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Colorectal Cancer Screening and Surveillance

William V. Harford, MD[a,b]

[a]*Veterans Administation Medical Center, Gastro 111B1, DVAMC, 4500 South Lancaster Road, Dallas, TX 75216, USA*
[b]*University of Texas Southwestern Medical Center, 5323 Harry Hines Boulevard, Dallas, TX 75390, USA*

It is estimated that colorectal cancer (CRC) mortality could be reduced by 28%–60% and CRC incidence reduced by 17%–54% if 75% of the eligible population were screened [1]. However, the most recent National Health Interview Survey and the Behavioral Risk Factor Surveillance System survey found that less than 45% of adults aged 50 or older have had any CRC screening within the recommended time intervals [2–4]. Despite this low percentage, awareness of the importance of CRC screening, and participation in screening are increasing, and efforts are being made to identify, study, and address obstacles to increased participation [5].

Risk factors

Screening is the testing of a group considered to be at normal risk for a disease, to discover those at increased risk. By convention, patients are considered to be at normal risk for colorectal cancer if they are $\geq$ 50 years of age and have no other risk factors. Surveillance is the testing of a group known to be at increased risk for a disease.

Age

CRC screening is generally advised for men and women $\geq$ 50 years old, because 95% of cases occur after that age. CRC risk continues to increase with advancing age, but published guidelines do not recommend changing screening strategy with age. The yield of screening increases with age (Fig. 1), but the prevalence of comorbidity and the risks associated with a colonoscopy also increase. For elderly patients who are in poor health, the risks of screening may outweigh the benefits [6,7].

E-mail address: wharford@worldnet.att.net

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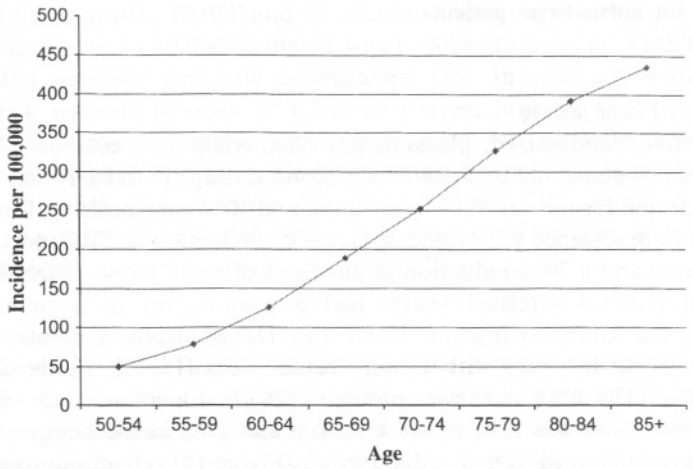

Fig. 1. Colorectal cancer incidence by age. (*Data from* Colon and Rectum Cancer (Invasive) SEER Incidence Rates, Age-adjusted and Sex-specific Rates, by Race and Sex. Surveillance, Epidemiology, and End Results (SEER) Program 1992-2002. Available at http://www.seer.cancer.gov/csr/1975_2002/results_merged/sect_06_colon_rectum.pdf.)

Symptoms and signs

Patients who are $\geq$ 50 years of age who report visible rectal bleeding of any type, who have an unexplained persistent change in bowel habits, or who are found to be iron deficient should be referred for colonoscopy.

Family history

About 25% of colorectal cancer cases are associated with a family history. Colonoscopy rather than ordinary screening should be considered for patients with a positive family history. About 2%–3% of CRC cases are associated with Lynch Syndrome (also termed Hereditary Non-polyposis Colorectal Cancer). Physicians should be aware of both the classic and attenuated presentations of Lynch Syndrome and familial adenomatous polyposis (FAP). A conscientious effort is necessary to obtain a complete family history [8].

Gender, obesity, smoking, and alcohol intake

Male gender, obesity, current smoking, and heavy intake of hard spirits or beer are risks associated with CRC, but have not been incorporated into screening guidelines [9–12].

Other risk factors

Patients who have a personal history of CRC, adenomatous polyps, or inflammatory bowel disease (IBD) for more than 8–10 years, are at increased risk of CRC and should be referred for colonoscopy.

Screening for normal-risk patients

Stool testing

Fecal occult blood testing

Prospective, randomized, placebo-controlled trials have established the effectiveness of guaiac-based fecal occult blood testing (FOBT). In the U.S. trial, rehydrated Hemoccult slides were used, and 10% were positive. For patients who were screened yearly, there was a 33% reduction in CRC mortality after 13 years and a 20% reduction in incidence after 18 years. Thirty-eight percent of patients screened yearly had a colonoscopy at some point [13,14]. In the United Kingdom (UK) and Danish trials, patients were screened every other year with unrehydrated slides [15–17]. Fewer slides were positive (1%–4%) and fewer patients (5%) had a colonoscopy. CRC mortality reduction was 15% in the UK trial and 11% in the Danish trial. In the Danish study, mortality reduction was higher (43%) among patients who completed all nine rounds of screening over the 18 years of the study [17].

Advantages of FOBT are accessibility, safety, and low initial costs, but sensitivity and specificity are limited. Sensitivity of a single 3-day FOBT is about 25% for CRC or advanced adenomas [18]. This improves with repeated testing, but high participation rates are difficult to sustain [17]. The positive predictive value (PPV) of unrehydrated FOBT for CRC is only 5% to 18% and for CRC and large adenomas it is 20% to 40% [19]. In research trials, compliance rates of 60%–70% with initial testing have been reported, but in clinical practice it is generally lower. In a study of US veterans, 51% of patients completed mailed FOBTs [20]. Compliance with repeated testing is lower. In the UK study, only 38% of subjects completed all the FOBTs offered. Physicians often do not follow recommended guidelines for FOBT screening [21]. Screening should not be done by testing stool obtained by digital rectal examination (DRE). The sensitivity of a DRE-FOBT is only 5%. A negative result has little predictive value [22]. However, a positive DRE-FOBT has the same PPV for CRC as a positive three-sample FOBT [23]. Patients with any positive FOBT should be referred for colonoscopy. In one study, only 34% of patients with a positive FOBT received a complete colon examination by colonoscopy or double contrast barium enema (DCBE) and flexible fiberoptic sigmoidoscopy (FFS) [24]. Physicians too often inappropriately repeat positive FOBTS or fail to refer patients for evaluation.

Fecal occult blood testing in patients on warfarin

The PPV of FOBT for CRC among patients on warfarin (8.5%) is not significantly different from that among patients not on warfarin (10.5%), which suggests that it is not necessary to discontinue warfarin for FOBT [25].

Fecal occult blood testing after colonoscopy

There are few data regarding the use of FOBT after colonoscopy. In a recent study, no cancers were found in 183 normal-risk patients who were

referred for a positive FOBT and who had a colonoscopy within the past 5 years. The authors concluded that it was prudent to suspend FOBT for 5 years after negative screening colonoscopy [26]. In contrast, a study of higher-risk patients (history of CRC or polyps, positive family history) who were in a colonoscopy surveillance program, off-year FOBTs were offered to participants. Of the patients who participated, 7% had a positive FOBT, and 25% of those were discovered to have CRC or an advanced polyp. The authors concluded that it was reasonable to offer at least one FOBT between surveillance colonoscopies [27].

Fecal immunochemical tests

Guaiac-based FOBTs may be false-positive in the presence of dietary plant peroxidases, meat, and upper gastrointestinal blood loss. They may be false-negative in the presence of peroxidase inhibitors such as vitamin C. Fecal immunochemical tests (FITs) detect only human hemoglobin in stool, do not require dietary restrictions, and have higher specificity than guaiac-based tests [28,29]. The American Cancer Society recommends FITs as more user-friendly than guaiac-based FOBTs [30].

Fecal DNA Tests

Exfoliated DNA from colonic neoplasms contains multiple genetic abnormalities. Human DNA can be isolated from stool and analyzed [31]. A DNA stool test (PreGenPlus, Exact Sciences, Marlborough, Massachusetts) is commercially available. In a large study of normal-risk patients, the sensitivity of fecal DNA was only 52% for CRC, compared with 13% for FOBT, and only 15% for advanced adenomas, compared with 11% for FOBT [32]. Fecal DNA testing is not currently cost-effective compared with other tests, but the technology is evolving quickly [29,33].

Fiberoptic sigmoidoscopy

Case-control studies support the effectiveness of fiberoptic sigmoidoscopy (FFS) screening for reducing mortality from rectosigmoid cancer by 50%–80%, and overall CRC mortality by 30%–45%. Risk reduction persists for 5–10 years [34–36]. Several ongoing large, prospective randomized studies will provide more information. The United Kingdom (FFS) trial was initiated in 1993. One-time FFS screening was offered to people between the ages of 55 and 64 years. The results of this trial should be available soon [37]. The Italian (SCORE) trial is a similar but smaller study [38]. In the United States (PLCO [prostate, lung, colon, ovarian]) trial, about 155,000 men and women aged 55 to 74 years have been randomized to CRC screening by FFS every 3 years, or to usual care, and will be monitored until 2015 [39]. The preliminary reports from these trials have provided important information. Participation rates have been 60%–80%. CRC has been found in 0.3%–0.54% and advanced adenomas in 4%–6%. About 5%–10% of the

participants have been referred for a colonoscopy. Complications have been rare (< 1/1000) [37,40,41].

Hyperplastic polyps are common in the distal colon, but do not signal an increased risk for CRC. The risk of advanced neoplasms is also small with single, small adenomas. Referral for colonoscopy may not be mandatory for these patients [42,43].

FFS can be done with modest preparation, inconvenience, and little risk. It provides substantial durable risk reduction. By training non-gastroenterologists and providing dedicated facilities, large-scale screening has been done successfully in the UK and by Kaiser Permanente [44]. There are problems with the use of FFS for screening. Few US primary care providers do many FFS screenings, and there are few trained non-physician endoscopists [21,45]; reimbursement for FFS does not cover the cost [46]; only part of the colon is examined, and about 2%–5% of patients with negative FFS examinations will have CRC or an advanced adenoma proximal to the reach of the sigmoidoscope. This number may increase since there has been a proximal shift in the distribution of CRC [47–49].

Fiberoptic sigmoidoscopy combined with fecal occult blood testing

The American Cancer Society endorses FFS every 5 years combined with yearly FOBT as an acceptable CRC screening strategy. Studies suggest that the primary benefit is provided by FFS, and that FOBT adds little to a FFS screening program [50,51].

Colonoscopy

There have been no controlled, randomized, prospective studies of colonoscopy in reducing CRC mortality, but indirect evidence is very strong. Case-control studies of colonoscopy screening from Italy and from the Veterans Administration showed risk reductions of 50%–65% [52,53]. The National Polyp Study was not designed to address the use of colonoscopy for screening, but CRC incidence was reduced by about 75% in subjects who had colonoscopy and polypectomy followed by surveillance colonoscopy, compared to expected CRC incidence as estimated by the Surveillance, Epidemiology, and End Results (SEER) Program of the National Cancer Institute [54,55]. The feasibility of colonoscopy for primary screening has been established by two large studies. In the Veterans Affairs Cooperative Study 380, the entire colon was examined in 98% of patients. Major complications occurred in 0.3% of cases, and no perforations or deaths were attributable to colonoscopy. CRC was found in 1%, and advanced adenomas in 9.5% of the patients [56,57]. A study of women (CONCeRN) was done in tandem with the VA Cooperative Study [58]. In another study, colonoscopy was used to screen 1994 normal-risk patients ≥ 50 years old enrolled in a corporate health plan. The entire colon was examined in 97% of cases. CRC

was found in 0.5%. Advanced adenomas were found in the distal colon in 3% and in the proximal colon in 2.5% of patients [59].

Many physicians and patients believe that colonoscopy is the best screening strategy because it is the most accurate. However, the US Preventive Services Task Force concluded in its report that "it is unclear whether the increased accuracy of colonoscopy compared with alternative screening methods ... offsets the procedures' additional complications, inconvenience, and costs" [60]. CRC risk reduction is greater with colonoscopy than with FOBT or FFS screening, but is probably closer to 50%–60% than the 75%–90% extrapolated from the National Polyp Study [35,52]. Although colonoscopy is accurate, recent studies comparing state-of-the-art CT colonography and colonoscopy suggest that up to 12% of lesions $\geq$ 10 mm may be missed by colonoscopy [61]. Purging for colonoscopy is unpleasant. The use of sedation requires patients to take an entire day from their normal activities. Up-front costs of colonoscopy are prohibitive for many patients who do not have insurance. It is not clear whether there is adequate colonoscopy capacity in the United States. The demand for colonoscopy has increased with Medicare coverage, public education, and celebrity endorsement [62,63]. Although there may be sufficient colonoscopy capacity to maintain a steady state, "catching up" with increased screening participation will take a number of years. Even if overall colonoscopy capacity is adequate, access to colonoscopy is not uniform [1,64].

Double contrast barium enema

Double contrast barium enema (DCBE) every 5 years is endorsed by the American Cancer Society and the Gastrointestinal Consortium as an alternative method of CRC screening [30,65]. There is no direct evidence that DCBE is effective. The accuracy of DCBE is much lower than colonoscopy. Sensitivity of DCBE for lesions $\geq$ 10 mm is about 50% [66,67]. The main advantage of DCBE is the fact that it is widely available and does not require sedation. DCBE can be used after incomplete colonoscopy, and significant neoplasms may be found in 3%–5% of such cases [68,69].

CT colonography

Multidetector CT scanners and improved software make it possible to construct high-resolution, three-dimensional images and to "fly–through" the colon, creating a view analogous to colonoscopy ("virtual colonoscopy"). In one report, expert radiologists using advanced techniques detected polyps $\geq$ 10 mm with a sensitivity of 94% and specificity of 96% [70]. However, in another report, CT colonography (CTC) as practiced in the general medical community was found have a sensitivity of only 55% for polyps $\geq$ 10 mm [71].

CTC is safe, no sedation is needed, and CTC can detect polyps missed on optical colonoscopy [61]. Important extraluminal abdominal conditions

may be detected [72]. Problems remain to be resolved. Sensitivity is unacceptably low without optimal techniques and expert interpretation. Incidental extraluminal abnormalities can be expected in about 5%–10% of cases and create difficult management problems [72,73]. Patient acceptance may not be better for CTC than colonoscopy unless the need for purging is eliminated. Fecal tagging and digital subtraction may make this possible [74,75]. The polyp cutoff size used to refer patients for a colonoscopy has important implications. At 10 mm, about 10% of screened patients will be referred; whereas, at 6 mm, about 30% will be referred [70]. Whether it is prudent to follow patients with polyps between 6 mm and 9 mm in size is not clear [76–78]. CTC has a role for patients at high risk of CRC who cannot have colonoscopy and for those patients in whom colonoscopy is incomplete [79].

Cost effectiveness and cost savings

The cost effectiveness of CRC screening compares favorably to that of other well-accepted cancer screening programs. A review for the US Preventive Services Task Force concluded that no one CRC screening strategy is clearly more cost effective than others. Recommendations for one strategy over another cannot be made on the basis of cost [80]. Except perhaps over an extended time frame, CRC screening does not result in net cost savings [1,81].

The American Cancer Society guidelines for CRC screening [30] indicate that beginning at age 50, both men and women at normal or average risk for developing colorectal cancer should follow one of the following screening options:

- FOBT or FIT every year. For FOBT or FIT, a take-home, multiple-sample kit should be used. A single FOBT test done in the doctor's office following digital rectal examination is not recommended. There is no justification for repeating FOBT in response to an initial positive finding. Toilet bowel FOBTs are not recommended. FITs are more patient-friendly and are likely to be equal or better in sensitivity and specificity.
- FFS every 5 years
- FOBT or FIT every year plus FFS every 5 years. FFS together with FOBT is preferred compared with FFS alone or FOBT alone
- DCBE every 5 years
- Colonoscopy every 10 years

Surveillance for increased-risk patients

Positive family history

About 25% of CRC cases are associated with a positive family history. A small number are associated with well-defined hereditary colon cancer syndromes such as Lynch Syndrome (2%–3% of cases), familial adenomatous

polyposis (< 1% of cases), and the hamartomatous polyposis syndromes (< 0.1% of cases). Uncharacterized cases have been termed Common Familial Colon Cancer. A family history should be obtained not only for CRC, but also for other Lynch Syndrome cancers. Common Familial Colon Cancer is also associated with a history of adenomatous polyps.

Family histories are often inadequate for cancer screening. In one survey, a cancer family history was obtained in 68% of patients, information about a specific relative and the type of cancer in 61%, and age at diagnosis in 39% of patients. Only 17% of patients who met criteria for early onset breast cancer were referred for genetic counseling [8].

Common familial colon cancer

Numerous studies have documented the relative risk for CRC according to family history. Table 1 summarizes information from these studies. In general, colonoscopy should be used for surveillance when patients have a positive family history. Most guidelines recommend that surveillance begin before age 50 years, and be repeated more often than every 10 years. Guidelines differ on whether to take into account relatives who develop CRC at ≥ 60 years, second-degree relatives, or relatives with polyps. Guidelines from the American Cancer Society, the Gastrointestinal (GI) Consortium, and the American College of Gastroenterology (ACG) for screening patients with a positive family history are summarized below [30,65,82].

One first-degree relative with CRC or adenomatous polyps diagnosed at age ≥ 60 years
ACS: Screening as for average risk
GI Consortium: Screening as for average risk, but starting at 40 years old
ACG: Colonoscopy every 10 years, starting at 40 years old
One first degree relative with CRC or adenomatous polyps diagnosed ≤ 60 years or multiple first-degree relatives diagnosed at any age
ACS: Total colon examination every 5-10 years, starting at 40 years old or 10 yrs younger than the youngest affected relative
GI Consortium: Colonoscopy every 5 years, starting at 40 years old or 10 years younger than youngest affected relative
ACG: Colonoscopy every 3-5 years, starting at 40 years old or 10 yrs younger than youngest affected relative (no statement on polyps)

Table 1
Relative risk of CRC according to family history

Family history	Relative risk
One first-degree relative with CRC	2–3
Two first-degree relatives with CRC	3–4
One first-degree relative with CRC diagnosed at age ≤ 50 years	3–4
One second- or third-degree relative with CRC	1.5
Two second-degree relatives with CRC	2–3
One FDR with an adenomatous polyp	2

Familial adenomatous polyposis

FAP is an autosomal dominant syndrome caused by germline mutations in the *APC* gene. Fifty percent of affected patients develop adenomatous polyps by age 15 and 95% by age 35. From 100 to thousands of polyps may be found. The average age at diagnosis of CRC is about 35–40 years, and the lifetime risk of CRC approaches 100%. FAP accounts for < 1% of all CRC cases [83].

There are no diagnostic problems associated with the clinical presentation of FAP patients, except in attenuated syndromes. Testing for *APC* gene mutations is commercially available and should be done first on an affected family member. A specific mutation can be found in about 70% of cases. When the test is positive, other family members can be screened for the same mutation. Those with negative tests can be reassured that they do not have FAP with a certainty approaching 100%, and should be offered normal-risk screening. If a specific mutation is not found in an affected family member (about 30% of cases), the responsible mutation may not be detectable by current techniques. In such cases, the genetic testing is uninformative and not helpful. Family members must have endoscopic screening. Generally, FFS can be used rather than colonoscopy (except in attenuated FAP), because many polyps occur throughout the colon, including the rectum.

Colonoscopic surveillance recommendations from the American Gastroenterological Association (AGA) and the ACG for FAP patients with uninformative genetic testing [65,82] are

GI Consortium: FFS every year beginning age 10–12
ACG: FFS every 1–2 years beginning age 10–12; if screening is negative by age 40, patients can revert to normal risk screening; older unscreened relatives of patients with FAP should have colonoscopy

When FAP is confirmed either by genetic testing or by endoscopy, total colectomy should be recommended because the lifetime risk for CRC is close to 100%. If a subtotal colectomy is done, the rectal remnant must be screened every year using FFS. Upper gastrointestinal endoscopy should be done every 1–3 years to screen for gastric or periampullary adenomas.

Attenuated polyposis syndromes related to the APC gene

There are several syndromes related to the *APC* gene. Affected patients present with fewer polyps and at a later age than those with classic FAP.

Attenuated FAP is a variation of FAP in which mutations occur in the 5′ end (first 5 exons), the 3′ end, or in exon 9, of the *APC* gene. Ten to 100 adenomas are found and there may be rectal sparing. Compared with classic FAP, there is a 10–20 year delay in onset of CRC, but lifetime risk is still very high. Gastric and duodenal adenomas are common. Colonoscopy, rather than FFS, should be used for screening. Depending on the number of polyps and the rate of polyp development, patients may be managed

by frequent colonoscopic surveillance and polypectomy, or by colectomy. Endoscopic surveillance of the stomach and duodenum is recommended. Genetic testing can be done as for FAP [84,85].

I1307K mutations in the *APC* gene cause genetic instability and predispose to a second downstream stop codon mutation, which leads to an attenuated FAP phenotype. The risk of CRC, breast cancer, and several other cancers is increased about twofold. The mutation is carried by about 6% of Ashkenazi Jews and in 28% of Ashkenazi Jews with CRC [83]. Patients are followed by surveillance colonoscopy and polypectomy.

MYH gene mutations may cause an autosomal-recessive polyposis syndrome. *MYH* is a base-excision repair gene. Inheritance of two mutated alleles causes G:C to T:A mutations throughout the genome, leading to secondary *APC* gene mutations. Patients with FAP-*MYH* polyposis present with 15-100 adenomas. Unlike attenuated FAP, transmission is not vertical (no history in parents or children), and there is no germline mutation in the *APC* gene. The incidence of CRC is 40%–50% at a mean age of 43–58 years [86,87]. A few patients have presented with early onset CRC and fewer than 15 polyps [87]. Genetic testing is done first by mutation-specific testing, because 80% of affected persons have one of two specific *MYH* mutations. If one of these is present, then sequencing is done to identify the other mutated allele [86–89].

Lynch Syndrome

Lynch Syndrome (hereditary non-polyposis colorectal cancer) is an autosomal dominant syndrome caused by a germline mutation in one of the DNA mismatch repair (MMR) genes, most commonly *MSH2* and *mLH1*, less commonly *MSH6* or *PMS2*. MMR mutations accumulate at a very high rate. Errors are more likely in non-coding DNA sequences with multiple repeats (microsatellites), leading to microsatellite instability (MSI). Lynch Syndrome is associated with 2%–3% of all CRC cases.. The lifetime risk of CRC is up to 70%. Colorectal cancers present at an early age, are often right sided, and have characteristic histology. Synchronous and metachronous CRCs are common. There is an increased risk of a number of tumors of other organs, including uterus, ovary, stomach, pancreas, ureter and renal pelvis, biliary tract, small bowel, and brain. Sebaceous adenomas and keratoacanthomas occur in the Muir-Torre variant [90,91]. The median age of patients who present with CRC in Lynch Syndrome may be later than previously appreciated. In a recent report, the median age of patients who had CRC was 54 years in men, but 70 years in women. The median age of patients who had endometrial cancer was 62 years [92]. It has been suggested that Lynch Syndrome should be considered in 0.5% to 1% of all patients who present for CRC screening, and in 10%–15% of all patients who present with CRC [93]. In one study, 19% of sequential CRC patients met the Bethesda Guidelines, but only 17% were referred for genetic testing [94].

Suspicion of Lynch Syndrome should be based on the family history or on particular presentations of CRC or another related tumor. Other elements in the diagnosis of Lynch Syndrome include confirmation of MSI in resected tumor tissue and determination of the specific germline mutation. The Amsterdam II Criteria for the Diagnosis of Lynch Syndrome and the Revised Bethesda Guidelines for Testing Colorectal Tumors for MSI are presented elsewhere in this issue in the article, "Surgical Implications of Colorectal Cancer Genetics" by Rodrigues-Bigas and colleagues.

Genetic testing for Lynch Syndrome

Genetic counseling should be offered to any patient who is being considered for genetic testing. If resected CRC tissue is available, it may be tested for MSI. An alternative tissue test is immunohistochemistry (IHC) staining for the protein gene products of *MSH2*, *mLH1*, and *MSH6* [83,93]. Both tests are commercially available, and can be done on fixed tissue. MSI or IHC testing should be done on patients meeting the Bethesda Guidelines. If the tumor is found to be MSI-high, or if IHC testing shows an absence of MMR gene product, the patient should be tested for a germline MMR mutation.

About 60% of patients who meet the Amsterdam II Criteria will have an MMR gene mutation. If a germline mutation is identified, family members at risk can be screened for that mutation. A negative result effectively rules out Lynch Syndrome. Individuals who do not carry the germline mutation can be reassured and offered normal-risk screening. Family members who carry the germline mutation must be offered intensive surveillance. If a germline mutation is not identified in an affected family member, genetic testing is not helpful, because not all mutations producing Lynch Syndrome are currently detectable. In this situation, all potentially affected family members must be offered intensive surveillance.

Surveillance by full colonoscopy should be started at age 25 years, or 10 years younger than the youngest affected family member, and should be repeated every 1 to 3 years. After 40 years of age, or whenever polyps are detected, colonoscopies should be done yearly. Intensive surveillance has been shown to reduce CRC mortality by 65% [65,95]. Prophylactic colectomy should be strongly considered in confirmed mutation carriers who are unwilling or unable to undergo surveillance. Total or subtotal colectomy should be done if CRC is found, because the risk for metachronous CRC is up to 40%. If subtotal colectomy is done, yearly screening of the rectal segment should continue, because the risk of rectal cancer is about 1% per year [96].

There have been no controlled studies of intensive screening for other common Lynch Syndrome tumors. Nevertheless, screening for endometrial and ovarian cancer has been recommended, beginning at age 30–35 and repeated every 1–2 years. When fertility is no longer desired, prophylactic total abdominal hysterectomy and bilateral salpingo-oophorectomy should also be considered, particularly if colectomy is to be done.

In families where gastric cancer or urinary tract cancer has been identified, surveillance gastroscopy, renal ultrasound, and bladder cytology should be considered, although there is no proof of benefit [91].

Attenuated Lynch Syndrome

About 10% of Lynch Syndrome cases are caused by mutations in *MSH6*. A closely related gene, *MSH3*, can partially compensate for mutations in *MSH6*. Cancers occur about 10–20 years later than in classic Lynch Syndrome, but by age 70, the cumulative risk of CRC is about 70% in men. By the same age, the risk of CRC in women is only 30%, but the risk of endometrial cancer reaches 70% [97].

Other hereditary syndromes

Several other rare hereditary syndromes are associated with an increased risk of CRC. These are discussed briefly below. For a more complete discussion, the reader is referred to an excellent recent review [90].

Peutz Jeghers is an autosomal dominant syndrome that leads to perioral pigmentation and histologically distinct gastrointestinal polyps. These occur predominantly in the small bowel but may occur anywhere in the gut. Mutations in the *STK11* tumor suppressor gene can be identified in 60% of cases. Clinical features are usually diagnostic. Benign complications of the polyps, such as small bowel obstruction or bleeding, occur at an early age. The lifetime risk of CRC is 40%, and of breast cancer $> 50\%$. Patients are also at increased risk for a number of other tumors, including gastric, pancreatic, small bowel cancer, ovarian, uterine, cervical, testicular, and pulmonary. Screening colonoscopy is recommended every 3 years, starting when symptoms present or in the late teens [93]. Screening gastroscopy and small bowel examination are also recommended every 2 years, starting at 10 years of age.

Juvenile polyposis is an autosomal dominant syndrome. It should be suspected if more than three juvenile polyps are found in the colon, or if juvenile polyps are found in other areas of the gut. Mutations have been identified in the *MADH4* (*SMAD4*), *BMPR1A* genes. Mutations are not familial in 25% of cases. Genetic studies may be helpful, because juvenile polyps also occur sporadically and the clinical features are not otherwise diagnostic. Benign complications of the polyps may occur in young children. The lifetime risk of CRC is 60% and the mean age of presentation is 34 years. Patients are also at increased risk for gastric, small bowel, and pancreatic cancer. A screening colonoscopy is recommended every 3 years, as well as a screening gastroscopy and a small bowel examination every 2 years, starting at 15 years of age [93].

Inflammatory Bowel Disease

The risk of CRC is increased in chronic ulcerative colitis (UC) and in Crohn colitis. For a patient who has extensive colitis (involving the colon

proximal to the splenic flexure), the risk for CRC is about 5% after 10 years, 20% after 20 years, and 40% after 25 years. Risk is lower in patients with left-sided colitis. No appreciable increased risk occurs with ulcerative proctitis. The risk of cancer is further increased in patients who have severe inflammation, sclerosing cholangitis, or a family history of CRC [98,99]. The risk of cancer may be reduced up to 40%–75% by the regular use of sulfasalazine or mesalamine [98,100,101]. This preventive measure should receive as much emphasis as surveillance [101].

In Inflammatory Bowel Disease (IBD), dysplasia may precede the development of CRC. The object of surveillance in IBD is to discover those patients at highest risk of CRC by detection of dysplasia with systematic biopsies, as well as to discover CRC at an early stage. Several small case-control studies have shown improved (Duke's) staging and lower CRC incidence among patients who have UC and who undergo surveillance colonoscopies [98,102,103]. There is no information regarding surveillance in Crohn's colitis [65]. Surveillance colonoscopy should begin after 8–10 years of extensive colitis and after 15 years of left-sided colitis. Patients with sclerosing cholangitis should begin surveillance upon diagnosis. Colonoscopies should be done every 1 to 3 years; the frequency should be increased as the duration of disease increases. Surveillance colonoscopies should be avoided during periods of active colitis. Four biopsies should be taken every 10 cm. Strictures and mass lesions other than pseudopolyps should be biopsied [65,104,105]. Patients found to have high-grade dysplasia (HGD), multifocal low-grade dysplasia (LGD), or dysplasia associated with a lesion or mass (DALM) are at high risk for CRC. In one study, 42% of patients who had HGD and 16% of patients who had LGD were found to have CRC at the time of colectomy. Of patients who had LGD and who were followed, 32% progressed to HGD or CRC [106]. If biopsies are read as indefinite for dysplasia, the frequency of surveillance should be increased to every 6 months. There is substantial variability in the interpretation of dysplasia among pathologists; a reading of LGD or HGD should be confirmed by an expert pathologist. Given the probability of sampling error, a finding of definite dysplasia cannot be mitigated by repeat colonoscopy with negative biopsies. Patients with IBD may develop sporadic tubular adenomas. When an apparent adenoma is encountered during surveillance colonoscopy, it should be removed, and biopsies of the surrounding mucosa should be obtained. Tubular adenomas with only low-grade dysplasia and with no dysplasia in surrounding mucosa, do not appear to be markers of CRC risk over short intervals and can be considered sporadic adenomas rather than DALM [65].

Surveillance after removal of adenomatous polyps or colorectal cancer

Adenomatous polyps

Surveillance colonoscopy after removal of adenomatous polyps has two objectives: (1) to detect and remove polyps missed during the first

colonoscopy, and (2) to detect and remove new polyps. The overall incidence of advanced neoplasms 3 years after initial colonoscopy is about 3% [54]. Risk factors for advanced neoplasms after initial colonoscopy and polypectomy, at index colonoscopy, are

- Adenoma $\geq$ 10 mm
- Multiple adenomas
- Advanced histology (villous, high-grade dysplasia)
- Proximal location of adenoma
- Older age at diagnosis of adenoma(s)
- Family history of CRC in a parent

Hyperplastic polyps are not considered a risk factor for subsequent advanced adenomas. Patients who have large sessile polyps removed at the index colonoscopy should have a follow-up colonoscopy within 6 months to insure complete excision [107].

Guidelines for surveillance after polypectomy are generally consistent, but differ in some details. Guidelines from the American Cancer Society and the Gastrointestinal Consortium [30,65] are summarized below.

- ACS
- 1 adenoma $\leq$ 10 mm 3-6 years
  If follow-up colonoscopy is negative, revert to average risk surveillance
- 1 adenoma $>$ 10 mm or $\geq$ 3 adenomas or advanced histology 3 years
  If follow-up colonoscopy is negative, repeat in 3 years, and if negative again, revert to average risk surveillance
- Gastrointestinal Consortium
- 1-2 adenomas $<$ 10 mm 5 years
- 1 adenoma $\geq$ 10 mm or $\geq$ 2 adenomas or advanced histology 3 years
  If follow-up colonoscopy is negative, continue colonoscopy every 5 years

Surveillance colonoscopy is frequently overused. In one survey, 50% of endoscopists recommended surveillance within 3 years after removal of one small adenoma, and many recommended surveillance after finding only hyperplastic polyps [108,109].

Colorectal cancer

When CRC is discovered, the entire colon must be examined for the presence of synchronous neoplasms. This can be done before resection or within 6 months after resection if obstruction precluded a complete initial examination. Surveillance colonoscopy after resection of colorectal cancer is done to detect local recurrence and metachronous neoplasms. Early surveillance after resection for colon cancer differs from that after resection for rectal cancer. The rate of local intraluminal recurrence of colon cancer is quite

low (about 3%). Most local recurrences are extraluminal, are best detected by surveillance CEA and CT, and are rarely resectable for cure. The American Society of Colon and Rectal Surgeons, the AGA Consortium, and the American College of Gastroenterology recommend that the first surveillance colonoscopy be done 3 years after resection if the entire colon was cleared perioperatively [65,107,110]. Frequent early colonoscopy for intraluminal recurrence of colon cancer offers no overall survival benefit [111]. The risk of local recurrence after resection of rectal cancer differs according to the technique of resection. Recurrence rates after excision by blunt dissection are as high as 45%, but less than 10% after total mesorectal excision, and as low as 2.4% if pre-operative radiotherapy is followed by total mesorectal excision [112]. If blunt dissection is used, it is prudent to recommend FFS every 6 months for the first 2 years [113]. Endoscopic ultrasound has been used for surveillance after resection of rectal cancer, and early detection of recurrences has been reported, but a survival benefit has not been proven [114].

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