satisfy all the needs, because either its sensitivity and specificity are limited, or it is potentially harmful, or social acceptance is far from being optimal [19- 21]. Currently, many tools are used for colorectal screening and can be grouped into two categories: [a]. tests that primarily detect colorectal cancer, which include tests that look for blood, such as guaiac faecal occult blood test and faecal immunochemical test, and a couple of other markers in stools; and [b]. tests that can detect cancer and advanced lesions, which include endoscopic and radiological exams, i.e., colonoscopy, doublecontrast barium enema (DCBE), and computed tomography colonography (CTC) (or virtual colonoscopy) [6]. However, these tests all have certain limitations.

Detection of occult blood from the stool

The methods are based on the assumption that the premalignant adenomatous polyps of large bowels and the early colorectal cancer are intermittently bleeding, one or the other component of the blood, as a marker, are detectable in the occult, invisible to the naked eye [22]. As the bleeding is discontinuous, in order to improve the chances, samples should be taken from more than one consecutive bowel movement. Faecal occult blood testing is what is known as a *qualitative test*. It only detects the presence or absence of blood in the sample, but does not indicate the site and quantity of bleeding. The non-negative test (positive FOBT) could indicate colorectal cancer, but not diagnose it. If blood is detected, additional testing by colonoscopy would be required. At present, guaiac-based chemical and immunochemical methods are used for colorectal screening.

A number of screening methods can be used including stool based tests every 3 years, sigmoidoscopy every 5 years and colonoscopy every 10 years.

Guaiac Faecal Occult Blood Test (gFOBT)

In fact, this is a chemical reaction to detect the haemoglobin component of the blood in the stool: hem-component of haemoglobin has a peroxidase-like activity, therefore when the hydrogen peroxide is dripped onto the guaiac paper, in the presence of blood, yields a blue reaction product within seconds.

(These tests are collectively known as “haemoccult test”.) The reaction is not specific for human haemoglobin; therefore, to avoid

false positive reaction, dietary restrictions are necessarily (e.g. red meals, some vegetables, some pharmaceuticals). Recent position is that because patient adherence can be an issue with FOBTs, and dietary restrictions can affect adherence in some populations, it is reasonable to abandon these recommendations without fear of substantially affecting specificity [23]. The American College of Gastroenterology has recommended abandoning gFOBt testing as a colorectal cancer screening tool, in favour of the faecal immunochemical test (FIT), [24].

Immunochemical Faecal Occult Blood Test (iFOBt, FIT)

This is a newer and more sensitive test than the guaiac-based FOBT. The immunochemical test detects the *globin* component of haemoglobin rather than the *heme* component: antigen-antibody reaction takes place against the globin component of human haemoglobin. The immunological reaction is specific for human haemoglobin, therefore, it does not require dietary restrictions before collecting the sample [25]. The test itself requires less effort because it involves simply brushing the surface of the stool in the toilet water and dabbing the brush on a test card. The test result can be read in an automated device; the investigator can choose the antibody concentration (“cut-off point”), over which the test is considered positive. In Japan, the iFOBt test has been used for population screening since 1992 [26].

For average-risk adults older than 50 years of age, evidence from multiple well-conducted randomized trials supported the effectiveness of faecal occult blood testing in reducing colorectal cancer incidence and mortality rates compared with no screening. Data from well-conducted case-control studies supported the effectiveness of sigmoidoscopy and possibly colonoscopy in reducing colon cancer incidence and mortality rates. A non-randomized, controlled trial examining colorectal cancer mortality rates and randomized trials examining diagnostic yield supported the use of faecal occult blood testing plus sigmoidoscopy. Data is insufficient to support a definitive determination of the most effective screening strategy.

Screening by endoscopy

By the endoscopic methods, the lumen of entire colon and rectum can be rendered visible to the eye, so the target condition of screening can be scrutinised.

Flexible sigmoidoscopy is an exam used to evaluate the rectum and most of the sigmoid colon, i.e. about 60 cm of the large intestine. It does not allow one to see the entire colon. As a result, any cancers or polyps farther into the colon cannot be detected with flexible sigmoidoscopy alone. If necessary, tissue samples (biopsies) can be taken through the scope during a flexible sigmoidoscopy exam. In the case of a positive test result, colonoscopy must be performed.

A longer version of a sigmoidoscopy is *colonoscopy*, by which the entire length of the colon and rectum can be brought into the field of view. It makes it possible to take samples for histology (biopsy) or to remove any suspicious-looking areas, if needed. It requires sedation. Several factors affect the outcome of a successful colonoscopy, including cecal intubation, careful mucosal inspection, and

withdrawal time [27]. Colonoscopy is a time-consuming, technically challenging procedure, its effectiveness in diagnosing and removing polyps depends on the technical aspects of the procedure. The other requirements of “quality colonoscopy” are described by Hungarian authors [28]. However, colonoscopy has several limitations that relate to the mechanics of the procedure, such as perforation, bleeding, or adverse consequences of sedation. Perhaps this is why the patients’ perceptions regarding colonoscopy frequently drives patients non-adherence recommended testing, both screening and diagnostic.

Virtual colonoscopy or CT colonography is a medical imaging procedure which uses x-rays and computers to produce two- and three-dimensional images of the large intestine from the lowest part, the rectum, all the way to the lower end of the small intestine and display them on a screen [29, 30].

Other screening approaches

There are few other tests that are not yet routinely used for screening purposes. It would seem reasonable to make immunological tests more sensitive by using a second marker, such as transfer rindipstick test [31], lactoferrin [32], α -1-antitrypsin [33]. At present, most evidence a poor disposal is for *albumin* as a second marker [34]. (In Hungary, this bi-specific immunochemical method had been tested in model programmes. The compliance was 32%. The yield of the test were encouraging, however, because of the lack of automation and that of European marketing authorisation subject experts considered the test as being in the experimental stage, and suggested omission of its use in population screening) [35]. The detection of cancer-associated biomarkers is not yet applied in population screening programmes.

There are a few molecular-biological methods, most of them in experimental phase, that can be seen as the methods of future, for example faecal DNA testing [36, 37, 38]. However, the detection of cancer-associated biomarkers is not yet applied in population screening programmes.

Effectiveness, sensitivity, specificity

Colorectal cancer screening reduces death from colorectal cancer and can decrease the incidence of disease through the removal of adenomatous polyps. Several available screening options seem to be effective, but the single best screening approach cannot be determined because of insufficient data [39].

The sensitivity of faecal occult-blood testing for colorectal cancer and especially for colorectal adenomas is low because neoplasms may bleed intermittently, and thus cannot be detected in this way. Comparison between guaiac and immunochemical FOBT in screening for colorectal cancer provides evidence that iFOBt is superior to gFOBt [40]. The high quality evidences for non-invasive screening exist for guaiac-based faecal occult blood tests (gFOBts), for which the disease-specific incidence and mortality reductions are modest.

The guaiac-based chemical detection of faecal occult blood is the only non-invasive screening method with proven effectiveness: annual or biannual screening reduces mortality by 15-33% through randomised controlled trials [41- 44]. On the other hand, in the only randomised controlled test, Chinese authors found that

immunological haemagglutination test (iFOB) was effective in reducing mortality from rectal cancer but not in reducing mortality from colon cancer or the incidence of colorectal cancer [45]. In case-control studies, 21-81% mortality reduction was published [46, 47]. Faecal immunochemical tests (FITs) offer better sensitivity and comparable specificity [48]. In addition, the participation and detection rates for advanced adenomas and cancer were significantly higher for immunological, as compared to guaiac-based FOBT, which significantly underestimates the prevalence of advanced adenomas and cancer in the screening population compared with iFOB [49].

Flexible sigmoidoscopy is a valid screening tool for the early detection of colorectal cancer. Recently published long-term data from UK Flexible Sigmoidoscopy Screening randomised controlled trial (UKFSST) demonstrate a 33% reduction in colorectal cancer incidence and a 43% decrease in colorectal cancer mortality with once-in-a-lifetime screening, and reported long term effects of only-once sigmoidoscopy screening after 17 years of follow-ups [50]. It is a resource-conserving strategy. Long-term follow-up of participants in the trial will be required [51]. Faecal occult blood test and flexible sigmoidoscopy have been proven to reduce colorectal cancer mortality by approximately 30%. [52]. Patients with a positive screen will be referred for colonoscopy with once-in-a-lifetime screening. [53].

Although colonoscopy screening is used in some countries, no randomized trials have been conducted to estimate its benefit. The standard (optical) Colonoscopy has the potential to be superior to FOBT and flexible sigmoidoscopy, but needs to be evaluated in randomized trials before any recommendation can be provided; such investigations are under way in several countries. The available data is of limited value. In observational studies, the incidence colorectal cancer was reduced by 76-90% in those screened, as compared to the reference population [54]. Colonoscopy may find more cancers in the proximal part of the colon but is associated with greater cost and more complications. The availability of a simple, non-invasive test that detects tumour-specific products with reasonable sensitivity and specificity might overcome barriers to screening among patients who are not willing to undergo more sensitive but more invasive tests, such as colonoscopy.

Despite technical advances in computed tomographic (“virtual”) colonoscopy, there is a lack of consensus about its role in screening. The low sensitivity of the faecal DNA panel for detecting clinically significant neoplasia might limit its value as a one-time test for cancer, since it misses most lesions identified on colonoscopy. However, the use of a less sensitive test at frequent intervals (e.g. biannually) may be as effective for the detection of colorectal anomalies as a more sensitive test that is used infrequently, such as colonoscopy.

Compliance with the screening programmes

The public acceptance of the offered screening is perhaps the most important prerequisite of the effectiveness and cost-effectiveness of colorectal screening. The tolerance of the target population should be kept in mind: the average-risk, asymptomatic, healthy or apparently healthy men and women between 50 and 70 years of age is much lower as compared to those who turn to a doctor because of their complaints. In the case of occult blood tests, the compliance of those participating

in clinical trials is relatively higher (54-67%) as in case of population screening (30-50%) [41- 44]. In observational studies the great majority of subjects (97%) refused total colonoscopy but accepted a non-invasive blood test (83%), because it was a more convenient and less time-consuming procedure. [55]. Asymptomatic persons are reluctant to accept an invasive method, such as sigmoidoscopy and colonoscopy; colonoscopy is considered particularly unpleasant [55, 56]. Because of fear of pain and anesthesia, fewer people undergo colonoscopy even where they are strongly recommended (3-10%) [57]. It is fair to say that *it is the compliance of the offered screening modality strategy that decides the applicability of a screening tool as a public health measure in favour of the “two-step” strategy.*

Discussion

Current guidelines in the European Union include recommendations for stool-based tests - faecal occult blood test (FOBT) and faecal immunochemical test (FIT) - and flexible sigmoidoscopy, whereas most US guidelines include those tests as well as colonoscopy [58].

In the United States, *clinically-oriented* scientific societies, such as the American College of Gastroenterology, the American Cancer Society, the American College of Radiology, the US Multi-Society Task Force on Colorectal Cancer, all take a stand on the screening practice, and the US Preventive Services Task Force develop consensus guidelines and recommend the strategy to follow, which is basically a “one step” strategy. Although colonoscopy is superior to other tests in some respects, the US Preventive Services Task Force has determined that no single test or strategy for colorectal-cancer screening can be endorsed on the basis of currently available data. Several approaches (faecal occult-blood testing, sigmoidoscopy, colonoscopy, and barium enema examination) are included as options in the screening guidelines. [59]. Therefore, all recommended tests are acceptable options and may be chosen based on individual risk, personal preferences, and access. The prevention of colorectal cancer should be the primary goal of screening, which is opportunistic in nature.

The “two step” strategy is characteristic to the European practice of colorectal screening, where the screening strategy is of *public health orientation*. The guidelines are set by authoritative professional organizations, such as the International Agency for Research of World Health Organisation (IARC/WHO), and International Union against Cancer (UICC), and, the provider initiated, personal invitation-based “mass” or population screening is the recommended practice. The guidelines issued by the European Commission argue for the “two steps” strategy: as a first step, the detection of the occult blood in the stool with a suitable screening method (gFOBt, FIT) should take place and, as a second step, patients with a positive screen would be referred for colonoscopy in order to clarify whether the likely target disease can be justified or not [60].

In 2017, all the countries of the European Union – with a few exceptions – have a colorectal cancer screening policy mandated by a law, or at least, a governmental recommendation. The programme is public funded, a test provided free of charge in all but a few countries [61]. Out of the 28 member states, 20 members have piloting, or rollout

complete for population-based colorectal screening programmes; in addition, three member states were planning to start population-based programmes in 2016. In most of the countries, the screening activity covers the entire country; in a few, they are being limited to one or more regions. The widest recommended target age, of 50 to 74 years, has been adopted by most countries. In most of the countries g/FOBT/FIT is used as a screening test.

Colposcopy is offered once in a lifetime in one country (Poland), as is the case for flexible sigmoidoscopy in two countries (Italy and United Kingdom).

The practicability of screening strategies are being scrutinised by other international organisations such as the International Colorectal Research Screening Network (ICRSN); [62]. they confirm that for colorectal screening as a public health measure, the generally accepted screening strategy is the “two-step” strategy, based on the detection of occult blood in the stool (gFOBT/iFIT). The “one step” strategy of colorectal screening for country-wide population screening has not been used. (The only exception is Poland, where those who opportunistically turn up in one of the approximately 40 endoscopy centres would undergo colonoscopy) [63].

In Hungary, according to the current protocol, the pilot programmes for colorectal screening are conducted under “two-step” strategy. The Public Health Authority has decided to use the detection of occult blood as screening tool because - although it is of limited sensitivity and specificity as compared to the endoscopic methods - and relatively frequent repetition is needed - it is a non-invasive method, therefore the public acceptance of the offered screening (“compliance”) is much better, rendering it more suitable for organised population screening.

In the meantime, the Society of Surgery and that of Gastroenterology has taken a firm stand in favour of the one-step strategy of colorectal screening, and suggested that a national screening program using sole colonoscopy as the method of screening be introduced (64). They argued with the heavy burden of colorectal cancer on the Society, the expected benefit of a screening programme. They stressed that the primary aim of colorectal screening is the detection and removal of the adenomatous polyps, by which colorectal cancer is preventable, and the mortality from the disease can be reduced by 20-30 %. Furthermore, “colonoscopy as the sole screening method is more promising than anything else”, because at the same time the polyps can be removed so the colonoscopy is also a therapeutic intervention. They argue for the “one-step” strategy, saying that the “once in a lifetime” colonoscopy seems to be a suitable method for a nation-wide colorectal screening programme. In conclusion, they think that “the reconsideration of strategy is fully justified.”

Beyond any doubt, total *colonoscopy* is the “golden standard” of colorectal screening: even when using the “two-step” strategy, each case of non-negative test result needs to undergo colonoscopy in order to verify the positive result of occult blood test. Total colonoscopy is the only detection method that can verify or rule-out the suspect or malignant target disease and, in this way, it can significantly contribute to the mortality reduction from colorectal cancer. Accordingly, the validation of the “two-step” strategy is also attributable to colonoscopy.

Nevertheless, colonoscopy, as such, is a complex diagnostic method and by no means a screening method to be used for public health purposes, i.e. population screening.

Colonoscopy makes compulsory the intensive examination of the physical status of the “patient” to be “screened”, and the determination of laboratory and blood coagulation parameters. It makes necessary the clean-up of the large bowel, sedation, sometimes anaesthesia. Colonoscopy requires proficiency, therefore between 1000-2000 examinations need to be performed each year; in some countries, it is subject to proficiency examination or accreditation. The examination itself is time-consuming; just the withdrawal time itself must not be shorter than 6 minutes. According to estimates, complications (bleeding, perforation) might occur in 1: 1000 cases, therefore post-intervention observation and sometimes hospitalisation is necessary. [65].

In Hungary, the clash of the two kinds of strategy has intensified over time: there is *an obvious conflict between the clinical and public health positions*. The clinical viewpoint supported by the clinical community seems to discredit the public health viewpoint. In order to find a new focus on the topic, a *consensus conference* had been convened with broad participation of all those concerned. The Conference has discussed all the contested issues, and made the following recommendations:

- The burden and the public health importance of colorectal cancer, and the suitability of screening for it, is urgent for the continuation of colorectal screening. The cost of delay or discontinuation of the programme would mean a great deal of salvable life years.
- According to the evidence-based health policy and evidence-based public health, the recommended methods of population screening, i.e. that of average-risk men and women between 50-70 years of age: the immunochemical detection of faecal occult blood (iFOBT or FIT), the effectiveness of which is scientifically justified. In the case of non-negative (positive) test results, the total colonoscopy needs to be performed at the source of bleeding in the bowel.
- In the personal invitation letter the attention of the invitee might be drawn to total colonoscopy as possible method of choice, stressing all the advantages and as well as the discomfort of it.

Furthermore, the Conference voiced the importance of the stimulation and motivation of the target population in the acceptance of the offered screening, while pointing out that the high compliance rate is the prerequisite of both effectiveness and cost-effectiveness in screening. Finally, the incorporation of endoscopy into the system of population screening, technical preconditions, and the required proficiency of providing total colonoscopy were stressed. Scarcity of colonoscopy capacity is a frequent problem. [66].

In conclusion, the implementation of colorectal screening as a public health measure had been delayed by a heated debate between proponents of the “one-step” vs “two-step” strategy. Clinical experts argued in favour of colonoscopy only to be used as the sole screening method of asymptomatic persons, saying that it is more sensitive

and specific, as compared to the occult blood tests, and able to remove adenomatous polyps, if necessary and as such, it is a primary preventive measure at the same time. On the other hand, those who represented the viewpoints of public health, argued that for population screening, the detection of faecal occult blood is the method of choice, as it is more simple, cheaper, and more accepted by the public at large; furthermore, if necessary, in the second step, as a verification test, it can be followed by colonoscopy.

Beyond any doubt, total colonoscopy is the “golden standard” of colorectal screening. However, it is a resource-demanding, time consuming intervention that requires special proficiency from the provider. Possible complications might occur; therefore it may not go beyond the medical practice. In addition, because of the discomfort it causes to the screened persons, the public acceptance of it is far from optimal; unacceptably low compliance is the main reason why colonoscopy does not get a place on the public health agenda.

According to the “state-of-the-art”, detection of faecal occult blood is the sovereign method of any organised colorectal screening programme on a public health scale, as being recommended by the European Council, in full agreement with the authentic professional organizations, such as the International Agency for Research on Cancer [4, 7].

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