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OPPORTUNISTIC SCREENING FOR COLORECTAL CANCER IN HIGH-RISK PATIENTS IN FAMILY MEDICINE PRACTICES IN THE REPUBLIC OF CROATIA

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SUMMARY – Colorectal cancer is a malignant neoplasm which has an increasing incidence and represents a global public health problem. The majority of patients are diagnosed after the age of 50, and the risk of developing it over lifetime is 5%. Development of preventive, diagnostic and treatment methods has resulted in a significant reduction in mortality and other negative clinical outcomes. Precisely because of the efficient method of prevention and early detection of this disease, numerous countries, including Croatia, have organized national colorectal cancer screening and monitoring programs. However, these programs are primarily organized for the population with the usual, i.e. average risk of developing colorectal cancer. High-risk groups include persons with endoscopically detected and removed colon polyps, persons surgically treated for colon cancer, persons with a positive family history of colorectal cancer, persons with inflammatory bowel diseases, individuals and families with

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hereditary disorders or genetic mutations that increase the risk of this disease several fold, persons with acromegaly, and patients who have undergone ureterosigmoidostomy. Recommendations for the detection and monitoring of high-risk groups are often not defined clearly, and some of the existing ones are based mostly on scarce scientific evidence. It is commonly accepted that screening in high-risk groups should start at an earlier age, with shorter intervals between follow-ups. The basic diagnostic method for screening and monitoring in these patient groups is endoscopic monitoring, or colonoscopy. The aim of this review paper is to present the characteristics of the abovementioned risk groups and provide clear screening recommendations.

Key words: *Opportunistic screening; Colorectal cancer; Family medicine*

Introduction

Colorectal cancer is a global public health problem that represents the third most common malignancy site in men and second in women at the global level, whereas in a large number of European countries it is the most common malignancy site in both sexes together. According to data from the Cancer Registry, in 2017 in Croatia the incidence in both sexes was 37.5/100,000 inhabitants[1]. The risk of developing colorectal cancer over one's lifetime is 5%, and the majority of cases are diagnosed in persons above the age of 50. New treatment approaches have improved clinical outcomes and reduced mortality of this disease, but this is accompanied by a significant increase in treatment costs[2]. High disease incidence, long duration of the preclinical development phase, known and treatable disease precursors, as well as high treatment costs and direct correlation between mortality and disease stage make colorectal cancer appropriate for screening at the overall population level[2].

The majority of professional associations recommend screening the population at moderate risk of colorectal cancer, most often above the age of 50[3]. Persons with increased risk are candidates for earlier initiation of screening with more intensive and frequent monitoring. The high-risk group includes persons in whom colon polyps were found and then removed during colonoscopy, persons having been surgically treated for colon cancer, persons with a positive personal or family medical history of so-called advanced adenoma or colorectal cancer, persons suffering from inflammatory bowel disease, persons with the syndrome of hereditary nonpolyposis colorectal cancer, and persons with genetically based polyposis syndromes. Despite the existence of different screening methods, all currently available guidelines and organizations recommend colonoscopy as the basic assessment to screen for colorectal cancer in the mentioned high-risk populations. Fecal immunochemical test is a testing option in high-risk persons not partial to colonoscopy, given the relatively high diagnostic accuracy (sensitivity 93%; specificity 91%)[3]. A summary of the above high-risk conditions, as well as the recommendation for the initiation of screening and monitoring interval is shown in Table 1, while the recommendations for monitoring of persons with detected colon polyps are shown separately in Table 2.

Considering that a certain share of colorectal cancers in high-risk groups are hereditary, i.e. a consequence of specific genetic mutations, genetic testing also represents an important component of screening and diagnostics. Certain characteristics suggesting the need for genetic analysis include development of colorectal cancer before age 50, positive medical history of multiple cancers, personal and family medical history of suspected Lynch syndrome, detection of specific mismatch mutations in the tissue of the dissected tumor, presence of more than 10-20 colon adenomas, presence of more than 3 colon hamartomas or 2 small intestine hamartomas, and family members with genetically established hereditary colorectal cancer[4].

Post-Postpolypectomy Monitoring

The risk of developing advanced neoplastic changes on the colon greatly depends on the results of the initial, i.e. prior colonoscopy, where the increased risk in patients who have had colon polyps detected and removed is defined on the basis of the number and size of the polyps, their location in the colon, and histological structure. Appropriate assessment of this risk, and thus the recommendation for monitoring depends, of course, on the quality and standards of the colonoscopy performed. High-risk persons include patients who have had three or more adenomas or so-called advanced neoplasms detected, i.e. adenomas sized ≥10

Table 1. Summary of conditions with increased risk of colorectal cancer and monitoring recommendations[3,20-22]

Condition	Basic characteristics	Prevalence	Initial colonoscopy (age, years)	Monitoring interval (years)
Positive family history	2 patients who are first-degree relatives of any age or 1 patient before age 50	1/3-1/10	40	5
Inflammatory bowel disease	Ulcerative colitis or Crohn's disease with colon involvement	84.3/100,000	8 after inflammatory bowel disease diagnosis	Low risk = 5 Intermediate risk = 2-3 Low risk = 1
Lynch syndrome	Most often diagnosed by confirming specific genetic mutations	1/300	*MLH1, MLH2* = 25 *MSH6, PMS2* = 35	2
Familial adenomatous polyposis	≥100 colorectal adenomas	1-9/100,000	10-12	1
Attenuated familial adenomatous polyposis	10-99 synchronous colorectal adenomas	Unknown	18-25	1-2
MUYTH polyposis	Most often <100 colorectal adenomas	<1/10,000	20-25	1-3
Juvenile polyposis	Multiple colon and rectum hamartomas; neoplasms of upper gastrointestinal tract and small intestine	1/100,000-1/160,000	12	1-3
Peutz-Jeghers syndrome	Hamartomatous polyposis; mucocutaneous pigmentations; extraintestinal neoplasms	1/50,000-1/200,000	15-18	2-3
Cowden syndrome	Different number and type of colon polyps; glycogenic acanthosis of the esophagus	1-9/1,000,000	15	2
Serrated polyposis syndrome	Minimum 5 serrated polyps proximally from sigmoid colon (two larger than 10 mm); serrated polyps proximally from sigmoid colon with a first-degree relative who has serrated polyposis syndrome; >20 serrated polyps of any dimensions and location	1/2000-1/3000	40	1-3
Acromegaly	Increased serum levels of growth hormone and insulin-like growth factor 1	2.8-13.7/100,000	40	3-5
Ureterosigmoido-stomy	Surgery for urinary bladder cancer	/	10 after surgery	1

Table 2. Recommendations for second postpolypectomy follow-up endoscopy based on the adenomas detected during initial and first follow-up colonoscopy[5]

Initial result	Recommended first follow-up (years)	Results at first follow-up	Recommended next follow-up (years)
1-2 tubular adenomas <10 mm	7-10	Normal results	10
		1-2 tubular adenomas <10 mm	7-10
		3-4 tubular adenomas <10 mm	3-5
		Adenomas ≥10 mm Tubulovillous/villous adenomas Adenomas with high-degree dysplasia 5-10 adenomas <10 mm	3
3-4 tubular adenomas <10 mm	3-5	Normal results	10
		1-2 tubular adenomas <10 mm	7-10
		3-4 tubular adenomas <10 mm	3-5
		Adenomas ≥10 mm Tubulovillous/villous adenomas Adenomas with high-degree dysplasia 5-10 adenomas <10 mm	3
Adenomas ≥10 mm Tubulovillous/villous adenomas Adenomas with high-grade dysplasia 5-10 adenomas <10 mm	3	Normal results	5
		1-2 tubular adenomas <10 mm	5
		3-4 tubular adenomas <10 mm	3-5
		Adenomas ≥10 mm Tubulovillous/villous adenomas Adenomas with high-degree dysplasia 5-10 adenomas <10 mm	3

mm, adenomas of tubulovillous or villous histological structure, those who have had verified high-grade dysplasia or invasive cancer component[5]. Persons with only hyperplastic polyps sized <10 mm found are considered to be at the same risk of developing colon cancer as persons with normal colonoscopy results, whereas the low-risk group includes persons with endoscopically detected 1 to 2 polyps of tubular histological structure sized <10 mm[1]. According to data from a meta-analysis on 10,139 subjects in 8 included trials, the risk of developing metachronous adenomas in persons without adenomas on initial colonoscopy and persons with 1 to 2 adenomas <10 mm was similar, i.e. 3.3% and 4.9%, respectively, over a 5-year period[6]. Conversely, in patients with high-risk adenomas detected, the cumulative 5-year risk was 17.3%[6].

In line with the latest published recommendations of the US professional gastroenterology associations and organizations, in case of normal results, follow-up colonoscopy is recommended or use of another screening method after 10 years, whereas in case of 1-2 tubular adenomas <10 mm detected, the recommended follow-up period is 7 to 10 years[5]. In case of detection and removal of 3-4 tubular adenomas <10 mm, follow-up is recommended in 3 to 5 years, and if 5-10 tubular adenomas <10 mm have been detected, follow-up is recommended in 3 years[5]. Three-year follow-up is also indicated in case of detection and removal of adenomas above 10 mm, adenomas of tubulovillous and villous histological structure, and adenomas with high-grade dysplasia[5]. If colonoscopy shows more than 10 adenomas, follow-up is recommended after 1 year[5]. In all cases of so-called piecemeal resection of adenomas >20 mm, follow-up endoscopy is recommended within 6 months[5].

In patients with up to 20 detected hyperplastic polyps irrespective of the location, follow-up is recommended in the same period as for normal results, i.e. in

10 years[5]. If hyperplastic polyps of ≥10 mm have been removed, follow-up is recommended in 3 to 5 years[5]. In case of sessile serrated polyps, the follow-up interval is 5 to 10 years if 1-2 polyps have been detected, or 3 to 5 years if 2-4 polyps <10 mm have been detected[5]. A 3-year follow-up interval is recommended if 5-10 sessile serrated polyps <10 mm have been detected, if they are ≥10 mm, or if signs of dysplasia are present[5].

Further patient monitoring naturally depends on the results of initial and follow-up colonoscopy. The above follow-up intervals and recommendations are presented in Table 2.

Postoperative Monitoring of Patients Treated for Colon Cancer

Postoperative monitoring is indicated in all patients with colorectal cancer following curative surgery and appropriate oncologic treatment. Persons surgically treated for colon cancer are at an increased risk of metachronous cancer development, especially in the first 2 to 3 years following surgery[7]. The said risk is 1.5-2 times higher than in the general population, and at long-term it amounts to 1%-2%[7].

The first follow-up colonoscopy is recommended 1 year after surgical treatment[3]. If patients were surgically treated for colon cancer without previous colonoscopy, colonoscopy should be performed within 6 months of the surgery[7]. The next follow-up, if postoperative results are normal, is indicated after 3 years, whereas the third follow-up in case of normal results is indicated after 5 years[7]. It is recommended to discontinue postoperative colonoscopy monitoring at the age of 80 or earlier if life expectancy is limited by comorbidities[7].

Positive Family History

According to the existing guidelines, colonoscopy as part of the screening is recommended for first-degree relatives of colorectal cancer patients, if the criteria for family risk of colorectal cancer have been met[8]. The said criteria include the presence of at least two family members who are first-degree relatives of any age, or one member with the disease before age 50[8]. Initial colonoscopy should be performed at age 40, or 10 years prior to the age of the youngest case of cancer in the family[8]. In case of normal results, follow-up examination is indicated at 5-year intervals, whereas in case of polyps, guidelines for the general population apply[8].

In case of existence of one second- or third-degree relative with colorectal cancer, the risk is about 1.5 times higher, and screening is recommended as for the general population, i.e. persons with average disease risk[3]. Second-degree relatives include grandparents, uncles and aunts, while third-degree relatives include great-grandparents and other more distant relatives.

Inflammatory Bowel Disease

Persons with an inflammatory disease are at an increased risk of developing colorectal cancer. The longer the duration of the inflammatory disease, the higher is the risk of cancer development, if diagnosed at a younger age and if the inflammatory process is inappropriately managed, or in case of severe forms of inflammatory bowel disease. The frequency of cancer development after a 30-year duration of inflammatory disease is about 18%, and increased risk on average occurs after 7-year duration of inflammatory disease[9]. The known association between primary sclerotizing cholangitis and inflammatory bowel disease, according to a meta-analysis of 16 observational studies, shows an additional significant increase of the said risk in patients with ulcerative colitis compared to individuals with ulcerative colitis without primary sclerosing cholangitis[10]. Additionally, a positive family history independently increases the risk of colorectal cancer 2-3 times in persons with inflammatory bowel disease[11].

Initial colonoscopy is recommended to be performed as part of the screening no later than 8 years after disease onset. The examination should include systematic biopsy *per* quadrant of colon mucosa every 10 cm with additional sampling of visible mucosa alterations. In the absence of risk characteristics and factors, the examination should be repeated at a 5-year interval[12]. In case of moderate risk, i.e. extensive colitis with mild to moderate inflammatory changes, post-inflammatory polyps or family history of colorectal cancer in a first-degree relative above the age of 50, colonoscopy should be repeated in 2 to 3 years[12]. In high-risk patients with extensive colitis and severe inflammatory changes or family history of colorectal cancer in a first-degree relative under the age of

50, colonoscopy is indicated at 1-year intervals[12]. In case of the presence of primary sclerotizing cholangitis, almost all professional associations recommend colonoscopy once a year, regardless of the extent or intensity of inflammatory changes and disease duration.

Lynch Syndrome

The most common hereditary colorectal cancer syndrome is also known as hereditary nonpolyposis colorectal cancer, which underlies 2% to 4% of colorectal cancers[8]. Persons suffering from this syndrome are at an increased risk of developing a range of other malignancies, and particularly significant in terms of frequency are endometrial and stomach cancers. The usual sequence of adenomas transitioning into cancer is significantly accelerated in this risk group, and the average time for this transformation is about 1.5 years, which is not uncommonly up to 10 times faster than in the general population. Lifetime risk of developing colorectal cancer can exceed 70%, whereas at the population level, its prevalence is 1/279 (3.8%). Lynch syndrome develops as a consequence of a pathogenic variant in one of the repair genes *MLH1, MSH2, MSH6, PMS2,* or *EpCAM* (Epithelial Cell Adhesion Molecule) 3'end deletion.

The results of various screening and monitoring programs for families with Lynch syndrome have suggested that appropriate monitoring of these patients has resulted in a reduction in colorectal cancer incidence by 62% and mortality by 65% to 70%[13]. The clinical tools available for identification of patients with Lynch syndrome are covered by the so-called Amsterdam II criteria (Table 3). In accordance with the European guidelines, carriers of *MLH1* and *MLH2* mutations are recommended to initiate screening at age 25, whereas carriers of *MSH6* and *PMS2* mutations, given the somewhat lower risk, are recommended to start colonoscopy screening at age 35[8]. Asymptomatic patients with Lynch syndrome require follow-up colonoscopies every 2 years, and in case of an inappropriate or incomplete examination, repeated colonoscopy in 3 months is indicated[8]. Symptomatic carriers of the said mutations should have initial colonoscopy even prior to the abovementioned ages, i.e. intervals[8].

Table 3. Amsterdam II criteria for identification of patients with Lynch syndrome[4]

Amsterdam II criteria for Lynch syndrome
At least 3 relatives with a Lynch-associated cancer (colorectal, endometrial, small intestine, ureter, renal pelvis); All of the below criteria must be present: • Person must be a first-degree relative of the other two • At least two successive generations affected • At least 1 relative diagnosed with a Lynch-associated cancer before the age of 50 • Familial adenomatous polyposis has been ruled out

Hereditary Polyposis Syndromes

Timely detection and early inclusion of patients with hereditary disorders that increase the risk of colorectal cancer development requires active engagement and cooperation of family practitioners and gastroenterologists. This is aided by several factors, primarily identification of burdened family history and specific clinical or physical features. Additional confirmation is made possible by specific genetic analyses and confirmation of the presence of certain mutations. This endeavor is demanding, mostly because of the rare occurrence of these symptoms, where of the total number of colorectal cancer patients, the said hereditary syndromes account for 3% to 5% of patients[14]. The list of hereditary polyposis and nonpolyposis syndromes with the basic mutated gene and risk of colorectal cancer is shown in Table 4.

Familial adenomatous polyposis

Familial adenomatous polyposis is an autosomal dominant hereditary disease characterized by the presence of more than 100 adenomatous colon polyps. It develops due to a mutation in the APC gene on chromosome 5q. In about 25% of patients, the mutation occurs *de novo* and in these cases family history is inconspicuous[14]. Without prophylactic proctocolectomy, practically everyone develops colon cancer by the age of 70. The risk of duodenal cancer is also increased, amounting to about 12% over lifetime, as well as the risk of stomach cancer, which is considerably lower at <1%[15]. There have also been reports on attenuated forms of familial adenomatous polyposis, in which there is a small number of synchronous colon adeno-

Table 4. Cumulative risk of colorectal cancer in hereditary syndromes (according to Syngal et al.[16])

Syndrome	Gene	Risk	Average age at diagnosis (years)
Sporadic cancers		4.8%	69
Lynch syndrome	*MLH1/MSH2*	M: 27%-74% F: 22%-61%	27-60
	MSH6	M: 22%-69% F: 10%-30% M/F: 12%	50-63
	PMS2	M: 20% F: 15%	47-66
Familial adenomatous polyposis	*APC*	100%	38-41
Attenuated familial adenomatous polyposis	*APC*	69%	54-58
MUYTH polyposis	*MUYTH*	43%-100%	48-50
Juvenile polyposis	*SMAD4* *BMPR1A*	38%-68%	34-44
Peutz-Jeghers syndrome	*STK11*	39%	42-46
Cowden syndrome	*PTEN*	9%-16%	44-48
Serrated polyposis syndrome	Unknown	~50%	48

M = male; F = female

mas, between 10 and 99, with marked proximal distribution. In addition to the smaller number of polyps, the risk of cancer is also lower than in classic familial adenomatous polyposis.

Screening should be initiated between the ages of 10 and 12, with examinations at 1-year intervals until the time when the need for surgical treatment arises due to the number and risk of polyps[16]. Prophylactic proctocolectomy is most often indicated before age 25, given that after this age the risk of colorectal cancer increases significantly. In case of postponement of surgical treatment due to the patient's decision or smaller number of adenomas that do not show signs of high-grade dysplasia, monitoring *via* 6-month endoscopy follow-ups is required. After prophylactic surgery, 1-year endoscopy follow-ups are necessary, given the existing risk of cancer developing in the residual anorectal mucosa[16]. This risk can be up to 29% in case of colectomy with ileorectal anastomosis, while it is considerably lower after proctocolectomy with ileoanal pouch[14].

Due to the already mentioned risk of upper gastrointestinal tract cancer, it is recommended to begin endoscopic monitoring between the ages of 25 and 30 in the form of esophagogastroduodenoscopy with follow-ups at intervals of 6 months to 4 years, depending on the risk factors, which pertain to the number, size and histology of polyps, and presence of dysplasia[16]. All patients should have their thyroid examined once a year, preferably by ultrasound.

MUYTH polyposis

This mutation in the gene of the same name is inherited following autosomal recessive principles and carries a high risk of developing colorectal cancer. Its prevalence is 1/10,000, and cancer presents most commonly between the ages of 50 and 70[3]. Colonoscopy monitoring should be initiated between the ages of 20 and 25, and assessment should be repeated every 1 to 3 years[14,15]. It is also recommended to initiate endoscopic monitoring of the upper gastrointestinal tract from the age of 30 onwards, with follow-ups at 3- to 5-year intervals[14,15].

Peutz-Jeghers syndrome

This syndrome is inherited in an autosomal dominant matter and is characterized by the development of hamartomatous polyps of the small intestine and colon with the development of mucocutaneous pigmentations, most often of the perioral area and buccal mucosa. It is quite a rare syndrome with a prevalence

estimated at between 1:50,000 and 1:200,000[16]. According to the available guidelines, endoscopic monitoring of the upper and lower gastrointestinal tract should be initiated in late adolescence and repeated every 2 to 3 years if the results are normal[17]. Assessment of the small intestine consists of using computed tomography (CT) or magnetic resonance imaging (MRI) enterography, i.e. video capsule endoscopy of the small intestine, also with follow-ups at 2- to 3-year intervals[17]. Due to an increased risk of pancreatic cancer, there is an indication for MRI cholangiopancreatography or endoscopic ultrasound of the pancreas between the ages of 30 and 35, repeated every 1 to 2 years[17]. The risk of breast cancer exceeds 50%, which is why mammography or breast MRI is indicated once a year in women from age 25 onwards[14].

Juvenile polyposis syndrome

Juvenile polyposis syndrome is also a hamartomatous polyposis syndrome, a term that primarily pertains to the type of polyp, and not the age at which it occurs. It describes the appearance of multiple hamartomas of the colon and rectum, which are characterized by smooth surface with a seemingly normal mucosa epithelium, dense stroma, and presence of inflammatory infiltrate. This disorder should not be mistaken for the isolated appearance of juvenile polyps in children, where most often there is no hereditary component to the disease and no increased risk of malignancy. The incidence is between 1:100,000 and 1:160,000[18]. Screening and monitoring include endoscopy of the upper gastrointestinal tract, small intestine, and colon. Initial colonoscopy should be performed around the age of 12, then repeated every 1 to 3 years[16]. Small intestine examination includes the use of MRI or CT enterography, i.e. video capsule endoscopy or enteroscopy. In case of impossibility of endoscopic treatment of polyps or polyp-caused symptoms, surgical treatment is indicated, which most often includes colectomy with the creation of ileorectal anastomosis.

Cowden syndrome

Cowden syndrome as the most common of the three hamartomatous polyposis syndromes, it also encompasses variants such as Bannayan-Riley-Ruvalcaba syndrome and PTEN hamartomatous tumor syndrome. This syndrome includes a different number and type of colon polyps, including juvenile polyps, adenomas, ganglioneuromas, lipomas, inflammatory polyps, etc. The presence of these colon polyps with glycogenic acanthosis of the esophagus represents the pathognomonic clinical picture of Cowden syndrome. Endoscopic screening for the upper and lower part of the gastrointestinal tract is indicated from the age of 15, with monitoring at 2-year intervals[16].

Serrated polyposis syndrome

This is a syndrome which, according to the World Health Organization criteria, is defined as the presence of ≥5 serrated polyps proximally from the sigmoid colon, with 2 or more larger than 10 mm; or any number of serrated polyps proximally from the sigmoid colon, with a first-degree relative with the serrated polyposis syndrome; or >20 serrated polyps of any dimensions[16]. The genetic background of this disease has not been established. In patients meeting the diagnostic criteria, colonoscopy monitoring with polypectomy is indicated at 1- to 3-year intervals[16]. In first-degree relatives of patients with this syndrome, it is recommended to perform initial colonoscopy at the age of 40, or 10 years before the youngest age at diagnosis in the first-degree relative[14].

Acromegaly

Acromegaly is an endocrinological disorder characterized by elevated serum levels of growth hormone and its tissue mediator, insulin-like growth factor 1 (IGF-1). Acromegaly patients are at a 2.4 times higher risk of colorectal adenomas and as much as 7.4 times higher risk of cancer compared to the general population, with the overall prevalence of colorectal cancer of 3.7%[19]. For that reason, colonoscopy screening is indicated in these individuals starting from the age of 40[14]. The monitoring interval depends on the results of initial colonoscopy and activity of the underlying disease. In case of detection of adenomas on initial colonoscopy or elevated IGF-1, monitoring is carried out every 3 years, whereas in case of normal results of initial colonoscopy and normal IGF-1 and growth hormone levels, monitoring is required every 5 to 10 years[14]. Development of a larger number of neoplastic changes in the ascending and transverse colon requires monitoring with total colonoscopy, which is often rendered difficult in these patients by the extended colon length and slower transition of intestinal content, requiring more intensive and longer preparation.

Ureterosigmoidostomy Patients

The risk of developing adenoma and cancer is increased in the area of ureter anastomosis and sigmoid colon in patients who have had this surgical procedure. These complications occur in as many as 24% of patients after 20 years of monitoring[14]. Given the location of anastomosis, sigmoidoscopy is recommended in monitoring, and initial examination should be performed 10 years after the surgical procedure with follow-ups at 1-year intervals[14].

Conclusion

Despite the existence of the national screening program for colon cancer in the Republic of Croatia, focused on persons at average risk of the disease, development and implementation of opportunistic screening in high-risk patient groups is becoming a dire need, in particular due to the generally insufficient response of the target population in the national screening program, low awareness of the existence and detection of high-risk persons, and also the reported increasing trend of the incidence of colorectal cancer in young adults in the last ten years. Timely identification of persons who belong to high-risk groups and the existence of clear recommendations would enable family practitioners to refer such patients directly to endoscopy. This would provide for faster direct contact with a specialist, more precisely gastroenterologist, while avoiding unnecessary referrals to unnecessary and, in this case, unindicated examinations within the national screening program, all with the aim to timely identify high-risk persons and enable their appropriate monitoring to prevent development of colorectal cancer, i.e. its detection at an early stage in order to reduce mortality and improve clinical outcomes.

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- Croatian Society of Family Doctors
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