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# COLON CANCER SCREENING AND PREVENTION

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**Abstract:**

***Introduction:*** *Colorectal cancer (CRC) is considered one of the most common cancers around the world, it is the second most common in women, and the third in men worldwide[1].CRC constitutes for about 10% of all cancers around the world with about 1.36 million people affected around the world, accounting for nearly 10% of cancers[2]. It is the second leading cause of mortality due to cancer both in the United States and worldwide [3]. CRC have a significantly slow rate of progression. Due to this slow progression and the relatively easy detection of the precancerous lesions, early detection of CRC is associated with a significantly better prognosis, and a better chances of reducing the burden and difficulties of the disease.*

***Aim of work:*** *In this review, we will discuss the most recent evidence in colon cancer screening and prevention.*

***Methodology:*** *We did a systematic search about colon cancer screening and prevention using PubMed search engine (http://www.ncbi.nlm.nih.gov/) and Google Scholar search engine (https://scholar.google.com). All relevant studies were retrieved and discussed. We only included full articles.*

***Conclusions:*** *Currently many various options exist for CRC screening. A quick review can reveal the great difference between screening programs all over the world. Additionally, another point that should be kept in mind is that most screening tests are still done opportunistically and without any plan or program, especially in low income countries. CRC screening programs must be optimized in order to achieve the target of reducing incidence of the CRC and eventually reduce its mortality. Another important point is that a higher and wider participation rates and adherence to the programs must be achieved in different screening programs by seeking correction of all the confounding factors. We recommend for future studies to focus focus on the characterization of the different complete screening programs, starting from the invitation to participate in the programs to the colonoscopy of the high risk groups and patient with positive other test results.*

**Key words:** *colon cancer, prevention, screening, colonoscopy.*

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## INTRODUCTION:

Colorectal cancer (CRC) is considered one of the most common cancers around the world; it is the second most common in women, and the third in men worldwide [1]. CRC constitutes for about 10% of all cancers around the world with about 1.36 million people affected around the world, accounting for nearly 10% of cancers [2]. It is the second leading cause of mortality due to cancer both in the United States and worldwide [3]. CRC have a significantly slow rate of progression. Due to this slow progression and the relatively easy detection of the precancerous lesions, early detection of CRC is associated with a significantly better prognosis, and better chances of reducing the burden and difficulties of the disease. While screening programs has been reported to be associated with a lower risk of mortality associated with CRC, the effectiveness of this early detection test is jeopardized by the many factors and affecting the test performance, like the poor compliance of the patients and the inaccessibility of the screening programs. Consequently, these factors are leading to a wide variation in the incidence and mortality of CRC globally[4]. Recently, many blood screening tests have been approved in order to overcome the above mentioned factors, this may lead to increase the participation in the screening programs and improve the compliance rates among the patients. In this article will discuss many tests used for the screening of CRC, particularly the new blood based test. Moreover, we will discuss the different scores used to assess the risk of CRC, the participation, compliance, and adherence to the screening programs, as well as the issue of total cost and coast effectiveness of the screening programs. Furthermore, we will propose a screening algorithm with the potentiality to attain attain higher rates of participation and adherence to the screening programs, especially in the countries with lower income.

In this paper, we will review the most recent evidence in colon cancer screening and prevention.

## METHODOLOGY:

We did a systematic search about colon cancer screening and prevention using PubMed search engine (http://www.ncbi.nlm.nih.gov/) and Google Scholar search engine (https://scholar.google.com). All relevant studies were retrieved and discussed. We only included full articles.

The terms used in the search were: colon cancer, screening methods, prevention, colonoscopy, and screening programs.

### Screening Tests:

In order for a test to be considered a good screening test, it should be highly sensitive and specific, cheap, available, convenient, safe, and efficient. The screening tests currently used for CRC screening are divided into two categories: non-invasive tests and invasive tests. The non-invasive tests include tests based on stool and blood analysis, in addition to the radiological tests. The currently available stool-based tests are the fecal immunochemical test (FIT), guaiac-based fecal occult blood test (gFOBT), and the newer fecal DNA testing. Stool-based tests are based on the concept of detecting traces of blood or shredded cell debris by vascularized polyps, adenomas and cancers [5]. The radiologic examinations include testing the patients with double contrast barium enema, capsule endoscopy and Computed tomographic colonography (CTC). The role of radiological tests revolves around the visualization and identification of the caner and the presence of any advanced polyps in the colon. Along to the possibility of detection of extra-colonic findings (by CTC). Recently, a new blood test has been used; (Epi procolon®) is consider to be a diagnostic qualitative test of chain reaction polymerase used in vitro (PCR). It is based on the concept of detection of mutated methylated septin9 DNA in EDTA plasma of the blood specimens acquired from patient. The Methylated SEPT9 has been strongly linked to the occurrence of CRC [7]. Invasive tests include flexible sigmoidoscopy (FS) and colonoscopy. The main role of this test is the direct detection and visualization colonic polyps or advanced neoplasias. Added to the advantage of getting a pathology specimen of the detected lesions. Currently, colonoscopy has been the primary tool in the screening of CRC in many countries around the world including The United States, Germany, Poland, Austria, and parts of Italy. GFOBT is still being used in France, Finland, and the United Kingdom. Netherlands while many other European countries have shifted from gFOBT to FIT. Sigmoidoscopy is identified to be the main screening option in the United Kingdom. In United States all the available methods of cereening are still being used.

### Screening Guidelines:

In the United States, there are mainly two guidelines for the screening of CRC: (1) The American Cancer Society, the United States MultiSociety Task Force on Colorectal Cancer, and the American College of Radiology uses the joint guidelines, [6]; and (2) The United States Preventive Services Task Force guidelines that was recently updated [7]. Many guidelines have been issued by many other organizations, such as the American College of Gastroenterology[8], the American College of

Physicians [9], and the National Comprehensive Cancer Network [10]. Table 1 summarizes the latest recommendations for average-risk individuals from different sets of the previous guidelines. Almost all the previous guidelines are similar in terms of their recommendations, with the lone exception of dropping the barium enema; as it have a relatively low level of sensitivity 48% [11]. Additionally, the frequency of using the stool DNA analysis has been put to controversy, as it is considered a rather new test. Nonetheless, all the other options of screening CRC are being widely used by all the societies as possible methods of screening.

**CRC Screening History, Incidence, and Mortality**

In the 1980's and 1990's, the main methods of RCR screening were FOBT and sigmoidoscopy. However, starting from the year 2000, the most common test used for screening of CRC in the United States changed to be colonoscopy, even though there is no solid randomized controlled trail to prove its effects on reducing CRC incidence and mortality. Therefore, the evident question would be weather has it been effective? The Data from a recent study examining CRC incidence established a drop in the incidence rates and the mortality of CRC both in male and female patients concomitant with the beginning of the screening programs. In addition, analyzing the data from the SEER database over a duration of 20-years between1991-2011, the incidence of colorectal cancer in the United States across all races and genders has shown a 35% reduction from 59.5 cases to 39.3 cases per 100000, accompanied with a 37% decrease in the mortality rates from 24.0 to 15.1 deaths per 100000 [12]. Moreover, The National Polyp Study (NPS) reported that the colonoscopy removal of adenomatous polyps have been paying a role in the prevention of CRC. They evaluate the benefits polypectomy over a of long-term period over CRC mortality Among 2602 patients who had been subjected to adenomas removal, after a median of 15.8 years, only 12 patients had died from CRC while 1246 patients died from any other cause. The expected CRC death in the general population was estimated to be 25.4, the standardized incidence-based mortality ratio was 0.47 (95%CI: 0.26-0.80) with the use of colonoscopic polypectomy, suggesting a 53% reduction in CRC mortality [13]. The NPS study findings was able to provide only an indirect estimate of the effect of removing adenomas. This is considered the main and primary measure in screening colonoscopy. Although the effect of screening colonoscopy on the general population neither was nor discussed. The findings support the theory suggesting that the colonoscopic removal of adenomatous polyps improves the CRC mortality rates.

**SCREENING OPTIONS**

**FS and colonoscopy**

Colonoscopy is considered the golden screening tool for CRC. It has a high sensitivity and specificity. It is the definitive test in cases where other screening tests are positive. It could detect, locate and resect other neoplasia and a precancerous lesion across the whole length of the large bowel .It is considered a safe test; the perforation rate in the latest data is suggested to be less than 1/1000. And mostly it is caused by polypectomy rather than the technique of colonoscopy itself. On the other hand, to perform a colonoscopy a full bowel preparation and sedation is mandatory [16-20]. Moreover, despite its availability, colonoscopy is not considered to be affordable to the general population, and its application on mass screening programs could be challenging [14]. Many studies including case-controle and prospective cohort studies have estimated the mortalities linked to CRC to be 68% to 88% lower among individuals who underwent a screening colonoscopy than those who did not [15]. An observational meta-analysis suggested that despite a 68% lower in the overall mortality, a limited beneficial effect of colonoscopy was seen with respect to cancer in the proximal colon [16]. Another study showed that the reduction in the overall CRC mortality was 29%, while the reduction of the distal CRC mortality was 47%, there was no significant reduction in mortalities from proximal CRC. Such results suggest that the benefit effect of colonoscopy is not uniform along the colon[17]. This discrepancy may be due to various factors affecting the technique itself and the quality of its application[18] (i.e., incomplete colonoscopy, inadequate training, lack of experience, the inadequate preparation of bowel, or technically difficult polypectomy in the proximal colon) or may be due to the possible differences in the biological characteristics of proximal and distal colorectal cancers [19]. To address these issues propperly, data from large controlled randomized trails are still lacking but are currently under way. The Colonoscopy vs Fecal Immunochemical Test in Reducing Mortality from Colorectal Cancer (CONFIRM) trial (ClinicalTrials.gov number, NCT01239082) is a randomized comparison of one-time colonoscopy with annual FIT plus colonoscopy as follow-up to a positive test, to examine CRC incidence and mortality over 10 years. A similar trial comparing colonoscopy with FIT is being conducted in Spain (COLONPREV) trail (ClinicalTrials.gov number, NCT00906997)[33]. Two additional European studies are comparing screening colonoscopy with no screening [the NordicEuropean Initiative on

Colorectal Cancer (NordICC)] trial (ClinicalTrials.gov number, NCT00883792) or with FIT or no screening [Screening of Swedish Colons (SCREESCO), NCT02078804] with respect to mortality from CRC

**Sigmoidoscopy**

Sigmoidoscopy requires a limited preparation of bowel in comparison to colonoscopy. In addition, many RCTs shown that in the cases of precancerous polyps, a screening test with FS followed by colonoscopy, reduces CRC mortality[20]. The beneficial effect of single and periodic sigmoidoscopy (every 3 to 5 years) have been confirmed by analysis from several large, randomized, controlled studies, patients who underwent FS screening had a 26% to 31% lower CRC mortality rate than those who underwent no screening [21]. However, the beneficial effect of sigmoidoscopy is limited to CRC in the distal colon (rectum, sigmoid, and descending colon), for which the reduction in mortality was reported to be 46%. Many programs have abandoned this strategy and switched to colonoscopy for better prevention results.

**gFOBT**

The concept of gFOBT is to detect the traces of blood in feces with a chemical reaction dependent upon the peroxidase activity of heme. This test is inexpensive, simple, and widely available. In order to evaluate the fecal occult blood test, 46551 participants aged between 50 to 80 years were randomized to screening for CRC on three groups, once a year, every two years, or to a control group. The results showed that the 13-year cumulative CRC mortality was decreased by 33% after annual fecal occult-blood test with sample rehydration [22]. In another randomized study the CRC mortality during 10 years after FOB tests with 2 years interval was compared with the unscreened controls. The results suggested that after 10 years of follow-up, screening every 2 years by FOB (Hemoccult-II without rehydration) was associated with an 18% reduced death from CRC. In patients aged between 45-75 years, regardless the of sex and age. In the he Minnesota Colon Cancer Control Study a 32% decrease in CRC mortality was associates with a 30-year follow-up of patients who were randomly assigned to an annual or bi-annual gFOBT vs patients on usual care. The reduction in mortality was clearer in men compared to women [23]. The association between this screening strategy and lower CRC mortality compared to no screening was shown in many other randomized, controlled trials[24]. However, this technique requires a moderate quantity of heme to establish a visible change in color. And hence is considered not very sensitive to the presence of blood.the sensitivity of a single test for cancer may reach 50% [25]. Many other studies indicate it to be lower. The concept of the test relies on simple oxidation, and therefore, any ingestion of external peroxidases, like the Heme produced from the reduction of the myoglobin in red meat, peroxidase in plants, etc., or any antioxidant, such as vitamin C, have the ability to alter the result of the test. The gFOBT is therefore an inherently non-specific test with a very low PPV of 3%-10% [26].

**FIT**

FIT is an antibody to human globin.it does have any not cross reaction with peroxidases from dietary sources. So it requires no need to avoid any specific foods with peroxidases. FIT mechanism of work is based on carefully measuring the colonic blood since upper gastrointestinal globin is degraded readily by digestive proteolytic enzymes. Compared to FOBT the FIT is considered a simple and easy test where less fecal samples are needed. Its sensitivity and ability to detect CRC and detect the presence of advanced adenomas are higher than both gFOBT. A cumulative sensitivity of 79% and specificity of 94% of FIT with an overall 95% accuracy in detecting CRC was shown in a recent meta analysis including 19 studies [27]. Moreover, a 22% reduction in the incidence of CRC was shown in Florence after an organized bi-annual or single FIT program for an average of 11 years follow up period with a sample of 6961 patients. FIT has some disadvantages as its low sensitivity for the presence of colon polyps. Additionally, many types of the test are available, the accuracy of the test may vary greatly between different technique, and according to how the test is applied (e.g., sample number) and according to the cutoff levels [28].

**CTC**

Virtual colonoscopy or CTC is a rapid noninvasive radiographic imaging test that does not require any preparation or sedation of the patient compared to colonoscopy [29]. In addition to the added advantage of evaluating the state of the extra colonic area. In a recent comparative metaanalysis the sensitivity and specificity to detect polyps in asymptomatic screened patients were 66.8% and 80.3% respectively for CT colonography, and 92.5% and 73.2% respectively for colonoscopy. Regarding the size of the tumor, the analysis showed that both studies have similar sensitivity in the case of large polyps. While CTC had lower sensitivity for polyps < 8 mm. for overall detection of CRC, both CTC and colonoscopy had statistically similar sensitivity o (96%) and (91%) respectively. However, there is the disadvantage the fact that the patient should take the same troublesome

preparation and the same discomfort and irritating technique of colonoscopy should be kept in mind. Moreover, side effect as allergy to the contrast material, the exposure to radiation, and the need to perform a colonoscopy in cases with findings are considered additional disadvantages of CTC. The risks of perforation still exist in CTC, although it is less common than colonoscopy [30].

**Stool DNA testing**

In August 2014, Cologuard® became the first multitarget stool DNA approved by the FDA to be used in the screening of CRC[31]. The concept of the Stool DNA test is to detect the presence of molecular debris and abnormal DNA in stool. in a multicenter study with the sample size of 10000 patients comparing Cologuard® to FIT with the use of colonoscopy as the gold standard the results showed that the test of stool for DAN was associated with higher sensitivity than FIT in the detection of CRC (92% vs 74%). Unfortunately, less than half of large advanced adenomas can be detected by Cologuard® (42%). Fecal DNA test showed a lower specificity at 87%-90% in comparison to FIT test (95%-96%). Moreover, in a new study from Stanford University comparing the effectiveness and cost effectiveness of screening with the MT-sDNA test vs FIT or colonoscopy. FIT and colonoscopy was found to have higher sensitivity and efficacy with less cost than the MT-sDNA test when participation rates were equal. For the MT-sDNA test to be cost effective, the screening program needed to achieve substantially higher participation rates than those for FIT, either in organized programs or in opportunistic screening setting that is more common in countries like the United States. Additionally, the different in screening interval between FIT and MT-sDNA makes a comparison of the effectiveness of any programed screening difficult.

**Methylated SEPT9**

Septins are a group of scaffolding proteins present during the cell division and provide structural support [32]. An individual septins exist in stable six-to eight-subunit core heteromers, and the octamer contains two molecules of each of SEPT2, SEPT6, SEPT7, and SEPT9 subunits [33]. It was suggested that SEPT9 is located at the terminal position in the complex and plays a key role in subunit polymerization and the whole octamer stabilization. It is also critical for the final separation of daughter cells during cytokinesis. Therefore, cytokinesis may be seriously affected by the expression of abnormal SEPT9 or no SEPT9 is, and this could have an important role in the carcinogenesis of CRC when the promoter region of the SEPT9 gene is hypermethylated and the transcription is compromised. Hypermethylated Septin9 DNA can be found in the tumor DNA that has been shed into the bloodstream from all intestinal anatomical sites. Epi proColon® (also referred to as the mSEPT9 assay) became FDA approved for CRC screening in April 2016, it is the first blood test used for this goal. The mSEPT9 assay relies on qualitative detection by Real-Time PCR of the methylated Septin 9 gene that is present in increased levels in patients with colon cancer[34]. In initial retrospective case-control studies, the mSEPT9 test showed a promising results in detecting CRC, with a sensitivity of nearly 70% and specificity of 90% [81,82]. A prospective trial in an asymptomatic screening cohort reported lower rates of sensitivity (48%) and specificity (92%) for CRC. However, this sensitivity decreased to 35% for stage I CRC and 11% for advanced adenomas almost totally eliminating its preventive role. In a prospective multi-center study that compared the Sept9 with FIT, the results showed similar sensitivity (68% vs 73%) but with markedly decreased specificity (97% vs 81%). While the overall sensitivity for CRC detection of Septin9 may be superior to gFOBT, it is non-inferior to that of FIT. However, comparing to Cologuard®, the Epi proColon®, Sept9 appears to have a decreased sensitive for both CRC and advanced adenomas in actual practice, but with a higher specificity for cancer. Nonetheless, evidence suggests that some patients with reported weak compliance to undergo the usual screening would show a better compliance and be more receptive to a blood test.

**CRC SCREENING PROGRAM ATTRIBUTES**

Dividing the population according to the risk to develop CRC offers to building and improve the efficiency of the screening program. A quick review of the literature reveals more than 50 proposed risk scores for colon cancer that have the ability to identify individuals at high risk. A systematic review that studied the available risk scores showed that the identification of the different risk models, and comparing them with the risk models used for other cancers. After dividing the different risk models into groups according their type and the number of the included variables showed no improvement in the discrimination; as increasing numbers of variables are added from self-completed questionnaires to routine data. A small number of risk models developed from case control studies of genetic biomarkers showed serious promise but still require further external validation in population-based samples. This review also showed that many different risk models exist, with the ability to divide the general population into risk categories, and allow

screening and preventive strategies to the groups with the highest beneficial possibility, while saving the groups with low risk of disease from the complications and side effects of the screening procedures. This might have positive effects on the cost-effectiveness of the screening programs. The use of risk prediction models would also potentially increase acceptance of screening and provide an opportunity to give information to encourage lifestyle modification [35].

Despite the existence of many different screening modalities for CRC, the usage of these screening tools in the population is still limited. Since the year 2010, the rates of usage of the different screening tool has not increased and remain at approximately 60%. Many different factors May affecting the patients participation and adherence in the CRC screening programs. Difficulties that face the screening programs include the high coast cost, lack of information about CRC, underestimating the benefits of screening programs, or simply the fear of participating in screening tests [36]. RCTs have showed many interventions to increase the rate of participation in the screening programs; such as sending reminders and invitations to participate in screening programs, either via mailing of telephone, the mailing of fecal occult blood test kits to patients' homes.

Several National screening programs that examined patterns of CRC screening using gFOBT and FIT concluded that there is 20%-29% rate of nonresponders. 3 or 4 cycles later an additional drop out of the program up to 30% could be seen. In the annual FIT screening program in California 48% initial participation with a 75% adherence was measured after 4 cycles. Analysis from those programs suggests a strong affection of sex and socioeconomics on CRC screening uptake and adherence rate. Repeated invitations to screening programs resulted in the involvement of non-responders in different program. Many of them responded to these invitations at least for a single time or over multiple rounds. Therefore, efforts to maintain and improve the rates of engagement of the people with high risk of developing CRC are essential to optimize the long-term benefit of organized screening programs [37].

## CONCLUSIONS:

Currently many various options exist for CRC screening. A quick review can reveal the great difference between screening programs all over the world. Additionally, another point that should be kept in mind is that most screening tests are still done opportunistically and without any plan or program, especially in low income countries. CRC screening programs must be optimized in order to achieve the target of reducing incidence of the CRC and eventually reduce its mortality. Another important point is that a higher and wider participation rates and adherence to the programs must be achieved in different screening programs by seeking correction of all the confounding factors. The compliance and adherence to the programs must be increased by using the different available tools in the correct way and setting of each population. Consistent with this goal, the complications and side effects of screening tests must be reduced by the adoption of cost-effective non-invasive methodologies, which will lead to the reduction of anxiety over the complications of CRC screening, and the improvement of the overall acceptance and compliance of the screening process would be highly recommended. Despite the current limitations, the non-invasive blood based markers may have a solid future. The idea of screening with a relatively inexpensive serum or plasma marker (or marker panel) could increase screening compliance and be cost-saving if participation and performance were both elevated. Such a marker has the potential to replace more difficult and complicated stool based test in programs that employ a 2-stage paradigm. However, after the publishing of the results of the trails studying the new blood markers. All the high expectation and the enthusiasm have faded away as the results were not that encouraging. At this point the significant variability in sensitivity and specificity the various tests have made it very difficult to suggest any test for mass screening. Regarding the non-invasive stool tests, the FIT is considered to be the optimum most appropriate test. Regarding the high risk groups, colonoscopy is considered the most appropriate screening test. We recommend for future studies to focus focus on the characterization of the different complete screening programs, starting from the invitation to participate in the programs to the colonoscopy of the high risk groups and patient with positive other test results.

## REFERENCES:

1. **Torre LA, Bray F, Siegel RL, Ferlay J, Lortet-Tieulent J, Jemal A.(2015)** Global cancer statistics, 2012. CA Cancer J Clin 2015; 65: 87-108 [PMID: 25651787 DOI: 10.3322/caac.21262].
2. **Ferlay J, Soerjomataram I, Dikshit R, Eser S, Mathers C, Rebelo M, Parkin DM, Forman D, Bray F.(2015)** Cancer incidence and mortality worldwide: sources, methods and major patterns in GLOBOCAN 2012. Int J Cancer 2015; 136:

E359-E386 [PMID: 25220842 DOI: 10.1002/.

3. **Siegel R, Desantis C, Jemal A.(2014)** Colorectal cancer statistics, 2014. CA Cancer J Clin 2014; 64: 104-117 [PMID: 24639052 DOI: 10.3322/caac.21220].
4. **Jemal A, Bray F, Center MM, Ferlay J, Ward E, Forman D.(2011)** Global cancer statistics. CA Cancer J Clin 2011; 61: 69-90 [PMID: 21296855 DOI: 10.3322/caac.20107].
5. **Carroll MR, Seaman HE, Halloran SP.(2014)** Tests and investigations for colorectal cancer screening. Clin Biochem 2014; 47: 921-939 [PMID: 24769265 DOI: 10.1016/j.clinbiochem.2014.04.019].
6. **Levin B, Lieberman DA, McFarland B, Smith RA, Brooks D, Andrews KS, Dash C, Giardiello FM, Glick S, Levin TR, Pickhardt P, Rex DK, Thorson A, Winawer SJ** American Cancer Society Colorectal Cancer Advisory Group; US Multi-Society Task Force; American Colle.
7. **US Preventive Services Task Force** Bibbins-Domingo K, Grossman DC, Curry SJ, Davidson KW, Epling JW Jr, García FAR, Gillman MW, Harper DM, Kemper AR, Krist AH, Kurth AE, Landefeld CS, Mangione CM, Owens DK, Phillips WR, Phipps MG, Pignone MP, Siu AL. Scre.
8. **Rex DK, Johnson DA, Anderson JC, Schoenfeld PS, Burke CA, Inadomi JM (2009)** American College of Gastroenterology. American College of Gastroenterology guidelines for colorectal cancer screening 2009 [corrected]. Am J Gastroenterol 2009; 104: 739-750 [PMID: 1924.
9. **Qaseem A, Denberg TD, Hopkins RH Jr, Humphrey LL, LevineJ, Sweet DE, Shekelle P** Clinical Guidelines Committee of the American College of Physicians. Screening for colorectal cancer: a guidance statement from the American College of Physicians. Ann Intern.
10. P**rovenzale D, Jasperson K, Ahnen DJ, Aslanian H, Bray T, Cannon JA, David DS, Early DS, Erwin D, Ford JM, Giardiello FM, Gupta S, Halverson AL, Hamilton SR, Hampel H, Ismail MK, Klapman JB, Larson DW, Lazenby AJ, Lynch PM, Mayer RJ, Ness RM, Rao MS, Regen.(2015)** National comprehensive cancer netwok. Colorectal Cancer Screening, Version 1.2015. J Natl Compr Canc Netw 2015; 13: 959-968; quiz 968 [PMID: 26285241]

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11. **Rockey DC, Paulson E, Niedzwiecki D, Davis W, Bosworth HB, Sanders L, Yee J, Henderson J, Hatten P, Burdick S, Sanyal A, Rubin DT, Sterling M, Akerkar G, Bhutani MS, Binmoeller K, Garvie J, Bini EJ, McQuaid K, Foster WL, Thompson WM, Dachman A, Halvorsen .(2005)** Analysis of air contrast barium enema, computed tomographic colonography, and colonoscopy: prospective comparison. Lancet 2005; 365: 305-311 [PMID: 15664225 DOI: 10.1016/S0140-6736(05)17784-8]
12. **Surveillance, Epidemiology, and End Results Program.(2014)** SEER Stat Fact Sheets: Colon and Rectum Cancer: Centers for Disease Control; 2014.
13. **Zauber AG, Winawer SJ, O'Brien MJ, Lansdorp-Vogelaar I, van Ballegooijen M, Hankey BF, Shi W, Bond JH, Schapiro M, Panish JF, Stewart ET, Waye JD.(2012)** Colonoscopic polypectomy and longterm prevention of colorectal-cancer deaths. N Engl J Med 2012; 366: 687-69.
14. **Ransohoff DF.(2009)** How much does colonoscopy reduce colon cancer mortality? Ann Intern Med 2009; 150: 50-52 [PMID: 19075200].
15. **Neugut AI, Lebwohl B.(2010)** Colonoscopy vs sigmoidoscopy screening: getting it right. JAMA 2010; 304: 461-462 [PMID: 20664047 DOI: 10.1001/jama.2010.1001].
16. **Brenner H, Stock C, Hoffmeister M.(2014)** 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: g246.
17. **Singh H, Nugent Z, Demers AA, Kliewer EV, Mahmud SM, Bernstein CN.(2010)** The reduction in colorectal cancer mortality after colonoscopy varies by site of the cancer. Gastroenterology 2010; 139: 1128-1137 [PMID: 20600026 DOI: 10.1053/ j.gastro.2010.06.052].
18. **Atkin W, Rogers P, Cardwell C, Cook C, Cuzick J, Wardle J, Edwards R.(2004)** Wide variation in adenoma detection rates at screening flexible sigmoidoscopy. Gastroenterology 2004; 126: 1247-1256 [PMID: 15131784].
19. **Rabeneck L, Paszat LF, Saskin R.(2010)** Endoscopist specialty is associated with incident colorectal cancer after a negative colonoscopy. Clin Gastroenterol Hepatol 2010; 8: 275-279 [PMID: 19879970 DOI: 10.1016/j.cgh.2009.10.022].
20. **Segnan N, Armaroli P, Bonelli L, Risio M, Sciallero S, Zappa M, Andreoni B, Arrigoni A, Bisanti L, Casella C, Crosta C, Falcini F, Ferrero F, Giacomin A, Giuliani O, Santarelli A, Visioli CB, Zanetti R, Atkin WS, Senore** C;

SCORE Working Group. Onceonly si.

21. **Atkin WS, Edwards R, Kralj-Hans I, Wooldrage K, Hart AR, Northover JM, Parkin DM, Wardle J, Duffy SW, Cuzick J**. Flexible Sigmoidoscopy Trial Investigators. Once-only flexible sigmoidoscopy screening in prevention of colorectal cancer: a multicentre ran.
22. **Mandel JS, Bond JH, Church TR, Snover DC, Bradley GM, Schuman LM, Ederer F.(1993)** Reducing mortality from colorectal cancer by screening for fecal occult blood. Minnesota Colon Cancer Control Study. N Engl J Med 1993; 328: 1365-1371 [PMID: 8474513 DOI: 10.1056/.
23. **Shaukat A, Mongin SJ, Geisser MS, Lederle FA, Bond JH, Mandel JS.(2013)** Church TR. Long-term mortality after screening for colorectal cancer. N Engl J Med 2013; 369: 1106-1114 [PMID: 24047060 DOI: 10.1056/NEJMoa1300720].
24. **Scholefield JH, Moss SM, Mangham CM, Whynes DK, Hardcastle JD.(2012)** Nottingham trial of faecal occult blood testing for colorectal cancer: a 20-year follow-up. Gut 2012; 61: 1036-1040 [PMID: 22052062 DOI: 10.1136/gutjnl-2011-300774].
25. **Lansdorp-Vogelaar I, van Ballegooijen M, Boer R, Zauber A, Habbema JD.(2009)** A novel hypothesis on the sensitivity of the fecal occult blood test: Results of a joint analysis of 3 randomized controlled trials. Cancer 2009; 115: 2410-2419 [PMID: 19288570 DOI: 10.
26. **Young GP, Symonds EL, Allison JE, Cole SR, Fraser CG, Halloran SP, Kuipers EJ, Seaman HE.(2015)** Advances in Fecal Occult Blood Tests: the FIT revolution. Dig Dis Sci 2015; 60: 609-622 [PMID: 25492500 DOI: 10.1007/s10620-014-3445-3].
27. **Lee JK, Liles EG, Bent S, Levin TR, Corley DA.(2014)** Accuracy of fecal immunochemical tests for colorectal cancer: systematic review and meta-analysis. Ann Intern Med 2014; 160: 171 [PMID: 24658694 DOI: 10.7326/M13-1484].
28. **van Rossum LG, van Rijn AF, Laheij RJ, van Oijen MG, Fockens P, Jansen JB, Verbeek AL, Dekker E.** Cutoff value determines the performance of a semi-quantitative immunochemical faecal occult blood test in a colorectal cancer screening programme. Br J Cancer.
29. **Pickhardt PJ.(2006)** Incidence of colonic perforation at CT colonography: review of existing data and implications for screening of asymptomatic adults. Radiology 2006; 239: 313-316 [PMID: 16641348 DOI: 10.1148/radiol.2392052002].
30. **Burling D, Halligan S, Slater A, Noakes MJ, Taylor SA.(2006)** Potentially serious adverse events at CT colonography in symptomatic patients: national survey of the United Kingdom. Radiology 2006; 239: 464-471 [PMID: 16569789 DOI: 10.1148/radiol.2392051101].
31. **Ahlquist DA.(2015)** Multi-target stool DNA test: a new high bar for noninvasive screening. Dig Dis Sci 2015; 60: 623-633 [PMID: 25492503].
32. **Longtine MS, DeMarini DJ, Valencik ML, Al-Awar OS, Fares H, De Virgilio C, Pringle JR.(10996)** The septins: roles in cytokinesis and other processes. Curr Opin Cell Biol 1996; 8: 106-119 [PMID: 8791410].
33. **Sellin ME, Sandblad L, Stenmark S, Gullberg M.(2011)** Deciphering the rules governing assembly order of mammalian septin complexes. Mol Biol Cell 2011; 22: 3152-3164 [PMID: 21737677 DOI: 10.1091/mbc.E11-03-0253].
34. **Grützmann R, Molnar B, Pilarsky C, Habermann JK, Schlag PM, Saeger HD, Miehlke S, Stolz T, Model F, Roblick UJ, Bruch HP, Koch R, Liebenberg V, Devos T, Song X, Day RH, Sledziewski AZ, Lofton-Day C.** Sensitive detection of colorectal cancer in peripheral b.
35. **Prediction Models for Colorectal Cancer(2016)** A Systematic Review. Cancer Prev Res (Phila) 2016; 9: 13-26 [PMID: 26464100 DOI: 10.1158/1940-6207.CAPR-15-0274].
36. **Brenner AT, Ko LK, Janz N, Gupta S, Inadomi J.(2015)** Race/Ethnicity and Primary Language: Health Beliefs about Colorectal Cancer Screening in a Diverse, Low-Income Population. J Health Care Poor Underserved 2015; 26: 824-838 [PMID: 26320917 DOI: 10.1353/hpu.201.
37. **Lo SH, Halloran S, Snowball J, Seaman H, Wardle J, von Wagner C.(2015)** Colorectal cancer screening uptake over three biennial invitation rounds in the English bowel cancer screening programme. Gut 2015; 64: 282-291 [PMID: 24812001 DOI: 10.1136/ gutjnl-2013-3061.