

## Adaptation of Clinical Practice Guideline for Colorectal Cancer Screening in People with Average Risk in Isfahan Province

### Abstract

**Background:** Colorectal cancer (CRC) is the third most common cancer among adults in Iran. The aim of colorectal cancer screening is to reduce the cancer burden in the population by diagnosing the disease in its early stages. **Methods:** We adapted this guideline for the moderate CRC risk population for Isfahan to determine how to screen them and when to start and end the CRC screening. This guideline was developed by clinical appraisal and review of the evidence, available clinical guidelines, and in consultation with members of the Isfahan Chamber of Iranian association of gastroenterology and hepatology. **Results:** In screening people with average risk for CRC who use personal resources and personally pay all the costs, colonoscopy is recommended as the first choice to be done every 10 years. In case of negative colonoscopy, we recommend FIT test to prevention of interval cancer every 5 years. In screening of people with average risk of CRC, FIT is suggested to be done every 2 years as a first-choice method test for those who use public resources and do not pay for this service personally. In screening individuals with average risk for CRC, g-FOBT is not recommended as the first method of choice. Repeating positive guaiac test is not recommended and if positive, colonoscopy is suggested.

**Keywords:** Colorectal cancer; guideline, practice guideline, screening

### Introduction and Epidemiology

Colorectal cancer (CRC) is the third most common cancer among adults in Iran, fourth in the United States second in Canada and Spain, and is the second leading cause of cancer-related deaths in the United States, Canada, Europe, and Hong Kong.<sup>[1-6]</sup> In 2018 over 140,000 cases of colorectal cancers have been diagnosed in the USA and it has been ranked the second leading cause of cancer-related deaths with more than 50,000 deaths per year.<sup>[1]</sup> In 2017, the incidence of new CRC cases in Canada was 26,800, and in America 135,430.<sup>[2]</sup> Also in Hong Kong, colorectal cancer is the most common malignancy, for example, 5,036 cases of malignancy were diagnosed in 2015 of which 16.6% were CRC cases.<sup>[3]</sup> According to data from International Agency for Research on Cancer, colorectal cancer with more than 432,000 new cases per year is the most common malignancy among men and women in Europe.<sup>[7]</sup>

Most colorectal cancers originate from adenomatous polyps and less from inherited

polyposis syndromes or IBD. These lesions are often benign however they can become cancerous over time.<sup>[2,8]</sup> Transformation of tissue to adenoma, and then to colorectal cancer is a gradual process, which occurs due to change in several suppressor genes in a period of 10 years. Progression risk depends on the amount, size, and histology of adenomatous polyps.<sup>[4-6]</sup> Prevalence of adenomatous polyps, which was discovered in colonoscopy, is 18-36%. After removing adenoma, a screening/surveillance plan will be scheduled for the patient who will be followed and treated in terms of adenoma relapse or cancer.<sup>[9]</sup> People with an average risk of 4 to 5% are likely to get colorectal cancer.<sup>[10]</sup> The burden of this malignancy can be decreased by cancer prevention and tumor identification at an earlier stage. Early detection of tumors will improve the prognosis.<sup>[11]</sup>

In the recent decade, many published articles study the knowledge, attitude, and screening methods in different countries.<sup>[12]</sup> After traffic accidents and cardiovascular mortality, cancer is the third leading cause of death in Iran. Cancers of the stomach,

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esophagus, and lung were more common in the north while higher rates of cancers of the breast and colorectal were found in central parts of Iran.<sup>[13]</sup> Epidemiologic studies in Iran have reported an accelerating trend of colorectal cancer in recent years in the country. According to the national registry of cancer program of the ministry of health and medical education and cancer research institute, most cancers occur in the stomach followed by the colon and rectum.<sup>[14]</sup>

Cancers of breast, prostate, skin, and colorectal are four common cancers in the Isfahan province. Colorectal cancer in men and women of Isfahan is respectively the third and fourth most common cancer.<sup>[15]</sup> Colorectal cancer's heavy burden (incidence, impairment, death), availability of precancerous lesions diagnostic tests, and good prognosis for treatment of early-stage colon cancer are all proper choices for the screening program.<sup>[16]</sup> Because of the high incidence of CRC in Isfahan and CRCs' heavy burden in general and on the other hand availability of early diagnosis and treatment of precancerous lesions, we had decided to adapt clinical practice guidelines for CRC screening in Isfahan.

General practitioners and family physicians who are the main audience of this guide line are the first-line medical professionals facing colorectal cancer patients. Screening, surveillance, and treatment as well as follow-up in the primary health care system is the responsibility of the general practitioners and family physicians. On the other hand, the clinical guidelines coordinate internists' and adult gastroenterologists' approaches to this disease. That is the reason that the purpose of adapting this clinical guideline based on Isfahan province's demographic characteristics is about determining the starting and ending the age of screening and choosing the type of screening test in people with average risk for CRC. This guideline was developed by clinical appraisal and review of the evidence, available clinical guidelines, and in consultation with members of the Isfahan Chamber of Iranian association of gastroenterology and hepatology. The average risk population that this guideline was drafted to plan their screening are defined as below:

1. Age of 50 or more
2. Without a personal history of polyp or colorectal cancer
3. Without a personal history of inflammatory bowel diseases
4. Without a family history of colorectal cancer which is defined as having a first-degree relative diagnosed before 65 or in two first degree relatives in any age
5. Without a family history of advanced adenomatous polyp in the age of under 65 in a first-degree relative (polyp smaller than 1 centimeter without advanced dysplasia and without villous component).

### Colorectal Cancer Risk Factors

Colorectal cancer is related to age and its incidence rate increases significantly in ages of more than 50. The average

age of colorectal cancer diagnosis among men is 68 and among women is 70; furthermore, CRC incidence and mortality decreases in the middle ages and grows after that.<sup>[3,8,9]</sup> Based on gender, colorectal cancer is the second cause of death among men and third among women. The probability of death resulted from CRC during the life of men and women is respectively 3.5% and 3.1%.<sup>[9]</sup> Also in Hong Kong, this cancer is more prevalent among men with a ratio of men to women of 1.3 to 1 new diagnosed cases in 2015.<sup>[3]</sup>

Incidence and mortality of CRC are different in various races, it is more common in African-American people than white people and it is lower in Asians and Pacific Islanders.<sup>[4]</sup> Risk factors for CRC to occur might be correctable or uncorrectable. Correctable risk factors such as smoking, obesity, overuse of alcohol consumption and red meat, not getting enough vegetables, fruits, fiber, and calcium in the diet, and not having physical activity increase the CRC risk. Uncorrectable risk factors include old age, male gender, positive family history, family history of adenomatous polyp, Lynch syndrome, colon polyp, and ulcerative colitis.<sup>[1,3,17]</sup>

### Clinical Symptoms of Colorectal Cancer

CRC might be symptomatic and be apparent with symptoms like intestinal obstruction, peritonitis, or in more rare cases by acute gastrointestinal bleeding, or it could be asymptomatic and be diagnosed during the screening program like colonoscopy, sigmoidoscopy, CT-colonography, or fecal occult blood test. Most CRC patients are asymptomatic and are diagnosed in the screening program.<sup>[18]</sup> Screening in cancer control is effective in populations with a considerable CRC burden. The aim of colorectal cancer screening is to reduce the cancer burden in the population by diagnosing the disease in its early stages. Evidence-based methods demonstrate that treatment in the early stages is much more effective. Colorectal cancer treatment in early stages with endoscopy increases life quality. Moreover, treatment of premalignant lesions with endoscopy prevents the progress leading to cancer. Clinical trials have shown that screening people with average risk usually results in a decrease in CRC incidence and mortality.<sup>[7,10]</sup>

Symptomatic individuals with symptoms such as rectal bleeding, bowel habit change, iron deficiency anemia, inflammatory bowel disease, adenoma, individual history, or strong family history of CRC, will be screened as high-risk patients.<sup>[19]</sup> The risk of CRC between different countries and in different parts of a country is diverse. Furthermore, this risk among different people is depended on the diet, lifestyle, and hereditary factors and changes according to them.

### Materials and Methods

We conducted a comprehensive literature search with the help of a librarian on these keywords (colorectal cancer,

screening, and guideline). Search engines like PubMed, NICE Guideline, Trip, Clinical Key, Google Scholar, and websites of credible and scientific associations such as American College of Gastroenterology (ACG), World Gastroenterology Organization (WGO), American Academy of Family Physicians (AAFP), American Society for Gastrointestinal Endoscopy (ASGE), Canadian Association of Gastroenterology (CAG) were reviewed Table 1. Guidelines in English and their complete issue was accessible, were collected. Simultaneously, medical contexts were verified in order to find the best evidence. The existing recommendations in different guidelines for CRC screening in people with average risk are briefly summarized in Table 4.

**Search words:** colorectal cancer, screening, guideline.

**Search time period:** 2019 –2020.

According to a specific timing schedule, based on gathered evidence and information from various guidelines a primary solution was written. The level of evidence about each recommendation is noted and categorized into four conditions especially based on ACG 2021 and the power of studies summarized in Table 2.<sup>[20]</sup> The processes specifically focused on 11 principal questions. Scope and Purpose Questions around screening for CRC in individuals with Average Risk in Isfahan Province identified. Each of the suggestions and solutions was adapted based on special conditions of the target population and situations in which the solution will be implemented and operated (healthcare, economic and cultural).

For this purpose, a consensus meeting consisting of 38 gastroenterologist experts, which were all of the members of the Isfahan Chamber of Iranian association of gastroenterology and hepatology was hold. In the end, all recommendations and solutions were presented. Each solution was voted on and the percentage was determined and categorized based on Table 3 and summarized in Table 5. As per the update, this guideline is specifically based on ACG 2021 clinical guideline updating,<sup>[21]</sup> the panel will decide that update schedule for this guideline based on the ACG guideline update time.

## CRC Prevention

### Primary Prevention

#### 1. What solutions are recommended for the primary prevention of CRC?

##### Recommendation:

For primary prevention of CRC increase in dietary fiber, red meat, and processed food intake reduction, calcium, vitamin D, and B6 consumption, physical activity, maintaining a healthy weight, avoiding smoking, and drinking alcohol are recommended.

#### 2. How much red meat intake increases CRC risk?

**Table 1: List of searched database and scientific associations**

Source	Address
PubMed	<a href="https://www.ncbi.nlm.nih.gov/pubmed/">https://www.ncbi.nlm.nih.gov/pubmed/</a>
NICE	<a href="https://www.nice.org.uk/about/what-we-do/our-programmes/nice-guidance/nice-guidelines">https://www.nice.org.uk/about/what-we-do/our-programmes/nice-guidance/nice-guidelines</a>
Trip database	<a href="https://www.tripdatabase.com/">https://www.tripdatabase.com/</a>
Google scholar	<a href="https://scholar.google.com/">https://scholar.google.com/</a>
Clinical key	<a href="https://www.clinicalkey.com/#!/browse/guidelines">https://www.clinicalkey.com/#!/browse/guidelines</a>
ACG	<a href="https://gi.org/guidelines/">https://gi.org/guidelines/</a>
WGO	<a href="https://www.worldgastroenterology.org/guidelines/global-guidelines">https://www.worldgastroenterology.org/guidelines/global-guidelines</a>
AAFP	<a href="https://www.aafp.org/journals/afp.html">https://www.aafp.org/journals/afp.html</a>
ASGE	<a href="https://www.asge.org/home/guidelines">https://www.asge.org/home/guidelines</a>
CAG	<a href="https://www.cag-acg.org/publications/guideline-library">https://www.cag-acg.org/publications/guideline-library</a>

**Table 2: Level of evidence**

Quality element	Description
High	Further research is very unlikely to change our confidence in the estimate of effect
Moderate	Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate
Low	Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate
Very low	Any estimate of effect is very uncertain

**Table 3: Level of agreement**

Leveling	Percent of agreement
Strong	More than 75 percent
Conditional	66-74 percent
Weak	50-65 percent

##### Recommendation:

Consuming red meat for more than 200 gr per week (average of daily 30 gr) accelerates the colorectal cancer risk.

#### 3. How many minutes of physical exercise in a week reduces the CRC risk?

##### Recommendation:

Activities of more than 150 minutes per week (indoor/outdoor physical activity) result in protection against CRC.

#### 4. How much daily alcohol increases the risk of CRC?

##### Recommendation:

Drinking more than 1 standard dose per day (10 grams daily) increases the risk of colorectal cancer.

##### Evidence:

In order to prevent CRC, primary prevention is essential for many of the risk factors that are amendable. The target of



primary prevention is the common population and evidence shows that at least 70% of colorectal cancers are preventable by changing diet and lifestyle.<sup>[3,22]</sup> Most studies have shown that eating fiber, vegetables and fruit are approximately 40-50% related to decreasing the CRC risk. Impacts of red meat (beef, lamb and etc.) and processed meat (Jambon, sausage and etc.) have been studied in many epidemiologic studies and link the acceleration in colorectal cancer or adenoma with higher intake of red meat and processed meat.<sup>[23,24]</sup> Moreover, reviewal papers and meta-analyses indicate that consuming calcium, vitamin D, and B6 can have a protective effect on colorectal adenoma generation and lowers the CRC risk. Daily physical activity not only maintains healthy body weight but also increases bowel movements, and to some extent related to the reduction in belly fat and significantly reduces colorectal cancer. It is estimated that physical activity lowers the CRC risk to 40-50% in those who do moderate exercise (such as walking). Walking with a rate of 3 mph (equals to 4.8 kph weekly), has had a protective effect against progressed adenomatous polyp in men. U.S. Centers for Disease Control recommends adults to have at least a 150 minutes moderate aerobic workout or 75 minutes of intense aerobic workout.<sup>[25]</sup> Drinking alcohol and liquors for more than 2 standard doses a day (30 gr daily) and smoking cigarettes increases the risk of colorectal cancer.<sup>[26,27]</sup> In 2011, a reviewal study published in *Annals of oncology* magazine, the growth in colorectal cancer caused by average alcohol consumption (1-4 drink/day, equal to 12.6-49.9 gr/day) is 21%, and by overuse of alcohol (more than 4 drink/day, equals to 50 gr/day) is 52%. In return, low alcohol intake (less than 1 drink/day equally less than 12.5 gr/day) is not accompanied by the risk of colorectal cancer.<sup>[28]</sup>

## Secondary Prevention

### 5. What methods are used for screening individuals with average CRC risk?

#### Recommendation:

In individuals with average risk, screening is done by two methods of fecal-based tests (g FOBT, FIT) and direct inspection with endoscopy and radiology (colonoscopy, sigmoidoscopy, CT-colonography).

#### Evidence:

Secondary prevention includes screening asymptomatic individuals in order to diagnose the disease or to determine individuals who are more prone to the disease. Since CRC is mostly made of adenomatous polyps in a long period of incubation, it is one of the few cancers which could be prevented by regular screening. Regular screening is one of the best and most crucial primary prevention methods used for this disease.<sup>[3,29]</sup>

Employing CRC screening is less common than breast cancer screening in spite of the fact that many findings indicate CRC screening to be effective in reducing disease

mortality. Of obstacles in the way of CRC screening lack of resources, unavailability of recommendations, logistical factors (like transportation, planning, and language), fear, and lack of science can be mentioned. These obstacles are more common in areas with limited economical and educational resources or of racial and religious minorities. Increasing awareness by education and making the diagnostic methods available and reducing unpredicted diagnostic costs are used to overcome these obstacles.<sup>[30]</sup>

Screening in people with average risk is done by two methods of fecal-based tests (DNA test, g-FOBT, FIT) and direct visualization by endoscopy and radiology (colonoscopy, sigmoidoscopy, and CT-colonography). FIT and g-FOBT tests are the cheapest and colonoscopy is the most expensive CRC screening test and the resting place in-between.<sup>[1]</sup>

Availability and accessibility of the test, number of screening times, place of screening (home versus medical center), need to liquid diet, colon preparation, invasiveness, need to use sedatives, costs, complications, and test accuracy are among the factors that affect on what kind of test should be chosen. If by a non-colonoscopy method, the screening is positive the determination will be by colonoscopy.<sup>[1,4,6]</sup>

Previous studies show that CRC mortality can be reduced 16-33% by fecal-based tests, 28% by sigmoidoscopy, and 61% by colonoscopy.<sup>[3]</sup> A summary of existing recommendations in different guidelines for CRC screening in average risked people is given in Table 3; also, the guideline summary is in Table 4.

### 6. What is the starting and ending age of colorectal screening in those with average risk?

#### Recommendation:

- a. CRC screening starting age in people with average risk is from 50 years old and in diabetic or overweight people is 45.
- b. Ending the age of CRC screening in people with average risk is 75.
- c. In people between 75-85, deciding on CRC screening health condition and patient's preference is considered.
- d. CRC screening in ages of more than 85 in those with average risk is not recommended.

#### Evidence:

ACG and MSTF suggest that screening starts at the age of 45 in the African-American population and in others at 50.<sup>[31-33]</sup> ACG's recommendation to screening 45-year-old African-Americans indicates the fact that CRC incidence is 12% more in African-Americans than in white people. Furthermore, the 5 years CRC survival in African-Americans is 16% less than in white people and also in African-Americans CRC is more occurrent in the right colon than in the white population.<sup>[32,33]</sup>

**Table 4: A summary of existing recommendations in different guidelines for CRC screening in people with average risk**

Guideline	Age (year) Start of screening	Age (year) end of screening	Colonoscopy	Flexible Sigmoidoscopy	CT-Colonography	FIT	g-FOBT	Fecal DNA Test
ACG <sup>[2,33]</sup>	50 (45 for African-Americans)	75	every 10 years	Every 5 to 10 years	Every 5 years	yearly	Is not done (instead of it, FIT, Hemoccult Sensa and fecal DNA are recommended)	Every 3 years + yearly Hemoccult Sensa
ACS <sup>[1]</sup>	45 (qualified)	85	Every 10 years	Every 5 years	Every 5 years	yearly	yearly	Every 3 years
ACP <sup>[4]</sup>	50 (strong)	75	Every 10 years	Every 10 years + FIT every 2 years	Not recommended	Every 2 years	High sensitivity FOBT every 2 years	Not recommended
ASGE <sup>[5]</sup>	50	-	Every 10 years	Every 5 years	Not recommended	yearly	yearly	Not recommended
MSTF <sup>[31]</sup>	50 (45 for African-Americans)	75	Every 10 years	Every 10 years	Every 5 years	yearly	-	Every 3 years + yearly FIT
USPSTF <sup>[6]</sup>	50	75	Every 10 years	Every 5 years + high sensitivity FOBT every 3 years	Lack of evidence	yearly	High sensitivity FOBT (SENSA) yearly	Lack of evidence
CAG <sup>[11]</sup>	50	75	Not recommended	Every 10 years or more	Not recommended	Not recommended	High sensitivity FOBT yearly	Not recommended
CTFPHC <sup>[9]</sup>	50-59 (slightly recommended)	74	Not recommended	Every 10 years	Not recommended	Every 2 years	Every 2 years	Not recommended
CEWG <sup>[3]</sup>	60-69 (highly recommended)	75	Every 10 years	Every 5 years	-	Yearly or every 2 years	Yearly or every 2 years	-
Australia <sup>[9]</sup>	50	75	Not recommended	Not recommended	-	Every 2 years	-	Not recommended
Saudi Arabia <sup>[34]</sup>	45	70	Every 10 years	Every 3 years (or every 5 years + yearly FIT)	Minimum recommended method	yearly	yearly	-

ACG: American College of Gastroenterology, ACS: American Cancer Society, ACP: American College of Physicians, ASGE: American Society for Gastrointestinal Endoscopy, MSTF: U.S. Multi-Society Task Force, USPSTF: U.S. Preventive Services Task Force, CAG: Canadian Association of Gastroenterology, CTFPHC: Canadian Task Force on Preventive Health Care, CEWG: Cancer Expert Working Group

**Table 5: Summary of colorectal cancer’s clinical guidelines for people with average risk in Isfahan province**

Recommendation	Level of agreement	Level of Evidence
What solutions are recommended for primary prevention of CRC? For primary prevention of CRC increase in dietary fiber, red meat and processed food intake reduction, calcium, vitamin D and B6 consumption, physical activity, maintaining healthy weight, avoiding smoking and drinking alcohol is recommended.	Strong	Moderate
How much of red meet intake increases CRC risk? Consuming red meat for more than 200 gr per week (average of daily 30 gr) accelerates the colorectal cancer risk	Strong	Low
How many minutes of physical exercise in a week reduces the CRC risk? Activities of more than 150 minutes per week (indoor/outdoor physical activity) result in protection against CRC	Strong	Moderate
How much of daily alcohol increases the risk of CRC? Drinking more than 1 standard dose during per (10 grams daily) increases the risk of colorectal cancer.	Strong	Moderate
What is the starting and ending age of colorectal screening in those with average risk? CRC screening starting age in people with average risk is from 50 years old and in diabetic or overweight people are 45.	Strong	Moderate
Ending age of CRC screening in people with average risk is 75.	Strong	Moderate
In people between 75-85 years, for deciding CRC screening health condition and patient’s preference is considered	Strong	Very Low
CRC screening in ages of more than 85 in those with average risk is not recommended.	Strong	Very Low
What is colonoscopy’s role in colorectal cancer? In screening people with average risk for CRC who use personal resources and personally pay all the costs, colonoscopy is recommended as the first choice to be done every 10 years	Strong	Low
In case of negative colonoscopy, we recommend FIT test to prevention of interval cancer every 5 years.	Strong	Low
What is flexible sigmoidoscopy’s role in colorectal cancer screening? Flexible sigmoidoscopy every 5 years is not recommended for colorectal cancer screening.	Strong	Moderate
What is the part that CT-Colonography plays in colorectal cancer screening? In CRC screening in people with average risk, CT-Colonography is not recommended as the first choice except for specific situations and based on patient’s preference.	Strong	Low
What is FIT’s role in colorectal cancer screening? In screening of people with average risk of CRC, FIT is suggested to be done every 2 years as a first-choice method test for those who use public resources and do not pay for this service personally.	Conditional	Low
If a person refuses doing colonoscopy the best replacement would be FIT which should be done every 2 years	Conditional	Low
In condition of positive FIT, repeating the test is not recommended at all.	Strong	High
In condition of positive FIT, for three months after report colonoscopy should be done.	Strong	High
In condition of positive FIT if the colonoscopy is normal, for the next 2 years FIT should be repeated. If repeated FIT is negative too, it should be repeated for the next 6 years and then we will go back to the normal 2-year process.	Strong	Low
In condition of positive FIT if the colonoscopy is normal, history about upper gastrointestinal tract must be taken and endoscopy should be performed if necessary.	Strong	Moderate
What is stool guaiac test’s (g-FOBT) role in colorectal cancer screening? In screening individuals with average risk for CRC, g-FOBT is not recommended as the first method of choice	Strong	Low
Repeating positive guaiac test is not recommended and if positive, colonoscopy is suggested.	Strong	Moderate
What is the role of fecal DNA test in colorectal cancer’s screening? Fecal DNA test is not recommended in screening of those with average risk for CRC.	Strong	Moderate

ACS states that the burden of CRC disease among different racial groups varies and the greatest incidence and mortality is in African-Americans, Native Americans, and Alaska Natives. The recent growth in CRC incidence in younger people, caused ACS to pass a qualified recommendation that screening began by 45 and strongly recommends to start screening at 50. ACS recommends doctors make the decision of CRC screening for people between 76 to 85 based on patients’ priorities, life expectancy, health condition, and past screening history, and also to prohibit people older than 85 from proceeding the CRC screening.<sup>[1,30]</sup>

Saudi Arabia’s guideline recommends beginning screening at 45 and ending it at 70 for there is increased risk and side effects. Undoubtedly it is to be considered that some people older than 70 and more might benefit from screening in conditions of health, without comorbidity with a life expectancy of more than 10 years.<sup>[34]</sup> Based on the CTFPHC guideline, there is a weak recommendation to screening at 50 to 59 and a strong recommendation to screening at 60 to 74, and after 75 and more is being said not to be needed.<sup>[9]</sup> ACP, CAG, Australia, and USPSTF recommend that considering significant efficiency and low risks, screening

starts at 50 and continues till 75.<sup>[3,4,6,11,19]</sup> CAG and USPSTF do not recommend that for the condition that colorectal adenomas increase by age, low efficiency and increasing screening risks between 75 and 85 and more than that; still, it is possible that according to person's health condition a situation happens in which screening be sensible. ACP indicates that individuals of more than 75 who have negative results or regular screening and adults who have 10 or less life expectancy do not need screening, people who lack CRC screening history might benefit from after 75 screening.<sup>[4]</sup>

## 7. What is colonoscopy's role in colorectal cancer?

### Recommendation:

- a- In screening people with average risk for CRC who use personal resources and personally pay all the costs, colonoscopy is recommended as the first choice to be done every 10 years
- b- In case of negative colonoscopy, we recommend the FIT test after 5 years for interval cancer prevention.
- c- If a person refuses to do a colonoscopy the best replacement is FIT (fecal immunochemical test) which should be done once every two years.

### Evidence:

Colonoscopy is the most preferred CRC screening method in America while in European countries is less in use.<sup>[30,31,33]</sup> Colonoscopy allows for a direct visual examination of the colon and diagnosis, biopsy, and removal of the polyp is done at the same session. For most of the patients who have had positive results in non-colonoscopy CRC screening examination, colonoscopy is also utilized. This method has the longest rescreening interval (10 years) among screening methods in patients with average risk or normal results.<sup>[1,5]</sup> If CRC is diagnosed in colonoscopy, considering the number and size of adenomas monitoring will be done every 3-5 years.<sup>[6]</sup>

Colonoscopy is an invasive method that needs the patient's bowel preparation and needs sedatives.<sup>[4]</sup> similar to other screening methods, colonoscopy has advantages and disadvantages which might harm the person. Its advantage is that it can take out small polyps that can be pre-cancerous. Moreover, detecting small polyps which have a low risk for developing into malignancy is highly possible in colonoscopy. Taking out these polyps which by itself sounds unnecessary, imposes the risks of polypectomy complications to patients and shortens time periods between monitoring and surveillance.

Colonoscopy might cause complications such as perforation, bleeding, severe abdominal pain and cardiopulmonary complications, sedation, and even death; especially if the patient is elderly or polypectomy is done by colonoscopy, however, these complications are rare and for example, perforation risk is 4 in every 10,000 colonoscopies and bleeding risk is 8 in every 10,000 colonoscopies.<sup>[1,5,6,9,11,31]</sup>

In adenomatous polyps particularly if they're placed in the proximal colon or if the patient's high-risk or if it is flat polyp (sessile adenoma), the risk of the mentioned complications is much higher. Additionally, the colonoscopy's quality is also important for it could cause interval cancer (which means that patient could get cancer before the next colonoscopy). Low-quality colonoscopy is defined by low adenoma detection rate which is connected with interval CRC and death by CRC.<sup>[30]</sup> Endoscopist skill, genetics, hereditary gastrointestinal neoplasm, old age, inflammatory bowel disease, and diverticular disease, and sessile serrated adenoma, forgotten lesions, or their incomplete resection are impactful on interval cancer creation.<sup>[35,36]</sup>

In ACS, ACG, and MSTF two methods used to screen CRC are colonoscopy and FIT. That is while colonoscopy is primarily suggested but if the patient is not willing or unavailable FIT will be done. Another criterion in choosing the screening method is a high prevalence of CRC in public; if the CRC prevalence is high, colonoscopy is recommended and if not FIT can be efficient.<sup>[1,31,33]</sup> ASGE, CEWG, and Saudi recommend colonoscopy as the first choice for CRC screening and to be continued every ten years.<sup>[3,5,34,37]</sup>

Meanwhile, CTFPHC, CAG, and Australia do not recommend colonoscopy for primary CRC screening. There is not enough RCT evidence to confirm colonoscopy's efficiencies, benefits, and risks in reducing the incidence and death of CRC. The waiting list for colonoscopies in Canada is long and has increased over years. In addition to that, colonoscopy requires more developed skills than sigmoidoscopy, bowel preparation diet, higher costs, more human resources, require sedation, and it can lead to more complications such as bleeding, perforation, and even death.<sup>[9,11,19]</sup> For individuals with average risk who have negative colonoscopy results for positive FOBT, CAG indicates that there is no need for colorectal cancer screening for the next ten years unless new intestinal symptoms develop. Also in each negative colonoscopy and positive FOBT upper endoscopy is not necessary the decision to whether perform upper endoscopy should be based on history and patient's results.<sup>[11]</sup>

## 8. What is flexible sigmoidoscopy's role in colorectal cancer screening?

### Recommendation:

Flexible sigmoidoscopy every 5 years is not recommended for colorectal cancer screening.

### Evidence:

Prior to the year 2000, sigmoidoscopy had been the main method for CRC screening, however today it is replaced by colonoscopy since it only visualizes the rectum and



one-third of the distal colon and needs shorter periods.<sup>[1]</sup> Flexible sigmoidoscopy is an invasive method that requires bowel preparation and unlike colonoscopy, it does not require sedatives. If a polyp or tumoral lesion is seen then a colonoscopy should be performed so that the entire colon is examined.<sup>[4,31]</sup> Enough evidence indicates that serious complications occur in 3.4 persons in every 10000 sigmoidoscopies performed.<sup>[6]</sup> England's 17-year-old studies demonstrate that sigmoidoscopy has decreased CRC incidence by 26% and its mortality rate by 30%.<sup>[1]</sup>

MSTF, CAG, and CTFPHC recommend flexible sigmoidoscopy for CRC screening for individuals with average risk to be performed every 10-years<sup>[9,11,31]</sup>; however, ACS and CEWG suggest this be done every 5 years.<sup>[1,3]</sup> Saudi Arabia's guideline recommends sigmoidoscopy every 3 years, for it is more affordable and has fewer complications than colonoscopy. This is due to the fact that in FS only tumors and polyps of the left colon are examined, it is recommended that FS be done every 5 years accompanied by yearly FIT. ASGE states that it can be taken into consideration to do a mixture of every 5 years sigmoidoscopy with yearly FOBT, in a way that FOBT test is done first and if positive, colonoscopy shall be done directly.<sup>[5]</sup> Australia does not recommend performing flexible sigmoidoscopy in CRC screening for people with average risk.<sup>[19]</sup>

#### 9. What is the part that CT-Colonography plays in colorectal cancer screening?

##### Recommendation:

In CRC screening in people with average risk, CT-Colonography is not recommended as the first choice except for specific situations and based on patient's preference.

##### Evidence:

Another method is CT-Colonography which requires colon preparation but not sedatives.<sup>[4]</sup> In such a way that a small flexible tube enters the rectum and is inflated then the patient will get in the CT scan. This method is less invasive than colonoscopy and sigmoidoscopy and will take about 10-15 minutes. If an adenoma bigger than 5 mm or other uncommon results are detected, the patient will be directed to colonoscopy preferably the same day. Studies have shown that CTC's effectiveness in cancer diagnosis and advanced adenomas is similar to colonoscopy but has less sensitivity towards smaller adenomas. Its disadvantages include exposure to radiation and also with a lesion detected there cannot be a treatment. More serious complications though rare, such as perforation, are estimated to happen in less than 2 persons in 10000. Detection of results outside the colon which is more common can be beneficial or not.<sup>[1,4]</sup> In more than 16% of individuals whose first CT-Colonography indicates abnormalities outside the colon, further examinations are required.

ACP, CAG, ADGE, USPSTF, and CTFPHC indicate that since there is not enough evidence regarding complications of exposure to radiation and increase in the use of radiations in diagnostic methods and disease surveillance, shorter time periods of follow-ups compared to colonoscopy (5 years versus 10 years), costs, requiring bowel preparation, abnormal findings outside the colon and more false-positive results, it is not recommended to use CT-Colonography.<sup>[4,6,9,11]</sup> Saudi Arabia's guideline for screening recommends CTC as the minimum method to be used and prioritizes colonoscopy to CTC unless the individual chooses non-invasive methods which in this case CTC might be appropriate.<sup>[34]</sup>

#### 10. What is FIT's role in colorectal cancer screening?

##### Recommendation:

- In the screening of people with an average risk of CRC, FIT is suggested to be done every 2 years as a first-choice method test for those who use public resources and do not pay for this service personally.
- If a person refuses a colonoscopy, the best replacement would be FIT which should be done every 2 years.
- In the condition of positive FIT, for three months after report colonoscopy should be done
- In the condition of negative FIT, for the next 6 years, FIT should be repeated and then we will go back to the normal 2-year process.

##### Evidence:

FIT specifically uses antibodies against human Hemoglobin in fecal that could discover bleeding caused by advanced adenoma or cancer. Since globulin is destroyed by gastrointestinal enzymes in the upper digestive system, FIT being positive is not affected by upper GI bleeding. Since antibody is specified for human hemoglobin, FIT is not vulnerable to drug intervention, animal hemoglobin (red meat), or peroxidase found in food, so they do not need limitations of diet recommended with g-FOBT.<sup>[1]</sup>

Repeating FIT after one test leads to false negatives since tumors and colon adenomas can bleed intermittently or in a small amount in a way that the second fecal sample can result in a false negative.<sup>[19]</sup> In case of positive FIT, it is necessary to perform a colonoscopy in three months.<sup>[4,19]</sup> FIT's sensitivity to diagnose CRC is between 73-88% and is its specificity which varies between 91-96%.<sup>[4]</sup>

CTFPHC, ACP, and Australia recommend 2-year screening with the FIT, while ACS, ACG, CAG, USPSTF, MSTF, ASGE, and Saudi recommend yearly screening and CEWG recommends yearly or every 2-year.<sup>[1,3-6,9,11,19,31-34]</sup> CTFPHC guideline and CAG suggest FIT and high-sensitivity-g-FOBT as the primary screening method for people with average risk. Limited access to flexible sigmoidoscopy can lead to the surveillance method in most Canadians being FIT or g-FOBT. It is to be noted that FIT is preferred



to g-FOBT for reasons such as patient's commitment, higher sensitivity, no need for diet limitations, easy to perform, requiring a smaller amount of fecal sample, and costs.<sup>[9,11]</sup> Saudi Arabia's guideline prefers FIT and g-FOBT to sigmoidoscopy because of affordability and merely examining the right colon.<sup>[34]</sup> ASGE suggests that the yearly FOBT (immunochemical and guaiac test) should be tested from each of the 3 consecutive fecal samples.<sup>[5]</sup>

### 11. What is the stool guaiac test's (g-FOBT) role in colorectal cancer screening?

#### Recommendation:

- In screening individuals with average risk for CRC, g-FOBT is not recommended as the first method of choice
- Repeating positive guaiac test is not recommended and if positive, colonoscopy is suggested.

#### Evidence:

The first tests which had been proven to be effective on CRC screening were stool guaiac tests (g-FOBT). These tests were built on chemical reactions which detect blood in fecal samples. 3 samples are taken in each measurement of this test which should be repeated yearly. Its false positive result is induced by consuming NSAID and red meat which should have been cut from three days earlier. Taking vitamin C and drinking beverages containing citrate is better to be avoided for it could cause false-negative results.<sup>[1]</sup> Guaiac tests with low sensitivity have been put aside in screening plans and been replaced by HS-g-FOBT and FIT.<sup>[1,6]</sup> Using g-FOBT has reduced mortality by 32% and caused a decrease of 20% in CRC incidence by discovering premalignancy large tumors in 30 years.<sup>[30]</sup> HS-g-FOBT's sensitivity in CRC diagnosis is 62-79% and its specificity varies in the range of 87-96%. The amount of false-positive results is 12.2 in every 1000 screenings and false-negative results are 5.5 in each 1000 screening tests.<sup>[4]</sup>

USPSTF, ASGE, ACS, and Saudi recommend yearly g-FOBT however ACP and CTFPHC recommend it to be done every two years.<sup>[1,4-6,9,34]</sup> Likewise, CAG and CEWG suggest two-year or yearly screening for CRC screening according to existing resources. G-FOBT's yearly screening results increase the number of years of life obtained in comparison to 2-year screening; nonetheless, required resources for yearly surveillance are much greater than for 2-year screening.<sup>[3,11]</sup> ACG has excluded g-FOBT and displaced it with other tests like the FIT, Hemoccult Sensa, and fecal DNA test.<sup>[1,33]</sup>

### 12. What is the role of fecal DNA tests in colorectal cancer screening?

#### Recommendation:

The fecal DNA test is not recommended in the screening of those with an average risk for CRC.

#### Evidence:

This test is called "multi-targeted" for it not only detects blood in fecal but it can also discover numerous mutations in the DNA of cells that have shed from the surface of tumoral lesion or advanced adenoma into the fecal. Surely there are several false positives, which from time to time could end in an unnecessary colonoscopy.<sup>[1]</sup> From the advantages of a fecal DNA test, can be mentioned its non-invasive nature, being accessible regardless of geographical location, high sensitivity in proximal lesions diagnosis, and its ability to screen all of the digestive systems.<sup>[11]</sup> A positive fecal DNA test in spite of negative results in colonoscopy might be caused by primary stages of neoplastic changes in the colon that are not yet visible or it could be a result of malignancy in the upper parts of the digestive system and not integrally colon. Patients with positive fecal DNA results and negative results in colonoscopy follow-ups could need invasive short-term follow-ups given a lot of concerns related to incorrect and false-positive results. The fecal DNA test's sensitivity for CRC surveillance is 92% and its specificity is 84%.<sup>[4]</sup>

CAG, ACP, ASGE, CTFPHC, Australia, and USPSTF do not recommend fecal DNA test for CRC screening.<sup>[4-6,9,11,19]</sup> USPSTF infers that currently there's not enough evidence to evaluate sensitivity and specificity of fecal DNA test for bowel's neoplasia and so an equivalent of advantages and disadvantages cannot be reached consequently, using it is not suggested.<sup>[5,6]</sup> For the uncertainty of time interval between screenings, the method of screening among patients with a positive fecal DNA test and negative colonoscopy, bigger costs compared to FOBT, and lack of evidence concerning functionality and efficiency of the fecal DNA test, CAG does not recommend this test.<sup>[11]</sup> MSTF suggests doing a combination of yearly FIT and fecal DNA tests every three years<sup>[31]</sup> and moreover, ACG infers yearly Hemoccult Sensa and fecal DNA tests for every three years.<sup>[33]</sup>

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