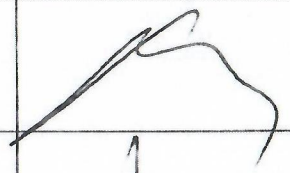
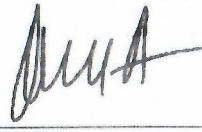
COLORECTAL CANCER SCREENING AND MANAGEMENT PROTOCOL

No.	Name and surname	Institution	Signature
1	Prof. Dr. Tamás Molnár	*University of Szeged, Department of Oncotherapy*	
2	Prof. Dr. Roxana Sirli	*Victor Babes" University of Medicine and Pharmacy Timisoara*	
3	Prof. Dr. Popescu Alina	*Victor Babes" University of Medicine and Pharmacy Timisoara*	
4	Prof. Dr. Sporea Ioan	*Victor Babes" University of Medicine and Pharmacy Timisoara*	
5	Dr. Musta Ioan	*Emergency Municipal Clinical Hospital Timisoara*	

"New approaches to prevention and treatment of common cancers"

Acronym 4C: Cure for Cervical and Colorectal Cancer

eMS Code ROHU 397

COLORECTAL CANCER SCREENING AND MANAGEMENT PROTOCOL

Autori: Prof. Dr. Ioan Sporea, Prof. Dr. Tamas Molnar, Prof. Dr. Roxana Șirli, Prof. Dr. Alina Popescu, Dr. Ioan Musta

Colaboratori: Dr. Bogdan Miuțescu, Dr. Felix Bende, Dr. Tudor Moga, Dr. Melania Ardelean

1. Epidemiology

Colorectal cancer (CRC) remains the third most commonly diagnosed cancer and the second leading cause of cancer death globally due to the unfulfilled screening programs, therapeutic strategy, and increasing incidence rates(1). In 2020, CRC accounts for 10% of global cancer incidence and 9.4% of cancer deaths, just under lung cancer that comprises 18% of deaths. The global number of newly diagnosed CRC cases is predicted to reach 3.2 million in 2040, having in mind the growth of the aging population and human expansion. There is an increasing body of evidence regarding the implications of western diet and lifestyle in the increased incidence of colorectal cancer (2).

Public health systems are currently facing many challenges in regards to CRC therapy, among which the financial burden is not negligible. This aspect is further augmented by the rise in CRC case numbers per total and in younger demographics, even though therapy outcomes are generally positive(3). There are, however, countries in which a declined or stabilized CRC incidence has been observed, those generally being countries with very high standards of life(4). These standards include active screening programs for the general population implemented approximately a decade ago, as well as a healthier lifestyle being had by individuals. Even in these countries there are marked inconsistencies regarding survival rates that can partially be explained by the stages in which CRC is diagnosed(5).

2. Risk Factors

CRC is considered to be one of the major cancers for which modifiable causes may be identified and prevented. The disease is associated with a wide range of cultural and social factors (6). CRC can be prevented through minimizing the exposure of an individual to these risk factors by living a healthy lifestyle. This includes avoiding the use of tobacco and alcohol, maintaining a healthy body weight, physical activities, a diet low in red and processed meats and high in fiber. Environmental and genetic factors can increase the likelihood of developing CRC (7). Although inherited susceptibility results in the most striking increases in risk, the majority of CRCs are sporadic rather than familial. These risk factors can be separated into those that confer a sufficiently high risk to alter recommendations for CRC screening, factors that may alter screening recommendations, and those that do not alter screening recommendations because they are thought to confer a small or uncertain magnitude of risk (8).

Factors that currently influence screening recommendations are for members of families with hereditary colon cancer syndromes, on the basis of personal or family history of CRC or adenomas in patients with inflammatory bowel disease, and in those who have been exposed to abdominal radiation therapy (9).

a. Colorectal cancer in young adults

Colorectal cancer (CRC) is the most common gastrointestinal neoplasia that affects usually people over the 5th decade of life. Screening for CRC is not usually indicated before 45-50 years old when there is a low risk. The onset of CRC at younger ages raises some issues regarding the emotional impact at diagnosis, the disease behavior and the possibility to be associated with genetic diseases (10).

The definition of age to be considered young is controversial. Most published studies and meta-analyses consider the age below 40 years as a young age for a CRC onset. The incidence of CRC diagnosed before 40 years of age varies from 0.8% to 5%, but recently, a greater incidence of young age CRC has been reported. While in this group of patients proper investigations to discharge hereditary types of CRC is crucial, CRC diagnosis in young people is difficult, both patients and doctors underestimate symptoms and postpone diagnosis and therapy (11)(12) .

Young patients have been considered to have a more aggressive biological behavior and a worst prognosis. A greater prevalence of mucinous and less differentiated tumors have been diagnosed in young populations and advanced stage III and IV were found more predominant. Given these aspects, there have been some discussions if CRC screening should start at the age of 40 years old (13)(14).

Identification of high-risk young people for screening and recognition of alert symptoms is a real medical problem. Some symptoms like persistent rectal bleeding, abdominal pain, or anemia should require endoscopic work-ups even in average-risk

young people and the main challenge in the young population is to distinguish sporadic from the hereditary forms of CRC.

Genetical aspects are very important in young patients with CRC. While 2%-5% of CRC are caused by highly penetrant genes, 15%-20% of CRC in the young age population are hereditary and a family history of CRC in almost one-fifth of hereditary syndromes patients is not recognized (15)(16).

How can we identify young patients with CRC or at risk of developing CRC? We need to identify and screen young patients with a high risk of developing CRC and to perform an endoscopic evaluation in symptomatic young patients with persistent rectal bleeding, abdominal pain or anemia.

Enhanced screening for CRC (10)(17) in a young population is recommended when we find a family history of the number of first-degree relatives (FDR) diagnosed with any of the following:

•Colorectal cancer (CRC)
•Documented advanced polyp with ANY of the following:
- Advanced adenoma
  - -Adenoma size ≥1 cm
  - -Adenoma with high-grade dysplasia
  - -Adenoma with villous elements
- Advanced serrated lesion
  - -Sessile serrated polyp (SSP) ≥1 cm
  - -Traditional serrated adenoma ≥1 cm
  - -SSP with cytologic dysplasia

The recommended age when to begin screening is 40 years or 10 years before the Youngest FDR's diagnosis and colonoscopy for screening should be repeated at five-year intervals in people with a family history of CRC. Also, the screening should be stopped at the age of 79 among persons with one FDR diagnosed after age 50, and 85 for persons with two or more FDRs diagnosed before age 40(10)(17).

In conclusion, CRC in young adults is usually diagnosed later and potentially associated with a worst prognosis and the current screening programs could miss the diagnosis of sporadic CRC in young people. Also, the genetic profile may affect CRC incidence and outcomes of treatments in different age cohorts.

b. Lynch Syndrome and the risk for colorectal cancer

Lynch syndrome (LS) is linked with a high risk of gastro-intestinal, gynecological and different other cancers. Inherited mutations affecting the DNA mismatch repair (MMR) genes, MSH2, MLH1, PMS2 or MSH6, or a deletion in the EPCAM gene can appear and will lead to methylation of the adjacent MSH2 promoter. It is an under-

diagnosed condition accounting for about 1–3% of colorectal cancers (CRCs) in the general population [1]. Currently, most patients with LS have been diagnosed following investigation due to their family or personal histories of multiple and/or early-onset cancers.

Patients diagnosed with MLH1, MSH2, MSH6 or PMS2 mutations, need special follow up programs in order to overcome cancer risk so that they can be offered appropriately targeted surveillance and treatment, however the published risk estimates are extremely variable. In clinical practice, Amsterdam I or Amsterdam II criteria and Bethesda guidelines or simply age at cancer diagnosis are used in order to correctly diagnose LS. Initial assessments of the cumulative risk at 70 years for CRC in MLH1 or MSH2 mutation carriers varies from 22% to 74%. MSH6 mutation carriers have lower penetrance and different patterns of expression and are thought to have an increased risk of endometrial cancer (18).

European society of gastrointestinal endoscopy, strongly recommends starting colonoscopy surveillance in dedicated units that practice monitoring of compliance and endoscopic performance measures, at the age of 25 years for MLH1 and MSH2 mutation carriers and at the age of 35 years for MSH6 and PMS2 mutation carriers. The routine use of high-definition endoscopy systems and chromoendoscopy (where high-def. endoscopy is not available) in individuals with Lynch syndrome is also recommended in LS patients, however practical consideration must be tailored keeping in mind the costs and training. The familial risk of colorectal cancer is defined as the presence of at least two first-degree relatives with colorectal cancer or at least one first-degree relative with colorectal cancer before the age of 50 years. In the situation of first-degree relatives of colorectal cancer patients, colonoscopy surveillance, preferable with high-definition endoscopy, is strongly recommended (19).

3. Colorectal cancer diagnosis

    a. Colonoscopy – diagnostic and screening method for colorectal cancer

Colonoscopy is the definitive test for the detection of precancerous adenomas and CRC with high sensitivity and acceptable specificity and allows for detection and biopsy of polyps and CRC and removal of precancerous polyps, all during one test.

Disadvantages of colonoscopy as a screening test include the inconvenience of bowel preparation and when conscious sedation is used, a recovery period is needed, and there is a potential for sedation-related complications. Also, some medications need to be temporarily held for a colonoscopy (anticoagulants).

Colonoscopy procedural risks include the possibility of perforation, major bleeding, and infection. The risk of perforation is increased by comorbidities,

increasing age, polypectomy, and less-experienced endoscopists. Also, there is a potential risk for dehydration or electrolyte disturbances resulting from bowel preparation. The availability of colonoscopy may be limited by the need for specialized equipment and trained endoscopists and by the cost.

The evidence of the effectiveness of colonoscopy is based on observational studies and indirect comparison with studies of other screening strategies. Screening colonoscopy significantly reduces deaths due to CRC. In a meta-analysis of six observational studies, screening with colonoscopy was associated with a 40 to 60 percent lower incidence and risk of death from CRC compared with screening with sigmoidoscopy(20)(21)(22).

Observational studies suggest that screening colonoscopy reduces CRC incidence. In a randomized trial of 94,959 people aged 55 to 64 years at average risk for CRC who had colonoscopy screening or no screening 40% had screening colonoscopy and 1.5% were diagnosed with CRC, 31% had adenomas, 10% had high-risk adenomas. For adenomatous polyps 6 mm or larger, a systematic review reported the sensitivity of colonoscopy for detection varied from 75 percent to 93 percent. Another systematic review of studies of tandem colonoscopies among 465 patients found an overall miss rate for polyps of any size to be 22 percent, with a miss rate of 2 percent for adenomas ≥10 mm, 13 percent for adenomas 5 to 10 mm, and 25 percent for adenomas <5 mm (23)(24)(25).

While colonoscopy is considered the gold standard test, it does not detect all advanced adenomas and CRC. Some studies suggested that colonoscopy is less effective in detecting and also preventing death from right-sided compared with left-sided lesions. (incomplete colonoscopic examination, biologic differences in right-sided tumors, flatter or rapidly growing neoplasms). Flat or depressed lesions can be difficult to detect even by colonoscopy (26)(27).

Available studies suggest that a 10-year interval is an acceptable strategy if the screening examination is negative and of adequate quality. In a large cohort study in Canada, the incidence of CRC following a negative colonoscopy remained reduced beyond 10 years. Other studies suggest that the duration of decreased risk for right-sided CRC may be shorter (seven years), or the risk of right-sided adenomas (28)(29).

4. Staging in colorectal cancer and its implication in disease management

Globally, CRC is the fourth most common cancer in men and the third most common in women, with mortality paralleling incidence. Despite evidence that five year survival is 90% when CRC is diagnosed at an early stage, less than 40% of cases are diagnosed when the cancer is still localized(30).

The natural history and staging of CRCs begins as intramucosal epithelial lesions, usually arising in adenomatous polyps or glands. As CRC grow they become invasive, penetrating the muscularis mucosae of the bowel and invading lymphatic and vascular channels to involve regional lymph nodes, adjacent structures and distant sites. Most CRCs have long grow rates, with long periods of silent growth before producing bowel symptoms. The mean doubling time of colon cancers determined radiologically in one study was 620 days. Comparative lesion sequencing using modern molecular tehniques combined with clinical observation suggests that it can take approximately 17 years of a large benign tumor to evolve to advance cancer, but less than 2 years to aquire the ability to metastasize(31).

Cancers of the rectum advance locally by progressive penetration of the bowel wall. Extension of the primary tumor intramurally and parallel to the long axis most often is limited, and lymphatic and hematogenous spread is unusual before penetration of the muscularis mucosae. Because rectum is relatively imobile and lacks a serosal covering, rectal cancers tend to spread contiguously to progressively involve local structures. Transrectal ultrasonography is useful in staging depth of rectal cancers.

CRCs can invade transmurally and involve regional lymphatics and the distant nodes. The liver is the most common site of hematogenous spread from colon tumors via the portal venous system. Pulmonary metastases result in general, from hepatic metastases.

Cuthbert Dukes proposed a staging classification in 1929, which has since been modified many times, in order to increase the prognostic value for both rectum and colon cancers. The most commonly modification of the Dukes system is that of Astler and Coller- the classification uses the following:

•A- tumors limited to the mucosa

•B1- tumors extending into, but not through the muscularis propria

•B2- tumors penetrating the muscularis propris, no lymph nodes involvement

•C- tumors with regional lymph nodes involvement

•C1 (Gastrointestinal Tumor Study Group)- in which 1-4 regional lymph nodes contain tumor

•C2 >4 lymph nodes contain tumor

•D- distant metastases

In an attempt to provide a uniform and orderly classification of the CRSs, the American Joint Committee on Cancer (AJCC)has introduced the tumor-node-metastases (TNM) classification for CRCs. This system classifies the extent of the

primary tumor (T), the status of regional lymph nodes (N) and the presence or absence of distant metastases (M). Cases are divided into five stages (0 to IV). Those five stages have become important in uniformly randomizing patients for therapeutic trials.

Duration of symptoms might not correlate directly with prognosis and some presenting symptoms, such as rectal bleeding, may be associated with better rates of survival. Bowel obstruction or perforation has been linked with poor prognosis.

The location of the primary tumor can influence outcome. Disease free survival at three years appears to be 2% to 14% higher after surgery for tumors of the left than on the right colon. Some studies suggest a survival advantage for patients with colon compared with rectal cancers.

The prognosis is worse in youngers than in older patients. Poor prognosis may be related to a higher percentage of more-advanced cancers and mucinous adenocarcinomas in these young patients (32).

Outcome is also related to preoperative serum CEA levels. Tumor recurrence is higher and the estimated mean time to recurrence is shorter, in patients with Dukes B and C cancers who have high preoperative CEA levels. The preoperative CEA level may be of prognostic value only in patients with Dukes C CRCs, with more than four lymph nodes involved, but not in patients with Dukes A and B lesions, or Dukes C with less than 4 lymph nodes involved (33).

Approximately one fourth of the patients with CRCs exhibit clinical evidence of hematogenous spread when seen initially, and one half of patients with CRCs eventually develop metastases to a distant site, usually the liver; such metastases show a poor prognosis at all times in the clinical course. The most important determinant of survival time for patients who present with liver metastases is the extent of hepatic involvement by tumor (34).

Still, rapid growth of knowledge about molecular and biological characteristics of CRCs has provided useful insights into the pathogenesis of these neoplasm and cancer in general. New insights also have been gained in regarding to primary prevention.

Rapidly evolving knowledge of CRC pathogenesis, especially in high-risk groups, is allowing the development of new tools to identify those who will benefit most from cancer surveillance and from adjuvant therapy following potentially curative treatment.

5. Colorectal cancer screening and surveillance

When referring to colorectal cancer (CRC), multiple guidelines are available that provide guidance to clinicians who counsel and refer patients to screening and the vast majority of them use colonoscopy or faecal tests as their first recommendation as a screening tool in average risk adults between 50 and 75 years. Guidelines have variable recommendations regarding the use of colonoscopy, optimal test to be first recommended, age interval for screening and screening interval (35).There are several guidelines that have been published or updated in the past few years.

In North America, in May 2018, the American Cancer Society (ACS) released updated colorectal cancer screening guidelines(36). One of the most important changes to the previous published guideline is the age at which screening should start. The recently published ACS guideline recommends that screening should start at the age of 45 years in average risk adults and regular screening should pe performed, according to patients' preference, with high sensitivity stool based or visual examinations(36). Previously, the ACS recommended that this population start CRC screening at age 50 years(37). Patients that use for screening other tests than colonoscopy and have an abnormal test result, should be scheduled for a colonoscopy. There is evidence that patients will have a preference for one type of screening test over others if provided sufficient information regarding these test attributes (38).

The American College of Gastroenterology (ACG) recommends that colorectal cancer screening should start at the age of 50 and colonoscopy should be performed at 10 years interval (39).

The US Preventative Services Task Force (USPSTF) recommends screening in average-risk individuals aged 50 to 75 years, with a decreased benefit after the age of 75, especially in adults with screening history. Nevertheless, a healthy person aged 76 to 85 without previous screening is very likely to benefit from screening. It is also recommended that patients aged 76 through 85 years to continue their screening if their overall health status indicates so. These recommendations are currently in the process of being reviewed and may be updated (40).

In 2012, The European Colorectal Cancer Screening Guidelines Working Group recommends screening individuals between ages 50 and 74. Authors conclude that current evidence is in favor of a 10 year surveillance period when colonoscopy is being used as a screening tool. Both faecal stool tests, gFOBT and FIT (fecal immunochemical test) are considered to be effective, but FIT is recommended to be superior in terms of specificity and sensitivity. The European Colorectal Cancer Screening Guidelines Working Group does not recommend FOBT with flexible sigmoidoscopy, virtual colonoscopy, faecal DNA testing or capsule endoscopy (41).

In 2014, The German Guideline Program in Oncology (GGPO) recommended to start screening in average-risk adults at the age of 50 years old without establishing an upper age screening limit. The authors concluded that this is due to a lack of studies concerning benefit in screening for CRC older individuals. They say that colonoscopy is recommended as "gold standard" (every 10 years) and CT and MR-colonography should be used in patients with incomplete colonoscopy, especially if they are requesting a complete colonic examination (42).

Like many other guidelines, the updated Asia Pacific Consensus Recommendations on CRC screening, published in 2015, mentions that screening

should be offered to average-risk adults between 50 and 75 years old. Colonoscopy is considered to be the gold standard and should be the preferred screening method among endoscopic examinations, but flexible sigmoidoscopy is also appropriate for screening. Stool based tests are recommended, but quantative FIT should be preferred over gFOBT (43).

Surveillance after colorectal cancer resection is recommended by multiple guidelines. Patients with colorectal cancer should undergo high-quality perioperative clearing with colonoscopy, either preoperatively or, in the case of obstructive colorectal cancer, within a 3-6–month interval after surgery. Patients who have undergone curative resection of either colon or rectal cancer should receive their first surveillance colonoscopy 1 year postoperatively (or 1 year after the clearing perioperative colonoscopy). Following the 1-year colonoscopy, the next colonoscopies should be 3 years and then 5 years, and thereafter at 5-year intervals until the benefits of continued surveillance are outweighed by decreased life expectancy. In the presence of neoplastic polyps during any colonoscopy, polyp surveillance intervals should be based on published recommendations. CT colonography is the best alternative to exclude synchronous neoplasms in those with obstructive colorectal cancer precluding complete colonoscopy. There is insufficient evidence to recommend routine use of FIT or fecal DNA surveillance following resection for colorectal cancer (44).

6. Inflammatory bowel diseases and colorectal cancer

Ulcerative colitis (UC) is a chronic inflammation of the colon with an unknown etiology. Inflammatory bowel disease (IBD) is associated with morbidity, mortality, and substantial costs to healthcare systems, therefore several studies have attempted to define the burden of the disease.

Colorectal cancer is the third most common cancer worldwide and accounts for 10-15% of all deaths in IBD [8]. IBD specific risk factors for CRC are ulcerative colitis and colon Crohn’s disease, longer duration of IBD (8 years or more after diagnosis), extensive colon inflammation and coexisting primary sclerosing cholangitis (PSC), while male gender, increasing age and positive family history to CRC are risk factors to sporadic CRC (45).

Colorectal cancer presented typically in the distal part of the colon by male ulcerative colitis patients with pancolitis or left-sided colitis with a long-standing disease course of IBD. The most common non-colorectal cancer malignancies were non-melanotic skin cancer, haematological cancer and lung cancer. Patients with non-colorectal cancer malignancies were typically female and older than colorectal cancer patients at the time of the diagnosis of malignancy with shorter disease-course of IBD and longer survival (46).

Previous research on UC and CRC has several limitations: most studies have assessed incident CRC leading to potential lead-time and surveillance biases (ie, repeat endoscopies and other investigations in patients with UC can identify cancers that would otherwise go

undetected for a longer time and result in biased estimates of relative risk for incident CRC compared with the general population). One way to avoid lead-time bias and to estimate the effect of surveillance would be to consider tumour stage, and another would be to specifically examine incidence-based CRC mortality (ie, CRC mortality restricted to CRC diagnosed after start of follow-up). However, there are insufficient data addressing whether mortality from CRC differs in patients with UC versus the general population, and whether any potential difference might be explained by tumour stage at diagnosis.Despite extensive endoscopy screening all over the world, patients with UC still have an increased risk of CRC mortality when taking tumour stage into account, indicating that, globally, current surveillance programmes could be improved (47).

Bibliography

1. Siegel RL, Miller KD, Jemal A. Cancer statistics, 2020. CA Cancer J Clin. 2020 Jan;70(1):7-30. doi: 10.3322/caac.21590. Epub 2020 Jan 8. PMID: 31912902.
2. Keum N, Giovannucci E. Global burden of colorectal cancer: emerging trends, risk factors and prevention strategies. Nat Rev Gastroenterol Hepatol. 2019 Dec;16(12):713-732. doi: 10.1038/s41575-019-0189-8. Epub 2019 Aug 27. PMID: 31455888.
3. Campos FG. World J Gastroenterol. Colorectal cancer in young adults: A difficult challenge. 2017;23(28):5041-5044. doi:10.3748/wjg.v23.i28.5041
4. Fidler MM, Bray F, Vaccarella S, Soerjomataram I. Assessing global transitions in human development and colorectal cancer incidence. Int J Cancer. 2017 Jun 15;140(12):2709-2715. doi: 10.1002/ijc.30686. Epub 2017 Mar 24. PMID: 28281292.
5. Allemani C, Matsuda T, Di Carlo V, Harewood R, Matz M, Nikšić M, Bonaventure A, Valkov M, Johnson CJ, Estève J, Ogunbiyi OJ, Azevedo E Silva G, Chen WQ, Eser S, Engholm G, Stiller CA, Monnereau A, Woods RR, Visser O, Lim GH, Aitken J, Weir HK, Coleman MP; CONCORD Working Group. Global surveillance of trends in cancer survival 2000-14 (CONCORD-3): analysis of individual records for 37 513 025 patients diagnosed with one of 18 cancers from 322 population-based registries in 71 countries. Lancet. 2018 Mar 17;391(10125):1023-1075. doi: 10.1016/S0140-6736(17)33326-3. Epub 2018 Jan 31. PMID: 29395269; PMCID: PMC5879496.
6. Bovell LC, Shanmugam C, Putcha BD, Katkoori VR, Zhang B, Bae S, Singh KP, Grizzle WE, Manne U. The prognostic value of microRNAs varies with patient race/ethnicity and stage of colorectal cancer. Clin Cancer Res. 2013 Jul 15;19(14):3955-65. doi: 10.1158/1078-0432.CCR-12-3302. Epub 2013 May 29. PMID: 23719259; PMCID: PMC3746330.
7. Fengju S, Guanglin W, Kexin C. Incidence of colon cancer in Tianjin, China, 1981-2000. Asia Pac J Public Health. 2005;17(1):22-5. doi: 10.1177/101053950501700106. PMID: 16044828.
8. Johnson IT, Lund EK. Review article: nutrition, obesity and colorectal cancer. Aliment Pharmacol Ther. 2007 Jul 15;26(2):161-81. doi: 10.1111/j.1365-2036.2007.03371.x. PMID: 17593063.
9. Nishihara R, Wu K, Lochhead P, Morikawa T, Liao X, Qian ZR, Inamura K, Kim SA, Kuchiba A, Yamauchi M, Imamura Y, Willett WC, Rosner BA, Fuchs CS, Giovannucci E, Ogino S, Chan AT. Long-term colorectal-cancer incidence and mortality after lower

endoscopy. N Engl J Med. 2013 Sep 19;369(12):1095-105. doi: 10.1056/NEJMoa1301969. PMID: 24047059; PMCID: PMC3840160.
10. Rex DK, Boland CR, Dominitz JA, Giardiello FM, Johnson DA, Kaltenbach T, Levin TR, Lieberman D, Robertson DJ. Colorectal Cancer Screening: Recommendations for Physicians and Patients from the U.S. Multi-Society Task Force on Colorectal Cancer. Am J Gastroenterol. 2017 Jul;112(7):1016-1030. doi: 10.1038/ajg.2017.174. Epub 2017 Jun 6. PMID: 28555630.
11. O'Connell JB, Maggard MA, Liu JH, Etzioni DA, Livingston EH, Ko CY. Do young colon cancer patients have worse outcomes? World J Surg. 2004 Jun;28(6):558-62. doi: 10.1007/s00268-004-7306-7. PMID: 15366745.
12. Fazeli MS, Adel MG, Lebaschi AH. Colorectal carcinoma: a retrospective, descriptive study of age, gender, subsite, stage, and differentiation in Iran from 1995 to 2001 as observed in Tehran University. Dis Colon Rectum. 2007 Jul;50(7):990-5. doi: 10.1007/s10350-007-0248-z. PMID: 17525859.
13. You YN, Xing Y, Feig BW, Chang GJ, Cormier JN. Young-onset colorectal cancer: is it time to pay attention? Arch Intern Med. 2012 Feb 13;172(3):287-9. doi: 10.1001/archinternmed.2011.602. Epub 2011 Dec 12. PMID: 22157065.
14. da Fonseca LM, da Luz MM, Lacerda-Filho A, Cabral MM, da Silva RG. Colorectal carcinoma in different age groups : a histopathological analysis. Int J Colorectal Dis. 2012 Feb;27(2):249-55. doi: 10.1007/s00384-011-1299-0. Epub 2011 Aug 16. PMID: 21845417.
15. Mork ME, You YN, Ying J, Bannon SA, Lynch PM, Rodriguez-Bigas MA, Vilar E. High Prevalence of Hereditary Cancer Syndromes in Adolescents and Young Adults With Colorectal Cancer. J Clin Oncol. 2015 Nov 1;33(31):3544-9. doi: 10.1200/JCO.2015.61.4503. Epub 2015 Jul 20. PMID: 26195711; PMCID: PMC4979241.
16. Chang DT, Pai RK, Rybicki LA, Dimaio MA, Limaye M, Jayachandran P, Koong AC, Kunz PA, Fisher GA, Ford JM, Welton M, Shelton A, Ma L, Arber DA, Pai RK. Clinicopathologic and molecular features of sporadic early-onset colorectal adenocarcinoma: an adenocarcinoma with frequent signet ring cell differentiation, rectal and sigmoid involvement, and adverse morphologic features. Mod Pathol. 2012 Aug;25(8):1128-39. doi: 10.1038/modpathol.2012.61. Epub 2012 Apr 6. PMID: 22481281.
17. Provenzale D, Gupta S, Ahnen DJ, Markowitz AJ, Chung DC, Mayer RJ, Regenbogen SE, Blanco AM, Bray T, Cooper G, Early DS, Ford JM, Giardiello FM, Grady W, Hall MJ, Halverson AL, Hamilton SR, Hampel H, Klapman JB, Larson DW, Lazenby AJ, Llor X, Lynch PM, Mikkelson J, Ness RM, Slavin TP, Sugandha S, Weiss JM, Dwyer MA, Ogba N. NCCN Guidelines Insights: Colorectal Cancer Screening, Version 1.2018. J Natl Compr Canc Netw. 2018 Aug;16(8):939-949. doi: 10.6004/jnccn.2018.0067. PMID: 30099370.
18. Møller P, Seppälä T, Bernstein I, Holinski-Feder E, Sala P, Evans DG, Lindblom A, Macrae F, Blanco I, Sijmons R, Jeffries J, Vasen H, Burn J, Nakken S, Hovig E, Rødland EA, Tharmaratnam K, de Vos Tot Nederveen Cappel WH, Hill J, Wijnen J, Green K, Lalloo F, Sunde L, Mints M, Bertario L, Pineda M, Navarro M, Morak M, Renkonen-Sinisalo L, Frayling IM, Plazzer JP, Pylvanainen K, Sampson JR, Capella G, Mecklin JP, Möslein G; Mallorca Group (http://mallorca-group.eu). Cancer incidence and survival in Lynch syndrome patients receiving colonoscopic and gynaecological surveillance: first report from the prospective Lynch syndrome

database. Gut. 2017 Mar;66(3):464-472. doi: 10.1136/gutjnl-2015-309675. Epub 2015 Dec 9. PMID: 26657901; PMCID: PMC5534760.
19. van Leerdam ME, Roos VH, van Hooft JE, Balaguer F, Dekker E, Kaminski MF, Latchford A, Neumann H, Ricciardiello L, Rupińska M, Saurin JC, Tanis PJ, Wagner A, Jover R, Pellisé M. Endoscopic management of Lynch syndrome and of familial risk of colorectal cancer: European Society of Gastrointestinal Endoscopy (ESGE) Guideline. Endoscopy. 2019 Nov;51(11):1082-1093. doi: 10.1055/a-1016-4977. Epub 2019 Oct 9. PMID: 31597170.
20. Brenner H, Stock C, Hoffmeister M. 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 Apr 9;348:g2467. doi: 10.1136/bmj.g2467. PMID: 24922745; PMCID: PMC3980789.
21. 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. Colonoscopic polypectomy and long-term prevention of colorectal-cancer deaths. N Engl J Med. 2012 Feb 23;366(8):687-96. doi: 10.1056/NEJMoa1100370. PMID: 22356322; PMCID: PMC3322371.
22. Doubeni CA, Corley DA, Quinn VP, Jensen CD, Zauber AG, Goodman M, et al. Effectiveness of screening colonoscopy in reducing the risk of death from right and left colon cancer: A large community-based study. Gut. 2018 Feb 1;67(2):291–8.
23. Bretthauer M, Kaminski MF, Løberg M, Zauber AG, Regula J, Kuipers EJ, Hernán MA, McFadden E, Sunde A, Kalager M, Dekker E, Lansdorp-Vogelaar I, Garborg K, Rupinski M, Spaander MC, Bugajski M, Høie O, Stefansson T, Hoff G, Adami HO; Nordic-European Initiative on Colorectal Cancer (NordICC) Study Group. Population-Based Colonoscopy Screening for Colorectal Cancer: A Randomized Clinical Trial. JAMA Intern Med. 2016 Jul 1;176(7):894-902. doi: 10.1001/jamainternmed.2016.0960. PMID: 27214731; PMCID: PMC5333856.
24. Lin JS, Piper MA, Perdue LA, Rutter CM, Webber EM, O'Connor E, Smith N, Whitlock EP. Screening for Colorectal Cancer: Updated Evidence Report and Systematic Review for the US Preventive Services Task Force. JAMA. 2016 Jun 21;315(23):2576-94. doi: 10.1001/jama.2016.3332. Erratum in: JAMA. 2016 Aug 2;316(5):545. Erratum in: JAMA. 2016 Oct 4;316(13):1412. PMID: 27305422.
25. van Rijn JC, Reitsma JB, Stoker J, Bossuyt PM, van Deventer SJ, Dekker E. Polyp miss rate determined by tandem colonoscopy: a systematic review. Am J Gastroenterol. 2006 Feb;101(2):343-50. doi: 10.1111/j.1572-0241.2006.00390.x. PMID: 16454841.
26. le Clercq CM, Bouwens MW, Rondagh EJ, Bakker CM, Keulen ET, de Ridder RJ, Winkens B, Masclee AA, Sanduleanu S. Postcolonoscopy colorectal cancers are preventable: a population-based study. Gut. 2014 Jun;63(6):957-63. doi: 10.1136/gutjnl-2013-304880. Epub 2013 Jun 6. PMID: 23744612.
27. Baxter NN, Goldwasser MA, Paszat LF, Saskin R, Urbach DR, Rabeneck L. Association of colonoscopy and death from colorectal cancer. Ann Intern Med. 2009 Jan 6;150(1):1-8. doi: 10.7326/0003-4819-150-1-200901060-00306. Epub 2008 Dec 15. PMID: 19075198.
28. Lee IM, Shiroma EJ, Kamada M, Bassett DR, Matthews CE, Buring JE. Association of Step Volume and Intensity With All-Cause Mortality in Older Women. JAMA Intern Med. 2019 Aug 1;179(8):1105-1112. doi: 10.1001/jamainternmed.2019.0899. PMID: 31141585; PMCID: PMC6547157.

29. Lakoff J, Paszat LF, Saskin R, Rabeneck L. Risk of developing proximal versus distal colorectal cancer after a negative colonoscopy: a population-based study. Clin Gastroenterol Hepatol. 2008 Oct;6(10):1117-21; quiz 1064. doi: 10.1016/j.cgh.2008.05.016. Epub 2008 Aug 8. PMID: 18691942.
30. Baron JA, Cole BF, Sandler RS, Haile RW, Ahnen D, Bresalier R, McKeown-Eyssen G, Summers RW, Rothstein R, Burke CA, Snover DC, Church TR, Allen JI, Beach M, Beck GJ, Bond JH, Byers T, Greenberg ER, Mandel JS, Marcon N, Mott LA, Pearson L, Saibil F, van Stolk RU. A randomized trial of aspirin to prevent colorectal adenomas. N Engl J Med. 2003 Mar 6;348(10):891-9. doi: 10.1056/NEJMoa021735. PMID: 12621133.
31. Soetikno RM, Kaltenbach T, Rouse RV, Park W, Maheshwari A, Sato T, Matsui S, Friedland S. Prevalence of nonpolypoid (flat and depressed) colorectal neoplasms in asymptomatic and symptomatic adults. JAMA. 2008 Mar 5;299(9):1027-35. doi: 10.1001/jama.299.9.1027. PMID: 18319413.
32. Ahlquist DA, Sargent DJ, Loprinzi CL, Levin TR, Rex DK, Ahnen DJ, Knigge K, Lance MP, Burgart LJ, Hamilton SR, Allison JE, Lawson MJ, Devens ME, Harrington JJ, Hillman SL. Stool DNA and occult blood testing for screen detection of colorectal neoplasia. Ann Intern Med. 2008 Oct 7;149(7):441-50, W81. doi: 10.7326/0003-4819-149-7-200810070-00004. PMID: 18838724; PMCID: PMC4016975.
33. Karapetis CS, Khambata-Ford S, Jonker DJ, O'Callaghan CJ, Tu D, Tebbutt NC, Simes RJ, Chalchal H, Shapiro JD, Robitaille S, Price TJ, Shepherd L, Au HJ, Langer C, Moore MJ, Zalcberg JR. K-ras mutations and benefit from cetuximab in advanced colorectal cancer. N Engl J Med. 2008 Oct 23;359(17):1757-65. doi: 10.1056/NEJMoa0804385. PMID: 18946061.
34. Imperiale TF, Wagner DR, Lin CY, Larkin GN, Rogge JD, Ransohoff DF. Risk of advanced proximal neoplasms in asymptomatic adults according to the distal colorectal findings. N Engl J Med. 2000 Jul 20;343(3):169-74. doi: 10.1056/NEJM200007203430302. PMID: 10900275.
35. Bénard F, Barkun AN, Martel M, von Renteln D. Systematic review of colorectal cancer screening guidelines for average-risk adults: Summarizing the current global recommendations. World J Gastroenterol. 2018 Jan 7;24(1):124-138. doi: 10.3748/wjg.v24.i1.124. PMID: 29358889; PMCID: PMC5757117.
36. Wolf AMD, Fontham ETH, Church TR, Flowers CR, Guerra CE, LaMonte SJ, Etzioni R, McKenna MT, Oeffinger KC, Shih YT, Walter LC, Andrews KS, Brawley OW, Brooks D, Fedewa SA, Manassaram-Baptiste D, Siegel RL, Wender RC, Smith RA. Colorectal cancer screening for average-risk adults: 2018 guideline update from the American Cancer Society. CA Cancer J Clin. 2018 Jul;68(4):250-281. doi: 10.3322/caac.21457. Epub 2018 May 30. PMID: 29846947.
37. Siegel RL, Fedewa SA, Anderson WF, Miller KD, Ma J, Rosenberg PS, Jemal A. Colorectal Cancer Incidence Patterns in the United States, 1974-2013. J Natl Cancer Inst. 2017 Aug 1;109(8):djw322. doi: 10.1093/jnci/djw322. PMID: 28376186; PMCID: PMC6059239.
38. DeBourcy AC, Lichtenberger S, Felton S, Butterfield KT, Ahnen DJ, Denberg TD. Community-based preferences for stool cards versus colonoscopy in colorectal cancer screening. J Gen Intern Med. 2008 Feb;23(2):169-74. doi: 10.1007/s11606-007-0480-1. Epub 2007 Dec 21. PMID: 18157581; PMCID: PMC2359177.
39. Rex DK, Johnson DA, Anderson JC, Schoenfeld PS, Burke CA, Inadomi JM; American College of Gastroenterology. American College of Gastroenterology

guidelines for colorectal cancer screening 2009 [corrected]. Am J Gastroenterol. 2009 Mar;104(3):739-50. doi: 10.1038/ajg.2009.104. Epub 2009 Feb 24. Erratum in: Am J Gastroenterol. 2009 Jun;104(6):1613. PMID: 19240699.

40. 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. Screening for Colorectal Cancer: US Preventive Services Task Force Recommendation Statement. JAMA. 2016 Jun 21;315(23):2564-2575. doi: 10.1001/jama.2016.5989. Erratum in: JAMA. 2016 Aug 2;316(5):545. Erratum in: JAMA. 2017 Jun 6;317(21):2239. PMID: 27304597.
41. European Colorectal Cancer Screening Guidelines Working Group, von Karsa L, Patnick J, Segnan N, Atkin W, Halloran S, Lansdorp-Vogelaar I, Malila N, Minozzi S, Moss S, Quirke P, Steele RJ, Vieth M, Aabakken L, Altenhofen L, Ancelle-Park R, Antoljak N, Anttila A, Armaroli P, Arrossi S, Austoker J, Banzi R, Bellisario C, Blom J, Brenner H, Bretthauer M, Camargo Cancela M, Costamagna G, Cuzick J, Dai M, Daniel J, Dekker E, Delicata N, Ducarroz S, Erfkamp H, Espinàs JA, Faivre J, Faulds Wood L, Flugelman A, Frkovic-Grazio S, Geller B, Giordano L, Grazzini G, Green J, Hamashima C, Herrmann C, Hewitson P, Hoff G, Holten I, Jover R, Kaminski MF, Kuipers EJ, Kurtinaitis J, Lambert R, Launoy G, Lee W, Leicester R, Leja M, Lieberman D, Lignini T, Lucas E, Lynge E, Mádai S, Marinho J, Maučec Zakotnik J, Minoli G, Monk C, Morais A, Muwonge R, Nadel M, Neamtiu L, Peris Tuser M, Pignone M, Pox C, Primic-Zakelj M, Psaila J, Rabeneck L, Ransohoff D, Rasmussen M, Regula J, Ren J, Rennert G, Rey J, Riddell RH, Risio M, Rodrigues V, Saito H, Sauvaget C, Scharpantgen A, Schmiegel W, Senore C, Siddiqi M, Sighoko D, Smith R, Smith S, Suchanek S, Suonio E, Tong W, Törnberg S, Van Cutsem E, Vignatelli L, Villain P, Voti L, Watanabe H, Watson J, Winawer S, Young G, Zaksas V, Zappa M, Valori R. European guidelines for quality assurance in colorectal cancer screening and diagnosis: overview and introduction to the full supplement publication. Endoscopy. 2013;45(1):51-9. doi: 10.1055/s-0032-1325997. Epub 2012 Dec 4. PMID: 23212726; PMCID: PMC4482205.
42. Guideline Program in Oncology G. Evidenced-based Guideline for Colorectal Cancer.
43. Sung JJ, Ng SC, Chan FK, Chiu HM, Kim HS, Matsuda T, Ng SS, Lau JY, Zheng S, Adler S, Reddy N, Yeoh KG, Tsoi KK, Ching JY, Kuipers EJ, Rabeneck L, Young GP, Steele RJ, Lieberman D, Goh KL; Asia Pacific Working Group. An updated Asia Pacific Consensus Recommendations on colorectal cancer screening. Gut. 2015 Jan;64(1):121-32. doi: 10.1136/gutjnl-2013-306503. Epub 2014 Mar 19. PMID: 24647008.
44. Kahi CJ, Boland CR, Dominitz JA, Giardiello FM, Johnson DA, Kaltenbach T, Lieberman D, Levin TR, Robertson DJ, Rex DK. Colonoscopy Surveillance after Colorectal Cancer Resection: Recommendations of the US Multi-Society Task Force on Colorectal Cancer. Am J Gastroenterol. 2016 Mar;111(3):337-46; quiz 347. doi: 10.1038/ajg.2016.22. Epub 2016 Feb 12. PMID: 26871541.
45. Loo SY, Vutcovici M, Bitton A, Lakatos PL, Azoulay L, Suissa S, Brassard P. Risk of Malignant Cancers in Inflammatory Bowel Disease. J Crohns Colitis. 2019 Sep 27;13(10):1302-1310. doi: 10.1093/ecco-jcc/jjz058. PMID: 30874294; PMCID: PMC6764102.
46. Olén O, Erichsen R, Sachs MC, Pedersen L, Halfvarson J, Askling J, Ekbom A, Sørensen HT, Ludvigsson JF. Colorectal cancer in Crohn's disease: a Scandinavian

population-based cohort study. Lancet Gastroenterol Hepatol. 2020 May;5(5):475-484. doi: 10.1016/S2468-1253(20)30005-4. Epub 2020 Feb 14. PMID: 32066530.
47. Olén O, Erichsen R, Sachs MC, Pedersen L, Halfvarson J, Askling J, Ekbom A, Sørensen HT, Ludvigsson JF. Colorectal cancer in ulcerative colitis: a Scandinavian population-based cohort study. Lancet. 2020 Jan 11;395(10218):123-131. doi: 10.1016/S0140-6736(19)32545-0. PMID: 31929014.