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Editorial

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Colorectal Cancer Can Be Prevented

Generally, in cancer therapy the best hope for a successful outcome lies in achieving early cancer detection, and curative surgical resection. Colorectal cancer (CRC) prevention is an exception, and has become an important goal for health providers, physicians and the general public. CRC is a highly prevalent disease, associated with considerable mortality and morbidity rates, with more than 1,000,000 new cases and 500,000 deaths expected worldwide in 2006. CRC has a natural history of transition from precursor to malignant lesion that spans, on average, 15–20 years, providing a window of opportunity for effective intervention and prevention. Despite efforts to improve performance characteristics, some CRC screening measures, in particular occult blood testing, are relatively insensitive for detecting adenomas. For this reason, colonoscopy has become a very popular means of CRC screening, both thanks to its sensitivity in detecting small adenomas, and its therapeutic benefit from polypectomy thus preventing subsequent CRC.

Prof. Regula has been responsible for launching a very successful national screening colonoscopy program in Poland. The program involves more than 100 centers, is sponsored by the Polish government, and is well-accepted by both physicians, and more importantly, by the public. So far, more than 150,000 patients have been enrolled for screening. The results are very promising, a significant number of lives have been saved, and the overall complication rate is very low.

Colonoscopy is the 'gold standard' for CRC screening in an 'average-risk' population according to some authorities. However, despite the proven efficacy of screening colonoscopy, the limitations of high cost, invasiveness, patients' reluctance to undergo a bowel purge and the relative unavailability of colonoscopy to the entire population, mean that only 30% of the public accept this form of screening. Some recently developed techniques may improve the yield of this program, e.g.

(1) Prof. Burt's group informs us how to better identify high-risk subjects. In the future, based on a fingerprint of one's genome and assessment of environmental risk factors, we should be able to choose those subjects who will benefit the most from CRC screening.
(2) Prof. Young describes novel noninvasive screening tests, some of which are already on the market, which have given very promising results thanks to their high sensitivity and specificity.
(3) Prof. Rösch and his colleagues tell us about the new colonoscopes which are on the horizon, that will make screening colonoscopy easier, cheaper and more patient-friendly. The safety and efficacy of these new devices have been shown in preliminary human studies, but the final proof will require randomized control studies.
(4) Drs. Blachar and Sosna update us about the strengths and weaknesses of virtual colonoscopy, and discuss its potential role for screening.

Early detection of CRC is not enough by itself. Surgery is still required, recurrence is possible, and anxiety persists. Recognition of the ability to prevent CRC by identifying and removing precancerous adenomas has led to a marked increase in the use of colonoscopy as a primary screening tool. As the emphasis of screening shifts towards precancerous adenomas, these adenomas become an attractive target for primary prevention methods. As promising as modern screening tests may be, they are relatively expensive, carry some risk, and require expertise. Most importantly, the level of patient willingness to accept screening is low in many countries, thus limiting its effectiveness.

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Overall, almost all epidemiological studies have clearly demonstrated that aspirin and NSAIDs can decrease the incidence and mortality from CRC. However, some of these agents are not without risk, and can cause serious gastrointestinal and cardiovascular side effects. In modern medicine, we should aim for personalized treatment. Cancer is an unwanted event resulting from multiple etiologies, both from genetic and environmental factors. In the future, we hope to be able to offer a method of prevention to an individual, based on the molecular signature of his genome, on the molecular profile of the adenoma that was removed, and on any other risk factors that he/she has been exposed to. In this issue, Prof. Jankowski and his colleagues share with us their vision about the current state of chemotherapy and its future.

Finally, Prof. Lynch reminds us that chemoprevention and early detection are not separate entities. It is important that in a high-risk population, a combined approach of endoscopy and drug treatment be used.

We are at the beginning of the journey, which promises to lead to prevention of CRC.

Nadir Arber, Tel Aviv

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Table 1. Colorectal cancer predisposition syndromes: presentation and screening

Syndrome	Colon presentation	Lifetime colon cancer risk	Extracolonic manifestations
FAP	Over 100 adenomatous colorectal polyps (average age of polyposis onset is 16 years)	Nearly 100%	Duodenal and periampullary cancers (3–5% risk), childhood hepatoblastoma, other cancers: pancreatic, thyroid, gastric, brain (all rare); desmoid tumors (20% risk); Gardner syndrome: osteomas (often of the jaw), epidermoid cysts, CHRPE, dental anomalies; Turcot syndrome: medulloblastoma
Lynch syndrome	Colon cancer (often early onset, average age of onset 44–61 years)	50–80%	Endometrial cancer (40–60% risk), ovarian cancer (9–14% risk); other cancers: stomach, renal, ureter, small intestine, biliary (all 10% or less); Muir-Torre syndrome: cutaneous keratoacanthomas, sebaceous gland tumors; Turcot syndrome: glioblastoma
AFAP	10–100 adenomatous colorectal polyps with a tendency toward polyps in the right side of the colon (average age of polyposis onset is 26)	80%	Similar to FAP
MAP	10 to over 100 colorectal polyps	Undefined, but increased over the general population	Not generally seen – some reports of patients with CHRPE, osteomas, dental cysts, duodenal adenomas, and/or gastric cancer
HMPS	Colorectal polyposis with polyps of different histologies (adenomas – classic, serrated, tubular; hyperplastic; juvenile; mixed juvenile-adenomatous or hyperplastic adenomatous)	Undefined	Rare extracolonic cancers including pancreatic, breast, thyroid, and kidney
HPS	Colorectal polyposis featuring large, hyperplastic polyps and some adenomas/ serrated adenomas	Undefined	None reported
Peutz-Jeghers	Colorectal polyposis involving characteristic hamartomatous polyps	39%	Blue/brown pigmentation (starting in childhood around the mouth, nose, and/or eyes and on the buccal mucosa and fingers; spots fade with age); upper GI polyposis (particularly small intestine); other cancers: breast, ovarian, pancreatic, small intestine, gastric, esophageal, cervical (adenoma malignum); sex cord tumors, Sertoli cell tumors
JPS	Colorectal polyposis involving juvenile polyps	17–22% by age 35, ~68% by age 60	Gastric polyps (if present, 21% risk of gastric adenocarcinoma), other cancers: pancreatic and small intestine
Cowden syndrome	Colorectal hamartomas	Unclear, around 9%	Breast cancer (30% risk in women), thyroid cancer (10%), upper GI hamartomas; macrocephaly, fibrocystic breasts, dermatologic features (80% of affected individuals) including oral papillomas, trichilemmomas, keratoses of the hands and feet, and lipomas

Table information summarized from references [1, 2, 5, 9, 15, 26, 27].

identified as being at a high risk for a cancer predisposition syndrome are provided with risk assessments tailored to their personal and family health histories. Explanations of the impact of a potential syndrome diagnosis are provided and genetic testing is coordinated. Later, the test results are discussed with the patient and a screening/treatment plan is created based on these results.

Most patients at high risk for colorectal cancer, however, present first to primary care physicians or general gastroenterologists, rather than to genetic services. Many

Screening/treatment recommendations
Annual colonoscopy or sigmoidoscopy starting between ages 10 and 12 (colonoscopies once colon polyps are identified). EGD starting between ages 20 and 25 and repeated every 1–3 years, depending on polyp severity. Colectomy once colorectal polyposis becomes too severe to manage through polypectomy. Consider chemoprevention.
Colonoscopy every 1–2 years starting at age 25 or 10 years prior to the earliest age of colorectal cancer diagnosis in the family. Subtotal or partial colectomy if colon cancer develops. Endometrial cancer screening every 1–2 years starting between ages 25 and 35 (or 5–10 years earlier than youngest endometrial cancer diagnosis in the family). Ovarian cancer screening every 6–12 months starting at the same time as endometrial screening. Consider prophylactic hysterectomy/oophorectomy. Consider upper EGD every 1–2 years depending on family history of upper GI cancers.
Annual colonoscopy starting in the late teenage years. EGD starting between ages 20 and 30 and repeated every 1–3 years, depending on polyp severity. Colectomy if polyp burden becomes to high to manage via polypectomy. Consider chemoprevention.
Colonoscopy recommended every 1–2 years starting at age 25–30 years. Upper endoscopies recommended every 2–5 years, beginning at age 25–35. Colectomy may be needed in patients with substantial polyposis
No set consensus – consider colonoscopies every 1–2 years starting at age 20. Colectomy may be needed if polyposis becomes too severe.
No set consensus – consider colonoscopy every 1–3 years depending on patient's level of polyposis. Colectomy may be needed when polyps can no longer be managed with polypectomy.
Colonoscopy screening starting at age 25 and repeated every 1–3 years. Upper endoscopy and small bowel examination starting between ages 8 and 10 and repeated every 2 years. Mammography every 2 years starting at age 20. Pancreatic screening starting at age 30 and repeated every 1–2 years (endoscopic ultrasound and abdominal ultrasound). Endometrial cancer screening annually starting at age 20.
Colonoscopy starting between ages 15 and 18 and repeated every 1–3 years. Upper endoscopy and small bowel examination every 1–2 years starting at age 15–25.
Self-breast exams starting at age 21 and annual mammography starting at age 30. Annual thyroid screening starting around puberty. Endometrial cancer screening starting between ages 35 and 40. No set consensus on GI screening – Schriebman and colleagues recommend colonoscopy, upper endoscopies, and small bowel examination starting at age 15 and repeated every 2 years.

health professionals in this first line of patient contact are unaware of how and when to contact genetic services regarding a patient. Gastroenterologists have a key role in identifying high-risk patients and ensuring they receive appropriate care. The ability for them to suspect a patient to be at risk for a cancer predisposition syndrome is crucial for a rapid diagnosis. In this review, the hallmark features of syndromes known to predispose to high-risk colorectal cancer will be presented, highlighting the typical age at presentation, common colonoscopy findings, pathology features, genetic basis, family history features, and associated extra-colonic cancer risks. We will start with the most well-described and easily identified syndrome, familial adenomatous polyposis (FAP), and move on to other syndromes that provide greater diagnostic challenges. Once a patient is diagnosed with one of these disorders through genetic consultation, they generally return to their general gastroenterologist for regular screening and surveillance. Disease-specific screening and surgical recommendations for affected individuals are given as part of the genetic consult and will be outlined here. Finally, we will touch on overall strategies for first identifying patients who may be at risk for one of these syndromes and how to refer them on for genetics evaluation.

Familial Adenomatous Polyposis

Classic FAP is one of the most striking and well-described genetic syndromes that results in colorectal polyposis. FAP affects approximately 1 in 10,000 persons [1]. Although the condition is relatively rare, the unique presentation of FAP renders it highly recognizable based on colonoscopy findings.

Presentation

FAP is characterized by the appearance of hundreds to thousands of adenomatous colorectal polyps in affected individuals. Polyps on average begin to appear at age 16 years [1, 2]. While the visual presentation of hundreds of colorectal polyps is the most striking feature, pathological confirmation of their adenomatous histology distinguishes FAP from polyposis syndromes that exhibit hamartomas or hyperplastic polyps, or polyps of mixed pathology. A definitive clinical diagnosis of FAP specifies that an individual have over 100 adenomatous colorectal polyps over his or her lifetime. Individuals affected with FAP can manifest extra-colonic features as well, including malignant and nonmalignant growths (table 1). Two variants of FAP, Gardner syndrome and Turcot syndrome, are also described in table 1.

Table 2. Availability of genetic testing for colorectal cancer predisposition syndromes

Syndrome	Gene	Inheritance pattern	Clinical genetic testing available?	Frequency of identifying a genetic mutation in an index case	Approximate cost of testing for index case
FAP/AFAP	*APC*	autosomal dominant	yes	80–90%	USD 1,650 (sequencing)
Lynch	*MLH1, MSH2, MSH6, PMS2*	autosomal dominant	yes	50–70%	USD 300–600 (MSI testing) USD 300–500 (IHC testing) USD 2,340–2,900 (for *MLH1, MSH2*, and *MSH6*) USD 1,200–2,400 (for *MLH1* and *MSH2* alone)
MAP	*MYH*	autosomal recessive	yes	~23% of individuals with 3–100 colorectal adenomas	USD 285 (two common mutation analyses) USD 500–1,035 (sequencing)
HMPS	candidate locus at 15q13–14; *BMPR1A* (reported in 1 family)	appears autosomal dominant	no	N/A	N/A
HPS	Unknown	uncertain – a few families with autosomal dominant inheritance, at least one with autosomal recessive	no	N/A	N/A
Cowden syndrome	*PTEN*	autosomal dominant	yes	80–90%	USD 775–1,540 (sequencing)
Peutz-Jeghers syndrome	*STK11*	autosomal dominant	yes	91% near 100%	USD 775–1,540 (sequencing)
JPS	*BMPR1A, SMAD4*	autosomal dominant	yes	~20% of JPS is caused by *BMPR1A* mutations ~20% of JPS is caused by *SMAD4* mutations	USD 1,030 (*BMPR1A* sequencing) USD 460–1,030 (*SMAD4* sequencing)

Testing for a known mutation in a family is significantly cheaper (~USD 300–500 per test) and the sensitivity of the test is >99%.
Table data summarized from reference [1] and individual laboratories identified on www.genetests.org.

Genetics (table 2)

Classical FAP has been associated with mutations in one gene: *adenomatous polyposis coli (APC)* [1–4]. The product of the *APC* gene functions as a tumor suppressor [1, 2]. Clinical genetic testing for mutations of the *APC* gene is commercially available. If an individual with FAP has an identifiable mutation in the *APC* gene, this allows for accurate testing of at-risk family members who may not have undergone any type of colon screening. Mutations in the *APC* gene are inherited in an autosomal dominant pattern. This means that each child of an affected individual has a 50% chance of having FAP. The *APC* gene also has a high new mutation rate when compared with other cancer predisposition syndromes. Up to 30% of all identified *APC* mutations are new mutations, meaning that they occurred during the process of conception or shortly thereafter, rather than being inherited from either parent [1, 2]. Given the early onset of polyposis, genetic testing of children at 50% risk for FAP is recommended to determine if appropriate screening is indicated. A general consensus in the genetics community encourages the genetic testing of minors who are at risk for a known genetic condition if a definite diagnosis would change medical management. Individuals affected with FAP are recommended to begin colonoscopy or sigmoidoscopy surveillance between ages 10 and 12 [4]. Thus, genetic testing for a child with possible FAP could be performed at age 10. Children born with an *APC* mutation also have an increased risk for developing hepatoblastoma, most commonly during the first 5 years of life [1]. At this time, there is no consensus recommendation for hepatoblastoma screening, but initiating screening with 6-month AFP blood testing and abdominal ultrasound would warrant genetic testing for at-risk children from birth.

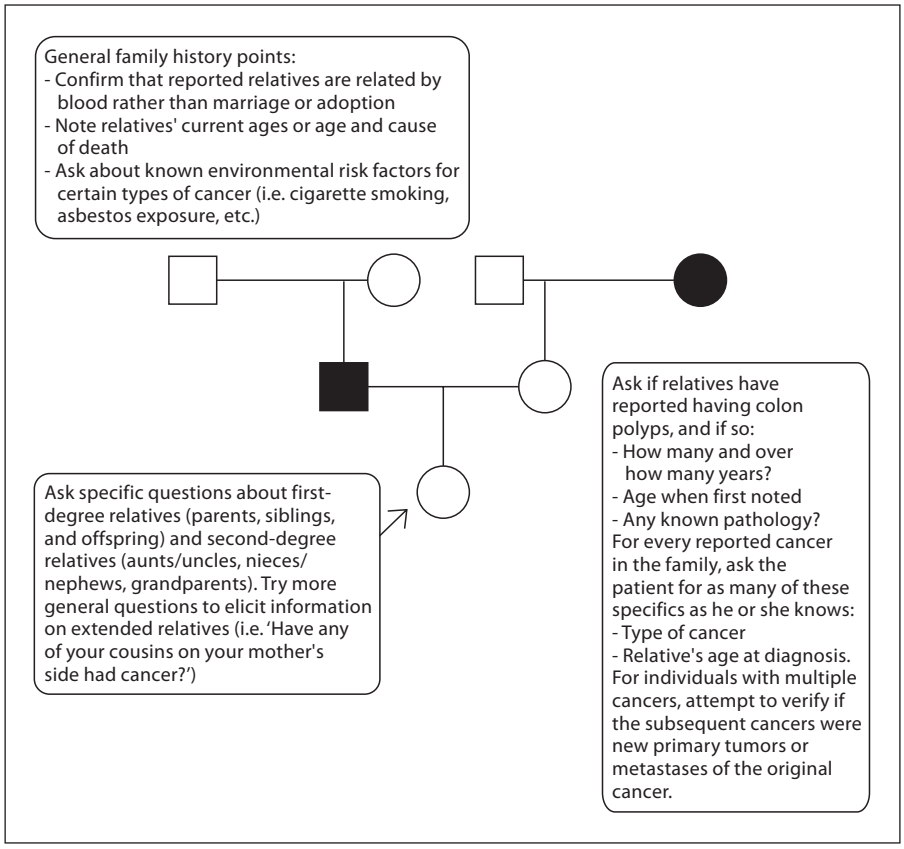

Fig. 1. Family history gathering for general gastroenterologists directed at identifying patients at high risk for a colorectal cancer predisposition syndrome.

Family History Features

Due to the relatively high new mutation rate in the *APC* gene, a family history of colorectal cancer may not always be reported in an individual presenting with features of FAP. Family history information may thus not always be helpful in raising the suspicion of FAP, but is still invaluable for the creation of a future testing strategy for other family members. Referral for genetic evaluation and *APC* genetic testing is recommended for individuals with the clinical features of FAP even in the absence of a suggestive family history. The family history may also reveal a known clinical diagnosis of FAP or other cancers or benign features of the disease.

Screening and Treatments after Diagnosis (table 1)

As discussed, screening colonoscopy or sigmoidoscopy is recommended to start between ages 10 and 12 in individuals genetically affected with or at risk for FAP [4, 5]. Once colorectal polyps are identified, colonoscopy should be repeated annually with polypectomy as appropriate, although removal or ablation of large numbers of small polyps is generally not undertaken [4]. Due to the increased risk for duodenal polyposis, esophagogastroduodenoscopy (EGD) is recommended to begin between ages 20 and 25 or prior to colectomy, and to be repeated every 1–3 years, based on the severity of the polyposis [1].

The significant colorectal polyp burden found in an individual with classic FAP, however, cannot be managed through colonoscopy surveillance and polypectomy alone [4]. Without surgery, affected individuals have a near 100% likelihood of colorectal cancer by age 39 [1, 2]. Colon removal is generally recommended for patients with FAP once polyps are too numerous to safely manage endoscopically [1].

Two primary surgical options for FAP patients are colectomy with ileorectal anastomosis (IRA) and proctocolectomy with ileal-pouch anal anastomosis (IPAA). Restorative proctocolectomy is also frequently done and is near equivalent to IPAA. A recent study by Aziz et al. [3] that reviewed the reported efficacy of these two techniques in FAP patients found that patients who had an initial IRA experienced less frequent bowel movements (including a decreased need to stool at night), less overall

incontinence, and were less likely to need incontinence pads when compared with patients who had an IPAA. However, individuals with an IPAA had a decreased need for urgent stooling, decreased need for further surgery to the involved area, and no reported instances of pouch carcinoma [3]. Rectal cancer was reported in follow-up of 5.5% of FAP patients after IRA [3]. Deciding which surgery to proceed with in a patient affected with FAP should be based on the patient's rectal polyp burden [5]. Active research into chemoprevention agents (i.e. sulindac, rofecoxib) to reduce polyposis in patients with FAP continues to be pursued [6]. Celecoxib is the only chemoprevention agent FDA approved for use in individuals with FAP to date, although its effect appears to be modest compared to sulindac [6].

Lynch Syndrome

Lynch syndrome, also known as hereditary nonpolyposis colorectal cancer (HNPCC), is more common than FAP, but presents more diagnostic challenges [4]. The classical clinical diagnosis of Lynch syndrome is based on the 'Amsterdam criteria'. A family must meet each of the criteria which are three relatives with colon cancer and: (1) 2 of the 3 cases must be first-degree relatives of the 3rd; (2) the cases must extend over at least two generations; (3) at least 1 case must be diagnosed at an age younger than 50 years. The Amsterdam II criteria are similar, except any of the malignancies that occur in Lynch syndrome (table 1) can be included. As only about half of families will be found if only the Amsterdam criteria are used, other clinical features of the disease must be considered in determining which individuals should be considered as possibly having the syndrome and therefore be considered for genetic testing.

Presentation

The colonoscopy findings seen with Lynch syndrome are not easily distinguished from sporadic colon adenomas and cancers, although individuals with Lynch syndrome usually develop colorectal adenomas and cancer at earlier ages than the general population. The average age at colorectal cancer diagnosis is 44 years [2]. A 2005 study by Hampel et al. [7], however, suggests that the average age at colorectal cancer development in Lynch syndrome may be higher than previously reported. Hampel et al. [7] compiled data on 88 probands and 373 family members from 70 families who each had a known genetic diagnosis of Lynch syndrome. The median age at colorectal cancer diagnosis in the probands was 44 years, but the positive family members had a noticeably later age at colorectal cancer diagnosis, with a median age of 61 years [7].

Colorectal polyps in Lynch syndrome appear to progress to malignancy more quickly than is seen in sporadic or FAP adenomas. But survival rates after cancer diagnosis are better in Lynch syndrome patients compared to sporadic colon cancers [1, 2]. Synchronous and metachronous primary colorectal malignancies are more common in Lynch syndrome and there is a higher frequency of right-sided lesions [1, 2]. The lifetime risk for colorectal cancer in an individual with Lynch syndrome is between 50 and 80% [1, 2, 7].

Multiple extra-colonic cancers likewise occur in Lynch syndrome (table 1). Women with HNPCC have significantly elevated risks for endometrial and ovarian cancers (table 1) [1, 4]. Two variants of Lynch syndrome, Muir-Torre syndrome and Lynch-associated Turcot syndrome, are also described in table 1. The malignancies that occur in the Lynch and related syndromes histologically exhibit a higher frequency of tumor-infiltrating lymphocytes [8].

Genetics

The genetic basis of Lynch syndrome is more complicated than that of FAP. It arises from mutations in one of four genes (*MLH1*, *MSH2*, *MSH6* and *PMS2*), which are each a part of DNA mismatch repair. Mismatch repair dysfunction results in an increased frequency of DNA mutations, particularly mutations in areas containing otherwise normal repetitions of DNA sequence [1]. Approximately 90% of DNA mismatch repair gene mutations that give rise to Lynch syndrome are found in the *MLH1* or *MSH2* genes [1, 2]. Genetic testing for mutation finding, and thus diagnosis of Lynch syndrome, is commercially available. This testing can be ordered if a family meets the Amsterdam criteria, but other features of the disease need to be considered as many if not most Lynch syndrome families will not meet these strict criteria.

One feature of Lynch syndrome colon cancer tissue is microsatellite instability (MSI). Assessment of MSI can be helpful in identifying individuals with this condition. MSI is a measure of how frequently certain sites of DNA repetition (called microsatellites) have errors or mutations [1]. Colorectal cancers in Lynch syndrome show a high frequency of MSI. However, MSI testing is not diagnostic of Lynch syndrome, as approximately 10–15% of sporadic colorectal cancers also exhibit MSI [8]. The presence of tumor-infiltrating lymphocytes, as described

above, is a histologic clue to the presence of MSI, but is similarly found in 10–15% of sporadic colon cancers. The presence of either of these features may lead one to suspect Lynch syndrome, and thus lead to taking a more extensive family history and referral to genetic counseling for assessment and possible genetic testing.

Immunohistochemistry (IHC) testing of colorectal cancers can look for the absence of gene expression of one of the four mismatch repair genes. It has similar sensitivities and specificities to MSI testing. In evaluating an individual for Lynch syndrome, IHC testing can be used on a colorectal cancer tissue to check for reduced expression of any of the four mismatch repair genes, but again, 10–15% of sporadic tumors can also have reduced expression resulting from acquired mutations of one of the mismatch repair genes. IHC results can also be difficult to interpret, requiring substantial experience in the pathology laboratory doing the testing. Most of the sporadic colon cancers exhibiting loss of DNA expression will show loss of *MLH1* expression that arises from methylation of the *MLH1* promoter [9]. Lack of expression from methylation is due to inherited or germline mutations. When used together, MSI and IHC testing will identify approximately 95% of colorectal cancers with a mismatch repair gene defect [10].

Multiple criteria have been formed to assist clinicians in identifying which patients/families could be at high risk for Lynch syndrome and thus need tumor MSI/IHC testing or DNA mutation analysis. The Amsterdam I and II criteria (see above) are used to identify families at highest risk for Lynch syndrome [11]. The Bethesda guidelines (original and revised) were created to identify patients in whom MSI or IHC tumor testing could be pursued to clarify the patient's risk for HNPCC, particularly in families who do not meet the Amsterdam criteria (I or II).

These criteria and models, however, have not proven highly specific or sensitive for Lynch syndrome on their own. One approach that is under consideration is testing all colon cancers for MSI and IHC. One study looking at this approach was published in 2005 by Hampel et al. [9]. Tumors of 1,066 patients recently diagnosed with a colorectal adenocarcinoma were tested for MSI and IHC. IHC was completed for all tumors positive for MSI and for tumors of 109 high-risk patients who were negative for MSI [9]. Genetic testing for Lynch syndrome was also completed for all of the MSI-positive tumors and 5 MSI-negative tumors which had IHC abnormalities. A total of 23 patients were found to have identifiable Lynch syndrome mutations. Five of these 23 patients did not meet the Amsterdam or Bethesda guidelines for Lynch syndrome [9].

If a patient appears to have features suggestive of Lynch syndrome, i.e. colorectal cancer in close family members, colorectal cancer occurring at early ages (less than age 50), multiple colorectal primary tumors in one individual, and/or a colorectal cancer pathologically suggestive of Lynch syndrome, a genetics specialist can assist in clarifying whether genetic testing, MSI or IHC testing is likely to prove informative.

Screening and Treatments after Diagnosis

Colonoscopy screening for individuals with Lynch syndrome is recommended to begin at age 25 years, or 10 years younger than the earliest diagnosis of colorectal cancer in the family, whichever comes first, and to be repeated every 1–2 years (table 1) [1, 5]. For women, endometrial cancer screening should be initiated between the ages of 25 and 35 years, or 5–10 years earlier than the earliest age of endometrial cancer in the family [1, 5]. Screening includes transvaginal ultrasound and endometrial sampling to be repeated every 1–2 years [1, 5]. Ovarian cancer screening should be completed every 6–12 months with transvaginal ultrasound and CA-125 tumor marker testing [5]. Regular screening for other cancers associated with Lynch syndrome has not been delineated; however, upper gastrointestinal endoscopy and other cancer screening could be considered every 1–3 years, depending on the extracolonic cancers observed in the affected family [1].

Unlike FAP, prophylactic removal of the colon is not recommended for individuals affected with Lynch syndrome. Subtotal or partial colectomy has been recommended once a colorectal cancer is diagnosed [1]. Prophylactic hysterectomy with bilateral oophorectomy can be considered for women with HNPCC who wish to reduce their risks of endometrial and ovarian cancers [5].

Polyposis Syndromes Causing >10 Polyps in an Individual

Some undiagnosed patients will present with a range of 10–100 colorectal polyps. Identifying a diagnosis in this subset of patients can be significantly more difficult than identifying an individual affected with classic FAP. This presentation is still suspicious for an underlying inherited predisposition to colorectal polyps and cancer. The National Comprehensive Cancer Network recommends genetic evaluation for any individual with over

10 colorectal polyps over the course of his or her lifetime [5].

Several syndromes have been recognized that result in a milder degree of polyposis and may include a mixture of pathologic polyp types. These syndromes include attenuated FAP (AFAP), *MYH*-associated polyposis (MAP), hereditary mixed polyposis (HMP), hyperplastic polyposis syndrome (HPS), and the hamartoma-related syndromes. The hamartoma syndromes are rare and would be considered based on a patient's colorectal polyp pathology. The common features of the hamartoma syndromes and the recommended screening for affected individuals are summarized in table 1.

Attenuated FAP

Individuals with AFAP develop significantly fewer polyps (average of 30 polyps, generally less than 100) and there is an older average age of polyp development (approximately age 26) [1]. The potential for colorectal malignancy is also delayed in individuals with AFAP by approximately 10 years [1]. However, the overall risk for colorectal cancer in patients with AFAP is still substantial with an approximate 80% expected lifetime risk [1]. Upper gastrointestinal tract polyps and cancers are also seen in AFAP as in classic FAP, and in fact do not appear to be attenuated, unlike the colonic phenotype (table 1).

Due to the substantial lifetime risk for developing colorectal carcinoma, a significant family history of colorectal cancer may be seen with affected individuals. However, given the reduced polyp burden compared to classic FAP, there is an increased chance for affected family members to be unaware of their syndrome status, especially if they have only a few asymptomatic polyps and have not yet received a colonoscopy.

Like classic FAP, AFAP is associated with mutations in the *APC* gene, giving an autosomal dominant inheritance pattern [1]. *APC* mutations resulting in AFAP tend to occur at the 5′ and 3′ ends of the *APC* gene, and in the splice donor site of exon 9, whereas *APC* mutations resulting in classic FAP are located more centrally within the gene [1, 12, 13].

Every 1–3 years, colonoscopies are recommended for individuals with AFAP, starting in the late teenage years and depending on the polyp burden [1]. Colon polyps in individuals with AFAP occur more frequently in the proximal colon, so surveillance with full colonoscopy is needed. EGD is also recommended every 1–3 years, starting between ages 20–30 [1, 5].

Surgical treatment with eventual subtotal colectomy and ileorectal anastamosis is recommended for individuals with AFAP when the polyposis cannot be managed colonoscopically. Approximately one third of AFAP patients will not need colectomy, even at older ages, because of paucity of polyps. Distinguishing AFAP from classic FAP can sometimes be difficult, particularly in younger individuals who may have only begun to develop polyps [1]. Family history and the location of mutation within the APC gene should be taken into consideration when making decisions about removing versus retaining the rectum in younger individuals.

Patients with FAP or AFAP may equate colon removal with an ileostomy or colostomy with the use of an ostomy bag based on past family experience or lack of knowledge of present approaches. Ileostomy or colostomy is rarely needed for FAP and virtually never for AFAP, which is almost universally successfully treated with colectomy and ileorectal anastomosis. Patients need to be made aware that current surgical techniques for FAP and AFAP rarely require ileostomy.

MYH-Associated Polyposis

The severity of polyposis seen in patients with MAP can vary between an AFAP presentation to a near classic FAP presentation [14]. The majority of reported patients with MAP have between 15 and 100 adenomatous polyps [15]. In a 2005 study of 40 Dutch patients with MAP, the average age at diagnosis was 45 years [15].

MAP is usually not reported to present a risk for cancers or benign findings outside of the gastrointestinal tract [14]. Reports of patients with MAP presenting with CHRPE, osteomas, dental cysts, duodenal adenomas, and/or gastric cancer have been published, but the associations are nonetheless not clear (table 1) [15].

MAP is seen in an individual who has mutations in both copies of the *MYH* gene. This autosomal recessive inheritance is the only example of recessive inheritance for a colorectal cancer predisposition syndrome [14]. *MYH* is involved in DNA base excision repair, placing it in a different functional pathway than *APC* [1]. However, dysfunction in *MYH* can result in mutations of *APC* and *KRAS* as acquired mutations in these latter two genes can persist without the intact DNA repair function of *MYH* [15]. Approximately 10–20% of patients with presentations consistent with FAP or AFAP in whom APC mutations cannot be identified will have identifiable mutations in *MYH* [1].

Due to the autosomal recessive nature of MAP, a horizontal rather than vertical disease pattern can be seen in the family tree. An affected patient's parents are presumably both carriers, which means that while they them-

selves are not at risk for MAP, their children each have a 25% chance of inheriting both mutated alleles and thus having MAP. Notably, being a carrier (only one mutated *MYH* allele) may be associated with a slightly increased risk for colorectal cancer [15]. This could complicate family history analysis and cause the inheritance pattern to appear more autosomal dominant than recessive. The children of a patient with MAP would not be at risk to develop MAP, unless the patient's partner also carried a MAP mutation.

For patients with MAP, colonoscopies are recommended every 1–2 years, starting between ages 25 and 30 [15, 5]. Upper endoscopies can begin between ages 25 and 35, and be repeated every 2–5 years [5, 15]. Polyposis may become so severe in patients as to warrant colectomy, as is the standard recommendation for individuals with FAP or AFAP [5, 15].

Polyposis Syndromes Involving Mixed Pathologies

The polyposis syndromes we have examined thus far cause the development of multiple adenomatous polyps. Other predispositions to colorectal cancer exist that result in polyposis with mixed pathological findings. We will examine two of these conditions: the HMP syndrome (HMPS) and the HPS.

HMP Syndrome

The HMPS is an extremely rare condition that was first defined in a family of Lithuanian Ashkenazi ancestry in 1997 [16, 17]. As the name suggests, individuals with HMPS present with a mixture of colorectal polyps, including adenomas (classic, serrated and tubular), hyperplastic polyps, juvenile polyps, and mixed juvenile-adenomatous or hyperplastic-adenomatous polyps [16]. The HMPS phenotype appears to be confined to the colon [16]. The average age of polyp presentation has been reported as being between age 28 and 32 years, with the youngest age of polyp presentation being 10 years of age [16, 17]. Colorectal cancer was diagnosed at an average age between 40 and 65 years [16]. The primary concern for cancer in persons with HMPS is colon cancer, although some affected individuals have been reported with cancers of the pancreas, breast, kidney, or thyroid [16, 17].

The underlying genetic basis for HMPS may be heterogenous as recent research suggests. Genetic linkage analysis on multiple families of Ashkenazi ancestry (including the original family) have shown linkage to the 15q13–14 region [16]. A study of two families of Chinese ancestry reported linkage to the 10q23.1–10q23.31 region in both families [17]. A deletion in the *BMPR1A* candidate gene in this region was identified as segregating with the HMPS phenotype in one of these families [17]. *BMPR1A* has also been associated with the juvenile polyposis syndrome (JPS), although Cao et al. [17] reported that both families studied had polyp presentations that were consistent with HMPS rather than classic JPS.

From reported families, HMPS appears to have an autosomal dominant mode of inheritance [16, 17]. Obtaining accurate pathology reports on relatives who are reported to have a history of polyps is particularly important in distinguishing this condition from AFAP or MAP.

A specific starting age and interval for colonoscopic surveillance in individuals with HMPS has not yet been defined. Participants in the 2003 Rozen et al. [16] study were offered colonoscopy with polypectomy every 1–2 years starting at age 20. Colectomy could also be considered if cancer occurs or the polyps cannot be managed through polypectomy [16].

Hyperplastic Polyposis Syndrome

Hyperplastic colorectal polyps were previously thought to be benign polyp findings without the associated risk to progress to malignancy found in adenomas. An increased risk for colorectal cancer, however, has been associated with HPS, which is defined as hyperplastic polyps that are larger (>1 cm) or more numerous (>30) than that seen in the general population. Other polyp types are also frequently observed in HPS including adenomas, serrated adenomas, and admixed hyperplastic/adenomatous polyps [18–20]. Whether the increased incidence of colorectal cancer in patients with HPS is due to the presence of adenomas or arises from the more numerous hyperplastic polyps themselves is still a subject of study [18, 19, 21]. Current research is examining whether the pathway to colorectal cancer formation is through serrated adenomas, which are believed to possibly arise directly from hyperplastic polyps [18, 21].

A clinical diagnosis of HPS can be made in an individual using the WHO International Classification of Tumor definition [22]: (1) At least five histologically diagnosed hyperplastic polyps proximal to the sigmoid colon, of which two are greater than 10 mm in diameter, or (2) any number of hyperplastic polyps occurring proximal to the sigmoid colon in an individual who has a first-degree relative with HPS, or (3) greater than 30 hyperplastic polyps but distributed throughout the colon.

HPS has not been reported to be associated with polyposis outside the colon or with extra-colonic cancers. A

genetic basis for hyperplastic polyposis has yet to be elucidated. Reports have defined rare families (approximately 6) that appear to have an autosomal dominant segregation of HPS in the family and there is at least one reported case of what appears to be autosomal recessive HPS [18].

In a 2004 study by Ferrandez et al. [20], colorectal screening for individuals with HPS could be completed with colonoscopy every 1–3 years, depending on the severity of the individual's polyposis. Colectomy may be necessary when polyps cannot be managed in view of the colon cancer risk.

Patient Identification and Referral Strategies

Thus far, specific colorectal cancer predisposition syndromes have been described in detail. Knowledge of the typical presentation, the potential for extra-colonic features or cancers, the polyp pathology, and the genetic basis of these syndromes assists with the identification of individuals with or at high risk for one of these conditions. Prior to a complete evaluation of the patient, it is helpful to consider a number of warning signs that may help in identifying patients that should be evaluated for one of the inherited syndromes.

The National Comprehensive Cancer Network lists the following features as warning signs that a patient could be at high-risk for a genetic predisposition to colorectal cancer [5]:

(1) Early-onset colorectal cancer (before age 50).
(2) Clustering of the same or related cancer in close relative(s). Pertinent cancers (considering Lynch syndrome) include colorectal, endometrial, ovarian, duodenal/small bowel, stomach, ureteral/renal pelvis, sebaceous adenomas or sebaceous carcinomas.
(3) Multiple colorectal carcinomas or more than 10 adenomas in one individual.
(4) The patient is a member of a family with a known hereditary syndrome associated with cancer (whether or not a causative genetic mutation has been identified in the family).

In an era where physicians have been required to become increasingly time-conscious during their appointments, family history questions are sometimes overlooked or greatly abbreviated [23, 24]. Focusing on the key family history features needed for a high-risk cancer assessment will allow a general physician to streamline the family history-taking process. If a patient is referred on for genetics evaluation, the genetics specialists will be

Table 3. Case studies

Case 1: AFAP
A 35-year-old man is referred to a gastroenterologist after finding blood in his stool. A colonoscopy examination reveals approximately 20 polyps in multiple areas of his colon. Pathology examination of these polyps reveals them all to be tubular adenomas. The gastroenterologist refers the man for genetics evaluation due to the finding of more than 10 polyps. When asked about his family history, the man reports that a paternal uncle had colon cancer in his mid-50s and his father had some polyps found on his first colonoscopy at age 50, but he is unsure how many. The genetic counselor obtained records from his father's past colonoscopies and found that he had a total of 15 adenomas over the last 10 years. Given the pathology and number of the polyps, the genetics clinic recommends testing of the *APC* and *MYH* genes, as either AFAP or MAP could be the cause of his adenomatous polyposis. The testing identifies a mutation in the *APC* gene associated with AFAP. His father is tested, and it is confirmed that the mutation was inherited from this side of the family. Genetic testing is then offered to the patient's paternal aunts and uncles as well as his 40-year-old sister. Several relatives tested positive and are able to initiate screening colonoscopies. The patient's sister tests negative and is reassured that she did not need to begin colon cancer screening until age 50. He is advised that each of his children have a 50% chance of having inherited the *APC* mutation from him. *APC* testing for his children is recommended when they reach their teenage years, before colonoscopies would begin if they were found to be affected. An EGD is recommended for the man and a few duodenal polyps are identified and removed. A repeat EGD will be preformed in 2 years. A repeat colonoscopy is scheduled in 1 year, and the options of colectomy and/or chemoprevention are discussed with the man, given his increased polyp burden.

Case 2: Hyperplastic polyposis
A gastroenterologist refers a 40-year-old woman for genetics evaluation after identifying over 50 colorectal polyps via colonoscopy. Only 20 of the polyps can be removed via polypectomy. The genetics clinic coordinator sends the woman a packet of information to fill out regarding her personal health and family history. Other than a history of anemia, the woman has been otherwise healthy. She has no known history of colon cancer in her family. The pathology report is completed before her scheduled genetics clinic visit and the results are reviewed by the genetic counselor and geneticist. 15 of her polyps are hyperplastic in histology, 3 are adenomas, and 2 are serrated adenomas. During her genetics evaluation, she is advised that she meets the diagnostic criteria for hyperplastic polyposis syndrome. She is told that genetic testing is not yet available to explain the underlying cause of HPS; however, HPS is known to be associated with an increased risk for colorectal cancer. Her large number of polyps cannot be managed through polypectomy alone, so a colectomy is recommended to most reduce her risk of colon cancer. Baseline colonoscopies are recommended for her at-risk relatives.

These case studies highlight the importance of screening and surgical recommendations for patients with a genetic predisposition to colorectal cancer.

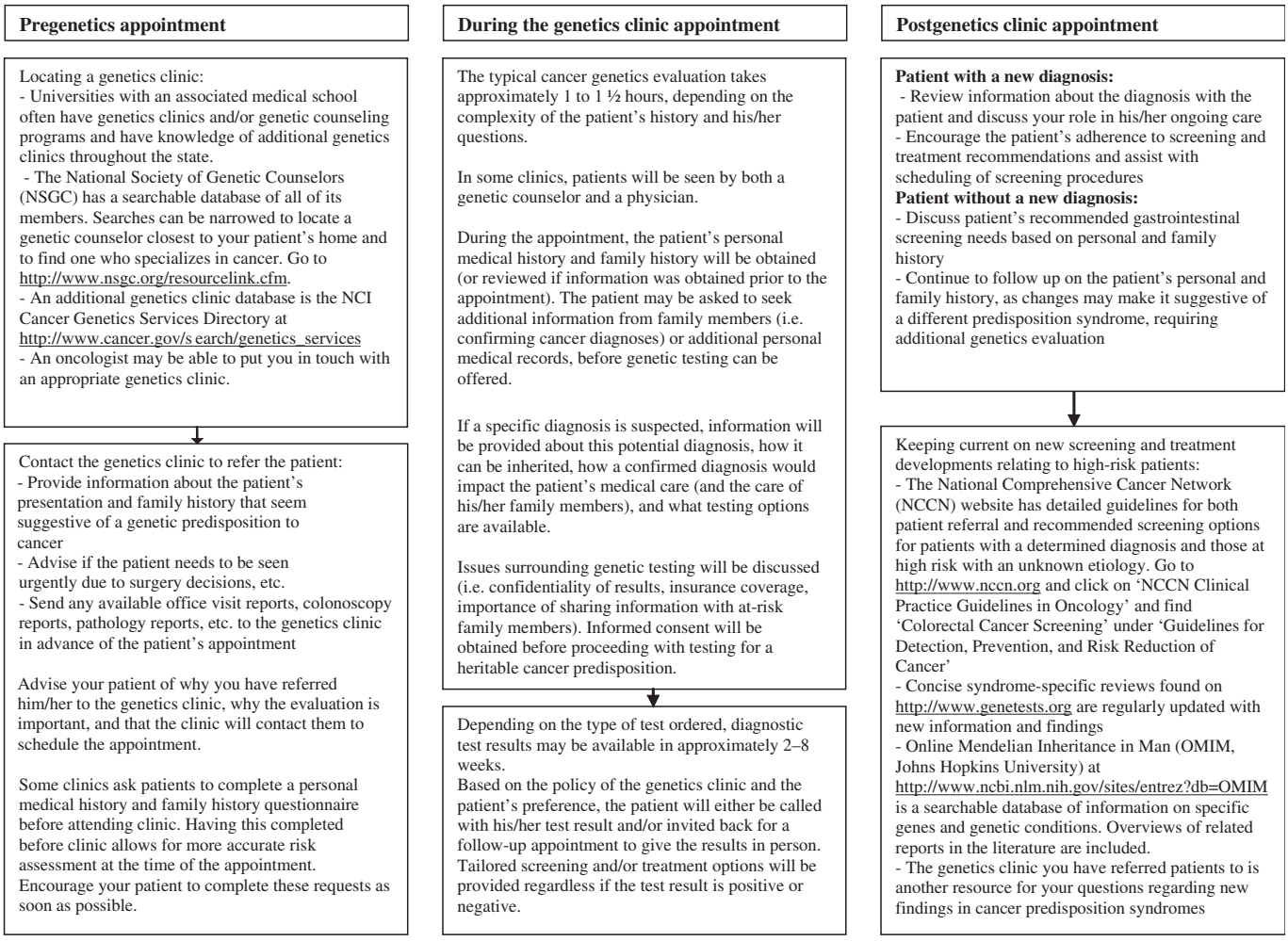

Fig. 2. Flowchart for genetics clinic referral, genetics appointment, and follow-up.

able to elicit the more comprehensive family history needed for their assessment. Figure 1 diagrams suggestions for eliciting an abbreviated family history focused on cancer genetics. It is also important to seek updated family history information from patients during return visits [24].

An individual's personal and family history has the potential to become suspicious for a hereditary cancer syndrome with follow-up. Keeping an accurate count of a patient's colorectal polyp number during each colonoscopy is crucial in the future identification of patients at risk for a polyposis syndrome. Keeping record of pathology reports on removed polyps is important as well. A patient with three adenomas on one colonoscopy is not concerning, but if the individual develops more than 10 adenomatous polyps over the course of his/her lifetime, this is now a warning sign for a high-risk polyposis condition. General gastroenterologists and their patients should work together in keeping track of polyp counts and pathology findings.

Some family histories can be very difficult to interpret. Cancer diagnoses in older family members may be inaccurate and difficult to verify through medical records. A family with multiple members who died at young ages from noncancer-related causes (i.e. accidents, illness, war, etc.) can obscure the presence of an underlying genetic cancer predisposition for multiple generations [25]. Small families and families with instances of adoption or unreported nonpaternity can also complicate family history analysis [8, 25]. Modern screening and removal of precancerous polyps may also mask a pattern of cancer from being evident in the family. If an individual

presents with features suggestive of an inherited cancer predisposition syndrome, but is lacking a significant family history, he/she can still be an appropriate referral for further genetic evaluation. A genetic consultation will provide a more thorough family history assessment or the patient may represent a de novo mutation.

Locating a genetics/high-risk cancer clinic that specializes in hereditary cancer evaluation can be a challenge as not all cancer clinics or hospitals have this expertise. Figure 2 provides a layout of the genetics referral process from finding a clinic to refer to, through the actual appointment, to the patient's return to their general gastroenterologist's care. This outline can also serve to prepare patients for what they may encounter during their appointment. Many patients are apprehensive about genetics clinic visits, given the familial implications of the consultation. Advising patients of why the referral is important, i.e. it may change their future health management and the health management of their family members, may help heighten their interest in the appointment. Telling the patient that they will be asked detailed information about cancer diagnoses in the family will also allow them to start gathering the needed information before their genetics clinic appointment.

Once a patient has been identified as high-risk and has undergone genetics evaluation, he/she may return to their general gastroenterologist with a new diagnosis or a still unknown etiology for their high-risk status. In either situation, the patient will likely have been provided with tailored cancer screening recommendations based on their genetic diagnosis or personal and family history. General gastroenterologists can have a significant impact in easing the coordination of frequent colonoscopies or other gastrointestinal surveys for their high-risk patients and in promoting adherence to screening protocols. Table 3 provides two case study examples of high-risk patients, outlining their increased screening/surgical needs and highlighting where general gastroenterologists have had a significant role in their diagnosis and/or management. There are multiple clinic and online resources available to clinicians to assist with remaining current on the screening and treatment guidelines for individuals at high risk for colorectal cancer (fig. 2).

While identifying patients at high-risk for colorectal cancer can often be difficult, there are many tools available to assist gastroenterologists and general physicians. Establishing regular communication between genetics professionals and other areas of medicine is crucial in providing the optimal care for high-risk patients. Although the initial challenges can be time-consuming, the benefits of providing tailored screening and preventative medicine to patients and their families are substantial.

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Disclosure Statement

Randall Burt, MD, consults for Myriad Genetics.

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This current review summarizes the available data on the major issues concerning CRC screening by colonoscopy, including a patient-tailored screening approach, the quality of colonoscopy and colon cleansing, and possible technological improvements targeting improved detection of lesions in the screening setting.

Patient-Tailored Colonoscopic Screening

Current recommendations for the timing of screening are based only on age and family history of CRC and include an enormous population of all people older than 50 years and those older than 40 who have a positive family history of CRC. This approach with colonoscopy as the screening tool would be so resource-intensive that it calls into question the practicality of screening whole populations. Therefore, the so-called patient-tailored screening policy has been proposed in order to improve the yield of colonoscopic screening.

Several factors that could be used to tailor CRC screening have been suggested. They include not only age and family history but also gender, race, ethnicity, body mass index (BMI), presence of diabetes mellitus, and different lifestyle patterns (smoking status, alcohol intake).

For many years, it has been well known that gender is the best-documented contributor to the risk:benefit ratio for CRC screening, and when taken into account, it could potentially improve screening yield. A cross-sectional study of 50,148 asymptomatic participants in the largest published, colonoscopy-based CRC screening program has shown in both derivation and validation data sets that male sex is independently associated with advanced neoplasia (adjusted odds ratio, OR, 1.73) [6]. The authors used advanced neoplasia rather than cancer as a primary end point because neoplasia is believed to be the most appropriate target for CRC screening in light of the prophylactic role of endoscopic polypectomy. A higher prevalence of age-adjusted advanced neoplasia among men is consistent with previously published data [7]. Valuable information came from the calculations of numbers needed to screen (NNS) in order to detect advanced neoplasia [6]. For example, this number is similar for men aged 50–54 years (NNS = 17) and women aged 60–66 years (NNS = 18) after adjusting for family history of CRC. These authors suggest that potential gender differences should also be taken into consideration when refining CRC screening recommendations.

Furthermore, colonoscopy parameters may differ for men and women. For example, it seems that both major (including perforation) and minor (bloating, nausea, abdominal pain) complications may occur more frequently in women [8, 9]. As a result of the frequent presence of altered pelvic floor anatomy arising from prior pelvic surgery, women have, on average, a poorer tolerance of the procedure and are also less likely to have undergone a complete examination [10, 11]. It can be hypothesized that lower completion rates may result in a higher probability of interval cancer following negative colonoscopy in women (relative risk, RR, 0.66) compared to men (RR 0.35) [11].

Despite ethnic differences in the prevalence of advanced neoplasia and CRC, current guidelines address all populations uniformly [12]. The African-American population is of particular concern; compared to whites, African-Americans exhibit a higher incidence of CRC, right-sided predominance, younger age at the time of diagnosis, lower attendance at screening, and lower survival rates, especially among men [12]. The cost-effectiveness of screening, adjusted for age-specific incidence rates, proportion of localized, left-sided cancers and life expectancy estimates is the highest in African-Americans, then Caucasians, then Asians and the lowest in Latinos [13]. Although the overall prevalence of adenomas in African-Americans seems comparable to that of the white population [14], available data may suggest a need for earlier initiation of CRC screening in African-Americans than in other populations [12].

Growing evidence points to smoking and alcohol intake status as altering the risk:benefit ratio for CRC screening. In a cross-sectional study, Anderson et al. [15] showed that current smokers, defined as those who had smoked more than 10 pack-years (current smokers or those who quit within 10 years), were more likely to have any adenomas (OR 1.89; 95% CI, 1.42–2.51) or significant neoplasia (OR 2.26; 95% CI, 1.56–3.27) than those who had never smoked. The term 'significant neoplasia' was defined as lesions with high-grade dysplasia, a villous component, diameter ≥10 mm, more than two adenomas of any size, or adenocarcinoma. An increased risk of advanced colorectal neoplasia for smokers (OR 1.85; 95% CI, 1.33–2.58) was also identified by Lieberman et al. [16]. In both studies, the significance of tobacco exposure was comparable to the family history of CRC. Recently, the critical tobacco exposure level was evaluated and established at 20 pack-years [17].

Although limited data exist, alcohol consumption patterns also may significantly affect colorectal neoplasia risk. Compared to abstainers, heavy drinkers (≥8 servings per week) of beer and spirits are at more than a two-

Table 1. Most important factors for customizing the CRC screening guidelines

Factors	Population at increased risk
Known	
Family history of CRC	First-degree relatives
Age	Increasing age
Possible	
Gender	Males
Ethnicity	African-Americans
Lifestyle patterns	Current smokers and heavy drinkers
BMI/diabetes	Obese/diabetics?

fold increased risk for significant neoplasia. On the other hand, heavy wine drinkers seem to have a decreased risk of significant neoplasia [18]. Lieberman et al. [16] found that heavy current alcohol use was independently associated with an increased risk for advanced colonic neoplasia in men. Although the data regarding lifestyle patterns are difficult to obtain and susceptible to a significant recall bias, the results of consecutive studies seem to demonstrate the impact of lifestyle on the risk of colorectal neoplasia.

The least abundant data are those addressing the prevalence of advanced adenomas and CRC in individuals with obesity, diabetes mellitus, or metabolic syndrome. The common core elements shared by these pathologies are hyperinsulinemia and insulin resistance, which are significantly associated with colorectal neoplasia and CRC [19]. Recent work showed that metabolic syndrome is associated with an increased risk of colorectal neoplasia (OR 1.35; 95% CI, 1.05–1.73) and synchronous adenomas (OR 2.30; 95% CI, 1.42–3.72) but not with advanced adenomas. Interestingly, there was no such correlation regarding individual components of metabolic syndrome such as obesity or serum cholesterol concentration [20]. However, Anderson et al. [21] found in their cross-sectional study that increasing BMI was linked with an increased risk for colorectal neoplasia in female patients undergoing screening colonoscopy. Moreover, previously published data suggest a significant rise in the risk of advanced adenomas among patients with BMI over 30 (OR 1.78; 95% CI, 1.0–3.2) after adjustment for other confounders [22].

Growing demands on colonoscopy and a huge target population for CRC screening require optimizing the use of currently available resources. Shifting the use of colonoscopy from lower-risk to higher-risk groups has been suggested. Current data form the basis for a proposed list of factors that might be useful in stratifying screening candidates (table 1). In our opinion, the strongest evidence favors a delay in initiation of screening in women until age 55–60 years. Other possible factors require further clarification before modification of screening recommendations.

Quality of Colonoscopy

In many countries, colonoscopy is regarded as the preferred screening tool, but the issue of quality is a great concern. A significant proportion of colorectal lesions can be missed during a colonoscopic procedure [23], possibly resulting in the occurrence of interval cancers (diagnosed within 3 years from the baseline colonoscopy) [24]. Evidence from tandem colonoscopy studies leaves no doubts: the pooled adenoma miss rate fluctuates around 22% (19–26%) [23]. With regard to CRC, miss rates range from 2 to 6% [24]. Recently published data also suggest a significant variation in adenoma detection rates and cecal intubation rates among examiners, which reflects the quality of performance [25, 26]. Chen and Rex [26] have shown that the individual endoscopist can be a more powerful predictor of adenoma detection at colonoscopy than well-established risk factors such as male gender and advancing age.

Because the effectiveness of colonoscopy in reducing CRC incidence and mortality depends on the appropriate clearance from neoplastic lesions during the baseline examination, continuous quality improvement (CQI) programs must be implemented to achieve desirable outcomes. Although professional societies have recommended such CQI programs [27], few endoscopic centers have followed the guidelines [28].

Recent data confirm that CQI programs are efficient in terms of improving cecal intubation rates. In one study, continuous cecal intubation rate measurement – with appropriate documentation of its landmarks including a photograph – during a 6-year period increased the percentage of complete colonoscopy from 88 to 93.7% [29]. In another study, a CQI program monitored colonoscopy completion rates and the prevalence rates of polyps. A 4-year program period allowed completion rate improvement from 89.1 to 96.3% and a reduction in the variation of the adenoma detection rate among endoscopists, in addition to overcoming the adenoma prevalence barrier of 20% among all endoscopists [30].

Barclay et al. [31] recently published a valuable study identifying a reliable quality indicator: a mean withdrawal time of less than 6 min. Endoscopists whose withdrawal time was shorter than 6 min detected significantly fewer adenomas (11.8 vs. 28.3%) and advanced adenomas (2.6 vs. 6.4%) than those with withdrawal times of at least 6 min.

Endoscopists should be encouraged to follow CQI programs. From the wide range of possible quality indicators, the most important and easiest to measure should be chosen to create a reliable and simple quality control model. Already mentioned indicators, including cecal intubation rate, adenoma detection rate, and withdrawal time, seem feasible. A newly developed system for automated documentation of the cecal intubation rate and withdrawal times could further improve the situation [32].

Optimal Bowel Cleansing Procedure

Bowel cleansing is a major contributor to the efficiency of colonoscopy and remains a problem despite the notice this issue has attracted for many years. Inadequate colon preparation determines both small and large polyp miss rates. Moreover, suboptimal colon preparation correlates with higher procedure difficulty and leads to lower completion rates and prolonged procedure time [33]. The level of inappropriate preparation reported in studies differs considerably, mainly because of the lack of standardized definitions. However, the mean percentage of poorly cleaned bowels varies between 20 and 25% [33, 34] and thus is a significant problem producing a substantial healthcare cost in repeated colonoscopies [35]. Determining the best bowel cleansing regimen is of paramount importance, and the key questions are: (a) what is the most effective, safest, and best tolerated available cleansing regimen?, and (b) what are the predictors (if any) of poor colon preparation?

Two bowel preparation regimens are used most often: polyethylene glycol (PEG) solutions and sodium phosphate on the day before the colonoscopy. Both are similar in terms of cleansing effectiveness [33, 36], but patient tolerance (poor for both) seems a little bit lower for PEG and may result in lower compliance with the preparation instructions [34, 37]. Although no differences in safety were detected between the two regimens in a healthy population [33, 36], caution should be taken when administering sodium phosphate because of possible electrolyte imbalance [36]. The timing of bowel preparation may play the crucial role in achieving the appropriate quality of cleansing. Chiu et al. [38] demonstrated recently in a randomized trial that the PEG-based regimen applied on the day of colonoscopy yields a better cleansing quality and higher detection of neoplasia. Although it necessitates performing the examination at midday or in the early afternoon, 6 h after cleansing initiation, it is suitable for screening colonoscopy, which is often performed during these times.

Because no ideal preparation regimen exists, to maximize quality it is feasible to identify those patients at increased risk for inadequate colonic preparation. In fact, certain patient characteristics, suitable for a screening population, are independently associated with poor colonic cleansing: male gender, increasing age, usage of tricyclic antidepressants, a history of stroke or liver cirrhosis, and late colonoscopy starting times [33, 34].

How can the currently available types of cleansing be modified to maximize the quality of colonoscopic screening and make it more feasible? Based on available data, we can suggest the following: (a) a switch to a same-day, more intense cleansing regimen should be considered, and (b) people of greater age may require more intensive or longer preparation protocols.

Technical Improvements

In the ideal world, all existing lesions in the colon and rectum would be identified and removed. However, current studies show significant adenoma miss rates and substantial variation in both adenoma detection and cecal intubation rates among endoscopists [25, 26].

Because most of the missed lesions are overlooked behind the proximal sides of the semilunar folds, technical developments are required to improve exposure of these areas. A short, transparent hood attached to the tip of the colonoscope facilitates depression of the folds, improving the polyp detection rate [39, 40] and shortening cecal intubation time for trainees [40]. Its simplicity, efficacy, and practicality encourage further studies on its effectiveness in the CRC screening. The other option is to widen the angle of view of current colonoscopes from 140 to 170 or 210°; however, this solution was not effective in two studies using prototype colonoscopes. Instead, wide-angle colonoscopes allowed a decrease in the time of insertion and withdrawal without losing the accuracy of inspection [41, 42].

Another technical development known as the third-eye retroscope is the retrograde-viewing auxiliary imag-

Table 2. Diagnostic accuracy (%) in a differential diagnosis of neoplastic and nonneoplastic colonic polyps by various imaging modalities

Author	Standard colonoscopy	NBI colonoscopy	Chromo-endoscopy
Chiu et al. [48][1]	67–68		
Su et al. [46]	81.8	92.7	92.7
Machida et al. [47]	79.1	93.4	93.4

[1] The diagnostic accuracy of low-magnification NBI colonoscopy and chromoendoscopy is 81–82 and 79–85%, respectively. The diagnostic accuracy of high-magnification NBI colonoscopy and chromoendoscopy is 87–90 and 91–92%, respectively.

ing device introduced through the working channel of the scope that provides a continuous retrograde view for the standard, forward-viewing colonoscope. It has allowed significant improvements in polyp detection rates in anatomic models and could become useful in screening if studies in humans confirm the results [43].

Chromoendoscopy is a technique that involves dyeing the entire colon to improve detection of colonic neoplasias. Although it improves detection rates of diminutive adenomas or flat adenomas [44], its practicality in the CRC screening setting is questioned [45]. It might be replaceable by narrow band imaging (NBI), a newly developed system that uses narrow bands of lights instead of the full visible wavelength range, providing superficial penetration of the colonic wall. NBI enhances visualization of the mucosal vascular networks, can be useful for detecting flat lesions, and may improve discrimination of neoplastic from nonneoplastic lesions with a simple click of the button on the endoscope [46, 47]. The diagnostic accuracy of NBI for detecting neoplastic colorectal polyps is superior to conventional colonoscopy and comparable to chromoendoscopy (table 2) [46, 48]. However, its negative predictive value seems insufficient for a precise determination of lesions without neoplastic potential that could be left intact in the colon. Recently published data may suggest a possible positive impact of NBI on the adenoma detection rate at least in a high-risk population [49]. Further studies, especially in the colonoscopic screening setting, are encouraged because NBI may potentially improve adenoma detection rates and reduce the costs and time required for the colonic examination.

Disclosure Statement

None.

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Table 1. Available fecal screening tests – basis for detection of neoplasia, strength of evidence and determinants of performance

Detection goal	Technology	Strongest evidence for benefit	Sensitivity determinants	Specificity determinants
Fecal blood	GFOBT	population RCT – reduced incidence and mortality	amount of heme in feces	dietary heme; bleeding nonneoplastic lesions
	FIT	comparative cohort – better sensitivity and/or specificity	amount of globin in feces	bleeding nonneoplastic lesions
Fecal neoplasm-derived DNA	multitarget fecal DNA test	comparative cohort – assessing sensitivity and specificity	spectrum of DNA changes shed into feces	unclear

Modified from Young and Allison [1] with permission.

- Follow up result with colonoscopy if indicated
- Treat any lesions found
- Repeat screening or implement follow-up surveillance if neoplasia found.

There are two main choices at the point where a test is offered: (1) One-step testing. The diagnostic test, colonoscopy, is the screening test. Selection for colonoscopy is based on age, and many people screened will not have neoplasia. (2) Two-step testing. Here, a simpler test is offered first, e.g. a fecal occult blood test (FOBT), then those with a positive result proceed to colonoscopy. A simple screening test calls attention to the likelihood of disease being present and serves to direct resources to those most likely to benefit from diagnostic and therapeutic procedures [3].

Stool Screening Tests Act by Refining the Likelihood that Neoplasia Is Present

In two-step testing, the stool screening test filters out from the broader population those who are most likely to have colorectal neoplasia. This concept is embodied in the pretest:posttest likelihood ratio and is mathematically expressed as test sensitivity divided by the false-positive rate (1 – specificity) [3]. Depending on the test type used, various FOBT return a ratio in the range of 8–40 [1] meaning that those with a positive test are that much more likely to have colorectal cancer than those with a negative test.

The Biological Basis of Fecal Screening Tests

The usefulness of such tests depends on whether a colorectal neoplasm gives rise to changes in the constituents in feces. Such constituents might derive directly from the tumor itself or be secondary to its presence. The processes giving rise to such products can be classified [4] as: leakage, secretion, or exfoliation.

Hemoglobin, and indeed other blood-derived proteins such as haptoglobin and albumin, represent examples of leaked products. Tests have been developed based on each of these, although hemoglobin-based tests are by far the most prominent (see the section 'Current Types of FOBT: Guaiac and Immunochemical Tests' below).

Mucins are an example of secreted products. No mucin-based test has, however, achieved significant usage.

The products of cell exfoliation create considerable options for detection. Certainly, cytological studies show neoplastic cells to be present in feces [4]. Tests for these might be based on DNA (see the section 'Nonhemoglobin Molecular Markers in Stool' below), RNA or proteins. A recent American Gastroenterological Association Future Trends Committee report on emerging screening and diagnostic technologies for colorectal cancer [5] identified a range of tests and procedures that might be appropriate. These include proteomics or the analysis of broad protein patterns, making it possible to assess small amounts of protein for the presence of identified cancer markers using new protein assessment tools and computerized artificial intelligence analysis.

The nature of the major fecal screening tests, either established or under study, is summarized in table 1. The efficacy of screening for colorectal cancer is supported by the highest level of evidence, namely randomized, controlled trials, at the population level for guaiac-based FOBT (GFOBT) [6–8]. Evidence supporting the other test technologies is not as strong, as summarized in table 1 and further outlined below in the sections 'Current Types of FOBT: Guaiac and Immunochemical Tests' and 'Nonhemoglobin Molecular Markers in Stool'.

Justification of New Test Development

Evaluation of Test Performance

Before considering the new developments in stool tests, it is worthwhile to consider whether we need new tests at all. To do this, we need to briefly consider what outcomes are important to the success of a screening program, i.e. what measures relate to a reduction in mortality and/or incidence in a cost-effective and acceptable fashion?

The measures of effectiveness of a screening program have been detailed elsewhere [1] and informative measures can be classified as:

- Behavioral, i.e. participation rates in screening
- Test performance, such as sensitivity (including neoplasia detection rates), specificity (including false positives) and predictive values
- Programmatic, namely reductions in incidence and mortality.

The most immediate measurable events when screening will be participation rate, test positivity rate, adenoma detection, downstaging of the detected cancers and, at a later stage, prolonged survival after treatment [1]. Presymptomatic detection of localized cancer will result in a reduction in morbidity and/or mortality [6–8]. If screening detects preinvasive lesions, namely dysplasia, it will reduce cancer incidence [9].

The published RCTs using GFOBT provide information on each of these measures; new tests can be tested relative to these.

Performance of GFOBT

An early measurable outcome in a screening program is *participation*, i.e. willingness of an individual offered screening to undertake the testing process. The RCTs of GFOBT have achieved rates of 53–67% when approaching the entire population, but other studies show lower rates [1, 6–8]. Clearly, the impact of a screening program on population outcomes would be greater if more people did a screening test [10]. It is also important to emphasize that FOBTs must be undertaken repeatedly for benefit to be shown, so ease of use is crucial.

Rates of detection of adenomas and cancers, together with stage of cancer, are the next obvious outcomes. In themselves they are difficult to meaningfully interpret when expressed relative to the size of the target population, but if two tests are compared directly, the results provide a relative indication of sensitivity for the target lesions. Improved sensitivity for cancer will translate into a greater reduction in mortality.

The published RCTs using the standard GFOBT, Hemoccult, have observed modest population mortality reductions (from colorectal cancer) of 14–21% when analyzed on an intention-to-screen basis [6–8]. This modest impact is a direct consequence of the low *sensitivity* of Hemoccult for cancer, estimated in a range of studies to be around 33% and no greater than 50% [1, 11]. Clearly, a more sensitive test seems likely to have a greater impact on mortality as a larger number of cancers will be detected by screening.

Cumulative *incidence* rates for colorectal cancer did not differ between the controls and screened groups in the RCTs using GFOBT after 13 years of follow-up. However, after 18 years of follow-up, the Minnesota study observed a significant impact on incidence whether screening was annual or biennial [9]. It seems likely that the higher sensitivity of rehydrated Hemoccult and the resultant higher colonoscopy rate [6] has resulted in a better detection (and thus removal) of adenomas. Obviously, improved sensitivity for adenomas would result in a greater impact on incidence.

Unfortunately, increasing the sensitivity of GFOBT leads to a marked deterioration in specificity [11] and this would also increase cost of the program as the colonoscopy rate is a major determinant of cost.

To summarize, we need new tests because there is much room to improve participation rates of those being invited to screen, to improve sensitivity for cancer, to improve sensitivity for adenomas, and to achieve the improved sensitivity without unacceptable deterioration in specificity.

Current Types of FOBT: Guaiac and Immunochemical Tests

The fact that microscopic bleeding may arise from curable cancers, and adenomas, provides the basis for screening using an FOBT [3]. However, the biology of bleeding is complex and the different FOBT technologies now available are influenced by the biological fate of blood in the gut [9].

Available FOBTs are based on two principal quite different technologies: chemical or immunochemical detection of one or other component of blood. The major features of these tests are outlined in table 2 [1, 12].

Chemical FOBT

The chemical tests (e.g. Hemoccult II) react to the peroxidase capacity inherent in the heme molecule [13].

Table 2. Characteristics of different types of FOBT [1, 12]

Type of FOBT	Chemical basis	Diet restrictions	Drug interference	Site of occult bleeding detected	Specificity for neoplasia[1]	Sensitivity for cancer[1]
Chemical (GFOBT)	guaiac detects peroxidase activity of heme	required: red meats; possibly certain raw plant foods[2]	vitamin C, possibly NSAIDs[3]	rectum > colon > stomach (in decreasing order of sensitivity)	90–98% depending on test brand and usage	35–67% with one-time testing; over 80% with repeated testing
Immunochemical (FIT)	anti-human hemoglobin antibody detects globin	none required	none	colon and rectum	around 95% depending on sensitivity level chosen[4]	65–90% with one-time testing; unclear for repeated testing

Presented in modified form with permission [1].
[1] Indicative estimates only.
[2] Delaying development for 72 h minimizes interference from plant foods and avoids need for their restriction with standard Hemoccult II. Red meats must be restricted when using a more sensitive GFOBT [12].
[3] Low-dose aspirin is not a problem, but therapeutic doses such as for rheumatic disorders may.
[4] Tests generally provide a qualitative result, but some newer FITs can be quantifiable.

Guaiac is the reagent in most chemical tests. These GFOBTs react to any peroxidase in feces (e.g. plant peroxidases or heme in red meat) and are affected by certain chemicals (e.g. vitamin C). GFOBTs may detect bleeding from any site in the gastrointestinal tract, including stomach [13], as heme remains relatively stable during transit.

GFOBTs that are more sensitive than Hemoccult, e.g. Hemoccult II Sensa, have been developed to improve sensitivity; in practice they appear to almost double sensitivity. While valuable, this is unfortunately at a cost of decreased specificity [11].

Fecal Immunochemical Tests

Fecal immunochemical tests (FITs) use antibodies specific for human globin. This technology provides several advantages. It is not affected by diet or vitamin C [5, 13, 14]. FITs as a class are subject to less variability in positivity rate than the sensitive GFOBT [15]. FITs are also highly selective for occult bleeding of colorectal origin because globin is rapidly degraded by digestive enzymes [13]. These provide specificity advantages over GFOBT, especially the more sensitive GFOBT.

These improvements in specificity have, depending on the brand of FIT, been combined with improvements in fecal sampling; these are discussed elsewhere in detail [12, 14, 16]. FITs have also been developed to provide for large scale development in the laboratory where quality assurance of test development is much easier to monitor and control. Laboratory development is preferred in many countries, especially for mass screening when many tests must be done and quality assurance is vital.

Comparisons of GFOBT with FIT

It is beyond the scope of this review to fully analyze all studies comparing these technologies. Several studies have been selected to demonstrate key issues about these two quite different technologies.

Population participation is essential for cancer detection [3]. FIT technology simplifies the testing process, removes the need for diet and drug restrictions, provides for preferred and more acceptable stool-sampling methods such as brushes or probes rather than a wooden spatula, and is achieved while collecting fewer fecal samples. Most branded versions of FIT require fewer than three fecal samples, the recommended number for GFOBT. Removal of dietary restrictions has been shown to enhance participation in screening with FIT relative to GFOBT, in one study by 28% [10]. Changing to a brush-sampling method also simplifies the process and enhances participation by 30%. Together, these two advances increase population participation by 66% [10].

A study of over 7,000 people undergoing screening in California was the first to provide a large-scale comparison of two types of GFOBT with an FIT [11]. It showed that a sensitive GFOBT, Hemoccult Sensa, doubled detection rate of Hemoccult II for cancer but required almost 5 times as many colonoscopies to achieve this. An FIT, no longer available commercially, also achieved double the sensitivity but with only a doubling of the colonoscopy rate. FITs provide for an improved sensitivity/specificity ratio; in other words, they can achieve better sensitivity without an unacceptable deterioration in specificity.

More recently, a new brush-sampling FIT (InSure) has been directly compared with Hemoccult Sensa in several

clinical and screening cohorts undertaking paired sampling of stools [14]. The FIT returned a true-positive result significantly more often in those with cancer (n = 24, 87.5 vs. 54.2%) and in those with significant adenomas (n = 61, 42.6 vs. 23.0%). The false-positive rate for any neoplasia was marginally higher with the FIT than the GFOBT (3.4 vs. 2.5%, 95% CI of difference 0–1.8%), while positive predictive values were 41.9 and 40.4%, respectively.

A recent study involving 1,486 subjects in Scotland further supports the observations that specificity remains acceptable with FITs even though they have improved sensitivity [17].

Table 2 shows performance estimates of the different types of the FOBT, i.e. GFOBT and FIT. As a general rule, FITs are at the more sensitive end of the range while GFOBTs vary widely across the range.

Obviously, FITs overcome most of the disadvantages presented by GFOBT, are superior to GFOBT in terms of participation as well as performance and should replace GFOBT in two-step screening [14, 16].

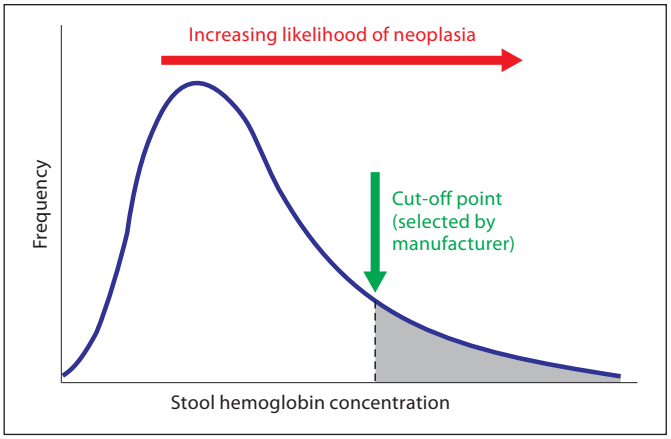

Fig. 1. Theoretical distribution of fecal hemoglobin concentrations in a target screening population showing a tail to the right as those with pathology will have higher concentrations than those with a normal colon. As the hemoglobin concentration increases, there is a continuous increase in the likelihood of finding neoplasia. Qualitative tests are set to react at a given hemoglobin concentration and so the likelihood of neoplasia varies with the cut-off selected. The proportion of the population falling in the grey-shaded area will be those who are colonoscoped.

Quantitative Immunochemical Tests

Several of the latest FITs, namely OC-Micro and InSure, provide for quantification of fecal hemoglobin [18, 19]. The relationship between fecal hemoglobin concentration and pathology has been explored in these studies and gives more insight into strategies for managing FIT-based screening programs. Several interesting guiding principles emerge from these studies:

- As pathology progresses, hemoglobin concentration increases (cancers bleed more than advanced adenomas which bleed more than small adenomas).
- Patients with advanced adenomas do show higher fecal hemoglobin concentrations than those without neoplastic pathology.
- Quantification enables one to select a cut-off corresponding to a particular chosen sensitivity/specificity ratio.

These studies clearly show that the greater the amount of marker present in the stools, the more likely is neoplasia to be present. If we represent a theoretical distribution of fecal hemoglobin concentrations in a target population (fig. 1), we would find that as the hemoglobin concentration increases there is a continuous increase in the likelihood of finding neoplasia. Qualitative FOBT are designed to return a positive at a set hemoglobin concentration, the 'cut-off' that defines positivity. Cut-offs vary between manufactured tests and so the likelihood of neoplasia being present varies according to where it is on the curve in figure 1. Qualitative tests fail to provide for flexibility in varying the cut-off. The same principle should apply for any other molecular marker in feces unless it is totally specific for neoplasia.

Several groups [18, 19] have shown how quantification provides flexibility by constructing an ROC curve, expressing the relationship between sensitivity and specificity at different hemoglobin concentrations. In practice, the hemoglobin cut-off used to trigger colonoscopy can be adjusted to correspond to a particular chosen sensitivity:specificity ratio. No longer is the test performance as set by a manufacturer important, since the flexibility provided by quantification allows those running screening programs to select whatever sensitivity:specificity ratio they want, while knowing that the lower the cut-off hemoglobin concentration selected, the greater is the chance of detecting significant neoplasia.

An even simpler way to apply this flexibility is to choose a hemoglobin cut-off that delivers a positivity rate that is manageable in terms of the resultant colonoscopy rate. For instance, if it is considered that 5% of the target population can be realistically colonoscoped, then the cut-off can be selected to achieve that. The real concern is what constitutes an acceptable rate. We know from

RCTs using the GFOBT Hemoccult II that a significant impact on mortality was achieved with a positivity rate of just 2% [7, 8]. So, we can be confident that working with a positivity rate higher than that will achieve better cancer detection and be more likely to deliver a similar or better reduction in mortality.

To summarize, the advantage of fecal hemoglobin measurement is that it returns full control of sensitivity and specificity to the end-user [3] who can establish the level of fecal hemoglobin that would trigger colonoscopy. At the population level, such an approach allows optimization of the test specificity:sensitivity ratio, so adapting the colonoscopy rate to the facilities and resources available for screening.

Nonhemoglobin Molecular Markers in Stool

Detection of molecular or genetic events that either cause cancer or else reflect development of neoplasia could theoretically be useful in selecting who undergoes colonoscopy. Because of the molecular heterogeneity of DNA in neoplasms, selecting the best panel of markers represents a challenge.

The first large-scale evaluation of the value of fecal DNA testing (using a 21-mutation multitarget panel) as a first-step test in two-step screening for colorectal cancer has recently been reported [20]. This version of the stool DNA test (PreGen Plus) is costly (in excess of USD 400) relative to GFOBT and FIT (up to USD 30) and requires a somewhat cumbersome stool collection that needs to be rapidly delivered to the processing laboratory [21]. The comparator tests were colonoscopy as the diagnostic reference standard and Hemoccult II (unhydrated) as the proven first-step screening test [20]. Results were analyzed in a subgroup of 2,507 which included all subjects found to have neoplasia as well as a range of subjects with normal colon or benign disease. The cancer detection rate using the fecal DNA panel compared to Hemoccult II was 16 of 31 (52%) versus 4 of 31 (13%, $p = 0.003$), respectively. While sensitivity was greater than that with Hemoccult II, it was lower than would be hoped for and the reported sensitivity of Hemoccult II was substantially lower than that reported in other studies for one-time testing [10]. The reasons for this seem likely to relate to the fact that Hemoccult II tests were developed at many different sites rather than at a centralized site paying full attention to quality assurance. The performance of both tests for detecting advanced adenomas was similarly disappointing: 61 of 403 (15.1%) for fecal DNA versus 43 of 403 (10.7%) for Hemoccult II. In those with negative (no finding of adenoma or cancer) colonoscopy, 5.6% had tested positive on fecal DNA compared to 4.8% on Hemoccult II (specificities of 94.4 and 95.2%, respectively). Fecal DNA testing did not identify the majority of neoplastic lesions found at colonoscopy.

Another recent study failed to find an association between *K-ras* mutations in the stool and development of colorectal cancer [22].

In this format (i.e. as PreGen Plus [20]) the fecal DNA test has not met expectations of sensitivity or specificity, and while it might be more sensitive for cancer than Hemoccult II, it is quite unclear as to whether it represents an advance over the newer FOBT types and especially FIT.

Further enhancements of fecal DNA testing are now emerging. These take advantage of certain epigenetic changes that can characterize colorectal neoplasia together with improved methods for stabilization of DNA. These two approaches have been combined in a new-generation fecal DNA test, PreGenPlus v2, where the main components of the test comprise an optimized method for detecting undegraded DNA ('DIA', a characteristic of neoplasia) together with a marker for methylation of the vimentin gene [23]. In a clinical cohort of 40 patients with cancer, the DIA component returned a 65% sensitivity, the vimentin test a 73% sensitivity and together an 88% sensitivity. At this stage, the performance in screen-detected cancers is not clear, nor has performance relative to FIT or GFOBT been studied. It is intriguing that a test based on methylation might achieve such a sensitivity, since tumors bearing the so-called methylation genotype, the CIMP pathway, seem likely to constitute no more than 20% of all colorectal neoplasia [24]. Clearly, there is overlap between molecular pathways of colorectal oncogenesis.

Specificity of the PreGenPlus v2 test has been determined in 122 people with a normal colon [23]. Combined specificity was 82%. This is not an improvement over FIT and is clearly inferior. This finding further demonstrates that DNA-based tests are not necessarily specific for neoplasia. The explanation for this is not clear, but the most likely possibility is that some molecular lesions emerge before focal lesions become obvious at colonoscopy. Whether such 'occult' lesions are likely to progress at a later stage is unknown. If they were, this might represent an argument for more intensive colonoscopic surveillance of such individuals, but this is pure speculation at this stage.

To summarize, fecal DNA tests require much more work before it is clear what the best markers are, how

these compare to GFOBT and FIT, and what the relative costs will be.

Nonetheless, it seems most likely that if stool tests can be improved, the new generation stool screening tests will emerge from discovery of new markers that improve sensitivity or specificity relative to FIT. DNA-based tests will continue to improve, but RNA-based and proteomic tests might also prove valuable.

Conclusions

The benefits of stool screening tests are several: they, particularly GFOBT, are proven by RCTs to have an impact on mortality and incidence, and they are acceptable to a majority of the population in that people will undertake such testing. Stool tests provide a simple introduction into the screening algorithm – they serve to profile risk for neoplasia and direct those more likely to have neoplasia to receive colonoscopy.

There are several disadvantages: fairly frequent testing seems to be necessary and sensitivity for incident lesions still leaves room for improvement whether they are based on blood or tumor DNA. No stool test is specific for neoplasia.

Recent developments in FITs, namely quantification, provide for a flexible approach to screening in that they do not commit the end-user to a particular sensitivity: specificity ratio and they have improved capacity to detect adenomas compared with GFOBT. As they are also more acceptable to people offered screening, FIT should replace GFOBT for screening. Perhaps, quantification represents the ultimate refinement of FIT and there might not be much room for further improvement.

Fecal DNA tests, especially the latest versions, need further evaluation in screening cohorts before we can be confident of their ability to detect cancers relative to FIT. They do appear to be more sensitive for cancer than the GFOBT Hemoccult II. As yet, fecal DNA tests have not been shown to have any advantage for adenoma detection and they are no more specific than GFOBT.

The challenge for fecal screening tests is to provide more reliable identification of those who might have an advanced adenoma in the colon. This would more effectively target colonoscopy to this group and reduce indiscriminate colonoscopic screening of everyone considered to fall within the at-risk age range. Fecal molecular tests have the potential to achieve this, but the ideal marker, or panel of markers, is yet to be identified.

Disclosure Statement

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KARGER

Until recent years, only conventional colonoscopy and double-contrast barium enema have been used for evaluation of the whole colon [5]. Conventional colonoscopy is considered to be highly sensitive and specific for the detection of colonic neoplasia, but it is not perfect and some lesions may be missed. In the study of Rex et al. [6], the miss rates were 6% for adenomas 10 mm and larger in diameter, 13% for adenomas 6–9 mm in diameter and 27% for adenomas 5 mm and smaller in diameter. In addition, conventional colonoscopy may be associated with serious complications when used as a screening tool in an average-risk population, limiting its acceptance as a broad-based screening test [3]. The aim of colonoscopy is to completely evaluate the colon and to reach the cecum, but this is not always possible. Even experienced colonoscopists may be unable to complete the colonoscopy due to multiple reasons such as severe diverticulosis, stricture, obstructing mass, or fixation of colonic loops due to adhesions after surgery. In addition, performing colonoscopy requires discontinuation of oral anticoagulation treatment that may not be advisable to some patients. The need for sedation coupled with substantial costs associated with conventional colonoscopy may make this method of screening less attractive in the large average-risk population above the age of 50. Recent studies show that double-contrast barium enema has a poor sensitivity with detection rates as low as 48% for polyps and adenomas larger than 1.0 cm [7] and may be associated with considerable patient discomfort. In addition, since this technique is used much less frequently, there is a significant decrease in the level of expertise of radiologists performing the examination, further lowering its accuracy. With acceptable screening techniques only 20–30% of all individuals at risk have undergone any form of colorectal screening.

CT colonography (CTC), also known as virtual colonoscopy, is a technique that uses data generated from CT imaging of the fully prepared and gas-distended colon to generate two-dimensional (2D) and three-dimensional (3D) images of the colon. It was first reported by Vining and Gelfand in 1994 [8] as a rapid, noninvasive imaging method to investigate the colon and rectum. With the advent of multi-detector CT and CT software, volumetric data of the entire colon are acquired in a few seconds of CT scanning with a total of 10–20 min of examination time. Assessment of the colon requires assessment of the 2D (axial and coronal planes) and 3D images which also includes endoluminal navigation of the colon. Since the advent of CTC, it has been regarded as a potential alternative technique to conventional colonoscopy for the detection of colorectal polyps and cancers.

Current Indications for CTC

Failed or Incomplete Colonoscopy

CTC can be performed following incomplete colonoscopy [9–12] that occurs in 5–15% of studies due to obstructing colorectal lesions or technical reasons such as a long and tortuous colon, or patient's discomfort [13]. CTC has the ability to complete the colon evaluation as well as identify the cause of endoscopic failure in a large percentage of cases [9]. In cases of occlusive carcinoma, CTC can detect synchronous carcinomas [9, 10], which occur in about 5% of cases [14]. In a very recent article [10], CTC depicted 88 endoscopically nonvisualized lesions of 6 mm or larger, including 12 masses greater than 20 mm. Intravenous contrast can add information about local tumor invasion and regarding metastatic spread [15].

Contraindication to Endoscopic Colonoscopy

Some patients that require colonoscopy can not have the procedure due to various reasons such as: severe comorbid disease, advanced age, bleeding disorders, very tortuous colon, prior allergic reaction to sedation, etc. These patients may benefit from CTC.

Patients' Refusal to Colonoscopy

Some patients that require colonoscopy refuse to have the procedure due to lack of information or fear and may agree to have CTC.

Extrinsic Compression of the Colon on Colonoscopy

A patient that underwent a complete colonoscopy that demonstrated suspected extrinsic compression on the colon may undergo CTC. The reason for the extrinsic compression (adjacent spleen, liver impression or distended bowel loops) may be demonstrated on the 2D images.

Screening for Colorectal Cancer

Although CTC is a promising technique, it has not yet been approved for colorectal screening in large-scale populations. In the near future, it may provide a rapid safe and effective screening test to screen the colon for neoplasia.

Patient Preparation for CTC Examination

Thorough bowel preparation is mandatory for an accurate CTC examination, since residual stool and large amounts of residual fluid may obscure small polyps and

adherent stool may mimic a polyp or mass. Contrary to endoscopic colonoscopy, residual feces and fluid cannot be aspirated. A well-prepared, well-distended colon reduces interpretation time as well as false-positive findings. Patients undergo bowel preparation for 24–48 h prior to the procedure using various products available on the market consisting of either a common barium enema preparation (magnesium citrate, bisacodyl tablets, cleansing enemas or suppositories) or a balanced polyethylene glycol (GoLYTELY; Braintree Laboratories, Braintree, Mass., USA) solution. A phospho-soda preparation is more commonly used since it is reported to result in significantly less residual fluid than a polyethylene glycol electrolyte solution preparation and is therefore less likely to obscure small polyps [16]. The use of spasmolytic agents such as glucagon to prevent collapse and spasm of the colon is controversial and usually avoided since it has been reported by some authors [17] to have no beneficial effect and may also lead to unwanted reflux of air into the ileum through the ileocecal valve.

Fecal and fluid tagging is a promising technique that is becoming more popular. It may be performed with or without electronic bowel cleansing. The patient ingests small amounts of barium or iodinated oral contrast with meals prior to CTC. The high attenuation contrast incorporates within the residual stool facilitating differentiation from polyps. When electronic bowel cleansing techniques are used ('digital cleansing'), a prep-less CTC examination may be performed. The high-attenuation-tagged stool is segmented from the data leaving only the colonic mucosa and filling defects attributed to polyps and cancerous masses [18]. Barium suspension given six to seven times over the course of 48 h prior to CTC has been reported to tag 80–100% of the stool and demonstrated good results for polyp detection without bowel cleansing [19]. In a recent study, the sensitivity and specificity of fecal-tagged CTC for the detection of colorectal polyps 10 mm and larger was reported to be 100% [20]. However, fecal tagging may sometimes obscure colorectal lesions, especially if large amounts of fecal residue are present and no electronic cleansing techniques are available [21].

It is clear that there is tremendous potential for using CTC as a screening study if limited bowel preparation is used, reducing patient discomfort associated with traditional cleansing techniques and resulting in an improved perception of the screening study [20]. However, currently, fecal tagging is used as an addition to the standard preparation and prep-less CTC is not commercially performed.

CTC Examination Technique

Patients are placed in the right lateral decubitus position on the CT table, a small catheter is inserted into the rectum and using a plastic bulb connected to the rectal catheter, room air, or CO_2, is gently insufflated into the colon. The amount of air or CO_2 that is insufflated is determined by patient tolerance, or by pressure-sensitive insufflator monitors that stop the insufflation once threshold pressure has been achieved ($PROTO_2L$, E-Z-EM, Inc., Westbury, N.Y., USA). Although many centers use room air since colonic distension is easily and reliably achieved with atmospheric air, carbon dioxide is becoming increasingly popular and is considered to be more comfortable, due to the more rapid absorption of CO_2 through the colon wall and blood causing less cramping after the procedure [22–24]. Adequate distension is crucial for accurate assessment of the colon as polyps may be obscured in collapsed bowel segments.

After the colon is insufflated, a CT scout image is obtained in the supine position to assess the degree of colonic distension. The patient is scanned in the supine position and then turned onto the prone position. A CT scout image is again obtained to assure that colonic distension is still adequate and the study is then completed. Dual positioning has been shown to improve colonic distension allowing confirmation of suspected findings [25] and to increase detection of colonic polyps $\geq$5 mm by approximately 15% compared with supine positioning alone [23, 26].

CTC Technical Aspects

CTC can be performed using a single or multi-detector CT scanner with the acquisition of volumetric data from the entire colon. The new multi-detector CT scanners allow 4–64 sections to be obtained in a single rotation of the X-ray tube enabling fast scanning, and shorter acquisition time, resulting in less motion artifacts due to breathing and bowel peristalsis and significantly improved demonstration of the colon compared with single-detector row CT [27]. Using the multi-detector scanners, the colon is usually scanned using a section thickness of 1–2 mm compared to 5 mm or more using single-detector CT scanners. Thinner scanning results in near isotropic data (data with equal resolution in all imaging planes), allowing excellent coronal, sagittal and endoluminal images. No significant differences in the detection of polyps larger than 10 mm has been demon-

strated between single- and multi-detector row CT [27]; however, evaluation of thinner slices improves diagnostic performance. Thicker slices were found to be inadequate for the evaluation of small polyps [28].

Intravenous contrast is not routinely used, although it has been shown to significantly improve readers' confidence, colonic wall conspicuity, and depiction of subcentimeter colorectal polyps [29]. However, the added value of administration of intravenous contrast material in colonic depiction has been modest. Intravenous administration of contrast material may rarely be associated with serious allergic reactions, but minor reactions are not uncommon (3–4% of patients). In addition, there is an associated increase in cost and substantial increase in examination time. Intravenous contrast is therefore mostly used for problem solving in selected groups of patients, including those who have suboptimally prepped colon seen during initial scanning in the supine position. It is also used in patients who have colonic masses, for assessment of pericolonic spread, lymphadenopathy and distant metastases.

CTC and Radiation

The lifetime risk of developing fatal cancer as a result of ionizing radiation exposure is estimated by the International Commission on Radiological Protection, or ICRP, to be approximately 5% per Sievert [30]. Because of the long latency period, radiation-induced cancer death becomes less probable the older the radiated person is. The targeted population for CTC is 50 years of age and older. The ICRP data indicate that the probability of inducing fatal cancer in this age group is approximately 2.5% per Sievert, and at the age of 70, the risk is half this value. The effective dose of CTC is estimated at about 8.8 mSv (range 4–12 mSv) and carries a risk of 0.02% in a 50-year-old individual and is lower for older patients [31]. In order to minimize the dose, efforts have been made to adapt the tube current to the minimum accepted dose while not diminishing study performance. No change was reported in the diagnostic efficacy when lowering the tube current from 140 to 70 mA using single-detector CT [32] and multidetector CT [31]. Low-dose CTC was shown to have excellent sensitivity and specificity for detection of colorectal neoplasms 10 mm and larger [33]. The performance of CTC using an ultra-low radiation dose of 10 mAs has been shown to compare favorably with conventional colonoscopy in the detection of polyps larger than 6 mm with markedly decreased performance for small polyps of 5 mm or smaller [34]. The reduction in tube current has been shown to result in more noise with degradation of image quality. However, it has recently been shown [35] that combined x-, y- and z-axis tube current modulation leads to significant reduction of radiation exposure without loss of image quality.

Interpretation of CTC Examinations

Acquired CT data are transferred onto a dedicated postprocessing workstation, equipped with navigator software, permitting the radiologist to obtain multiplanar reformations (MPR, 2D), as well as to construct an endoluminal model of the air-distended colon (3D model). The endoluminal model allows fly through capabilities in the distended colon enabling viewing of the distended colonic lumen, in both the antegrade and retrograde directions. Some navigator software also allows 'virtual dissection', or 'filet mode evaluation' of the colon, where the colon is divided along its long axis and is opened for display, giving a panoramic view of the details of the colonic lumen (fig. 1, 2). This feature gives CTC an important advantage over endoscopic colonoscopy, overcoming the presence of blind areas due to haustral folds in both forward and reverse views, thereby reducing the chances of missing polyps. We find this feature to be extremely useful. Most workstations allow simultaneous viewing of the 3D and 2D images and also provide a 3D map of the colon, indicating the position along the colon of the area being viewed. There is usually an option that enables locating a suspected pathology simultaneously, on all views and reconstructions.

There are two primary techniques for data interpretation: a primary 2D approach and a primary 3D approach, where the 2D or 3D images, respectively, are evaluated primarily with the alternative views used as a problem-solving tool [36, 37]. In 2D imaging, the colon is 'tracked' from the rectum to the cecum using the supine and prone axial images that can usually be displayed adjacent to each other. Images are viewed in suitable windows for viewing the colonic wall and polyps and then in abdominal windows for evaluation of flat polyps, circumferential colonic masses and extra-colonic findings in the abdominal and pelvic organs. In 3D viewing, the radiologist 'flies through' the colon using the reconstructed 3D model.

Residual fecal material may simulate polyps. Three signs may allow distinction of fecal material from polyps: mobility, lesion morphology and internal attenuation.

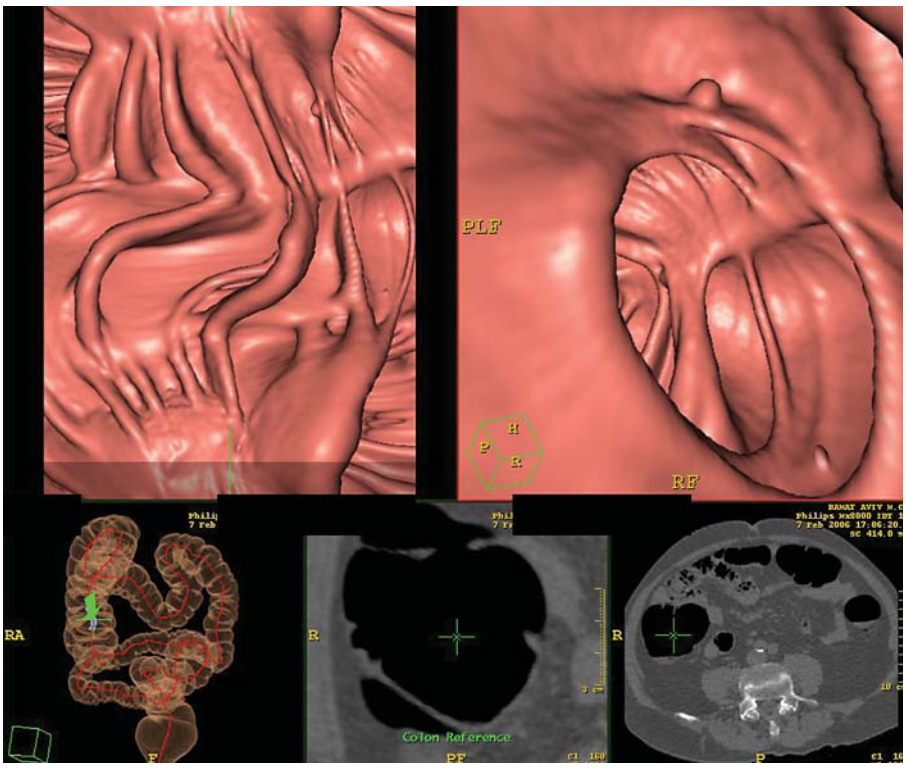

Fig. 1. A screen view of a 4-mm ascending colon polyp (Philips MX 8000 workstation). The polyp is well demonstrated in the right upper fly through image. The left image is a filet view of the colon cut along its center. The location of the polyp can be appreciated on the lower images demonstrating the 3D colonic model (left) and on the enlarged and actual axial images (mid and right images).

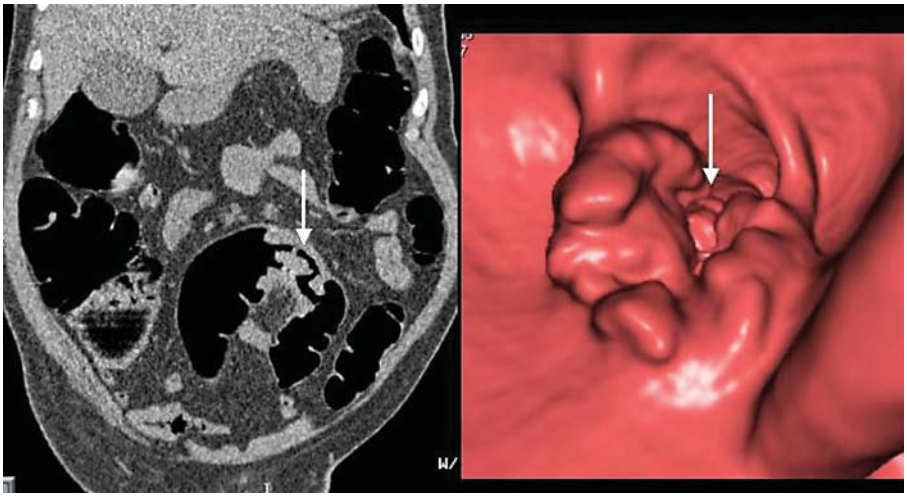

Fig. 2. A screen view of a transverse colon-obstructing carcinoma (Philips MX 8000 workstation). The mass is well demonstrated on the left axial CT image as well as on the endoluminal view right image.

Fecal material is usually mobile, although this sign must be interpreted with caution since the colon segments are mobile and pedunculated polyps may also be mobile. Polyps may be sessile pedunculated or flat, and are usually visualized as round, oval or bilobed lesions with well-delineated contour. Fecal material exhibits commonly a geometric form with irregular sides that change between the two scans. Internal attenuation of polyps is usually homogeneous, lacking internal gas or areas of high attenuation typical of fecal material.

A typical CTC study produces 700–1,200 axial CT images as well as multi-planar reconstructions and 3D views. The evaluation of this large data requires considerable time and effort. Computer-aided detection of polyps

may reduce radiologists' interpretation time, as well as increase the diagnostic accuracy of polyp detection. Current methods of computer-aided detection generally rely upon shape-based algorithms to localize potential polyps [38, 39]. One of the drawbacks of this technique is the possible large number of false-positive lesions. Additional filters can be applied to minimize their number to an acceptable level of 2.5 false-positive findings per patient [39], and it is likely that better results will be obtained in the future.

CTC Performance: How Good Is It?

Multiple studies have documented the ability of CTC to detect patients with polyps greater than 10 mm in size with sensitivities ranging from 50 to 100% [10, 21, 23, 27, 40–50]. The wide range in sensitivity for the detection of polyps may be explained by significant differences in the techniques used in data acquisition and analysis [51–53] and by the readers' expertise. The sensitivities for polyps 6–9 mm are lower reaching 60–70%. The performance of CTC for small polyps less than 6 mm in size is poor, but from a clinical perspective these are the least important lesions. Based on available results, CTC seems to have an excellent specificity record (false-positive results of up to 10%) with specificity for polyps larger than 10 mm of 90–95% [40–50]. Recent meta-analyses [54, 55] showed a pooled per patient (finding a patient with polyps irrespective of the number of polyps found) sensitivity and specificity for polyps 10 mm or larger of 88 and 95, and 84 and 65% pooled per patient sensitivity for polyps 6–9 mm and 5 mm or smaller, respectively. Another recent meta-analysis [56] evaluating 4,181 patients showed an even higher per patient sensitivity and specificity for polyps 10 mm and larger of 93 and 97%, respectively. The sensitivity and specificity decreased to 86% when medium-sized polyps were included. The sensitivity for detection of cancer was 96% with 144 of 150 tumors detected. It is clear that the performance of CTC in detection of polyps is improving as the technology and experience of radiologists' progress.

The pitfalls of CTC are beyond the scope of this review. It is important to realize that although CTC is a powerful tool for colonic polyp and tumor detection, there are many pitfalls for misdiagnosis. These include: (1) technical errors: due to suboptimal patient preparation with a large amount of residual stool or fluid, under distension or spasm of the colon, respiratory and metallic artifacts, image noise; (2) pitfalls related to evaluation technique such as incorrect window settings, 3D threshold values; (3) pitfalls related to reading such as failure to detect lesions and misinterpretation of findings [57].

When considering the performance of CTC as a possible screening technique for colorectal cancer [58], it must be remembered that most reported clinical studies comparing CTC to conventional colonoscopy have included high-risk patients. This may result in an increased positive predictive value due to the higher prevalence associated with this population in comparison with a screening population where the prevalence of disease is lower. It must also be remembered that conventional colonoscopy is not perfect as 6% of polyps can be missed [59]. Therefore the comparison of CTC is not with another perfect technique but rather with one that is about 95% sensitive for polyps larger than 10 mm. The new developments in data acquisition, as well as faster and more accurate image interpretation and better residual stool and fluid tagging techniques, will likely improve results, reduce cost and provide a rapid, safe, reasonably convenient method for colon cancer screening.

An important advantage of CTC over conventional colonoscopy is the ability of CTC to evaluate extra-colonic structures such as the lung bases, the abdomen and the pelvis. The frequency of extracolonic findings at CTC varies between 11 and 15% [60, 61], but only 3–5% of these findings are clinically important. It is therefore important for the radiologist to make an assessment of the importance of these findings and to avoid excessive caution and ambiguity when describing findings that are almost certainly benign. Hara et al. [61] found that in 7% of patients further examinations were performed and nearly 2% of patients had abnormalities requiring surgical intervention.

Complications

Until recently, it was thought that the only complications of CTC were mild to moderate abdominal discomfort due to the colonic insufflation and radiation exposure. Two articles published recently [62, 63] that evaluated large patient cohorts of 11,870 and 17,067 patients, respectively, reported a risk of colonic perforation during CTC of 0.06–0.08%. Older age and underlying concomitant colonic disease such as inguinal hernia containing the colon, severe diverticulitis and obstructing colonic mass were present in most patients with perforation [62].

Conclusion

CTC is a fast, safe, rapidly evolving examination that is accurate in detecting clinically significant colorectal polyps. The specificity and sensitivity of CTC are improving with time and are excellent for detection of colorectal tumors and polyps larger than 10 mm. Further improvement of this newly emerged technique may be expected with the introduction of techniques undergoing development, including computer-aided diagnosis, as well as better fecal tagging with electronic cleansing of the bowel, eliminating bowel preparation.

Disclosure Statement

None.

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no miss rate, no time – and those following a more skeptical approach, based also on the fact that colonoscopy with all its inherent complexity, expenditure and risks may not be an ideal and appealing screening test for the future. How good colonoscopy actually performs in and outside of so-called expert centers has only sporadically been explored and is gaining increasing attention in the published literature.

Rex et al. [20] as well as others have started some 10 years ago to assess polyp miss rates by a tandem colonoscopy approach, and some 15–30% of missed adenomas, mostly small, have been described in these studies [20–22], and this discussion has recently been revitalized by one group reporting colonoscopy miss rates compensated for by virtual CT-based colonography [23, 24]. Further fuel has been given by retrospective analyses of missed colorectal cancers [25, 26]. The miss rate has therefore been the topic of several randomized studies reported below. Various factors influencing adenoma miss rates such as bowel preparation [27], examiner time and care [18, 28] have recently been highlighted.

Cecal rates have been reported as main parameter of colonoscopy quality control [29], and rates vary greatly in recent broad-based analyses of screening colonoscopy: Whether there are differences in quality between countries or whether these are at least partially explained by study methodology (audit vs. self-reporting) is still a matter of debate. Worrisome low cecal rates from a large UK study (77%, even lower when adjusted) have been partially ascribed due to lack of adequate training [30]. Large European screening programs such as the one in Germany [31] have reported very high cecal rates, confirming previous figures from regional quality assurance programs [32]. Reports from other countries have been variable as well [33–35]. These data, however, clearly show the need of easier colonoscopy.

Sedation during colonoscopy [36] is the topic of another debate with religious beliefs fighting each other. It seems that in most parts of the Western world, sedation is preferred by both patients/screenees and physicians. Whether pain-free colonoscopy, if achieved by newer colonoscopes (or finally the colon capsule if effective), will enhance compliance and patient acceptance of colonoscopy and of colorectal screening by imaging, remains to be seen.

Modifications of Conventional Endoscopes – Small Steps, No Breakthrough?

As outlined above, there are several aims to improve colonoscopy; recent studies have mainly centered on ease of colonoscopy and cecal intubation as well as on reduction of polyp miss rates. Regarding the first aim, simple methods such as water- or oil-lubricated colonoscopy [37, 38] have been shown to be useful in randomized trials, but have obviously not gained widespread acceptance. The effect of external localizers has been studied in randomized trials, with apparent benefit only with trainees involved, but not with experienced colonoscopists [39, 40]. Colonoscopes with variable stiffness functions were mostly found to be superior in terms of patient pain and ease of introduction in 4 randomized trials [41–44]. Modification of the colonoscope tip to include an additional passive angulation capacity was designed to better get around curves; in a recent randomized study in 280 patients initially scoped without sedation, cecal intubation rates (87 vs. 85%) and the rates of secondary sedation (7 vs. 11%) were not significantly better with the new scope. The only difference seen was the percentages of examinations without pain/with minimal pain (77 vs. 63%) [45].

The use of a transparent cap at the tip of the colonoscope was tested for better introduction as well as for – the second aim mentioned above – improved adenoma detection rates. In a pilot study from Hongkong in 100 difficult colonoscopies (no passage of sigmoid colon and/or cecal intubation), the cecum could be finally reached in 94% of cases, but at the cost of one perforation [46]. A randomized study from Japan included 684 unsedated routine colonoscopies allocated to three groups (mucosectomy cap, short distance cap, no cap). The cecal rate (95%) was not significantly different between the three groups. The group with a mucosectomy cap had shorter introduction times to reach the cecum (11.5 vs. 14 min) as well as higher polyp detection rates (49 vs. 39%). The short cap did not offer any advantage [47].

As far as adenoma detection rates are concerned, wide-angle colonoscopy did not lead to an increased pick-up [48]. Two French studies assessing the role of dye staining [49, 50] reached contradictory conclusions: In the tandem design study [49], a higher rate of high-grade dysplasia was found, but on the first pass before staining; in general, there was no increased yield. In the other study, using a simple comparative design, staining did not increase the overall adenoma detection rate, although flat adenomas were found more frequently [50]. In both studies, the rate of hyperplastic polyps was also significantly in-

Fig. 1. NeoGuide colonoscope function. A tip position sensor (**a**) constantly measures tip position, whereas an external position sensor (**b**) measures tip depth. **c** A 3D colon map is generated as the scope is advanced.

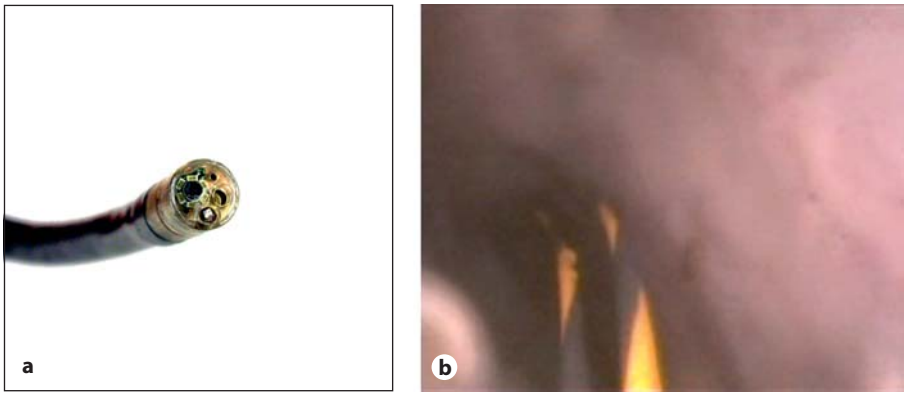


Fig. 2. Cathcam endoscope tip (**a**) and guidewire introduced through the endoscope channel (**b**).

creased [49, 50]. Similarly, two randomized trials on the application of narrow band imaging, recently published, did not offer consistent benefit in terms of increased adenoma detection (at different adenoma rates in both trials); again, significantly more hyperplastic polyps were found [51, 52]. Thus, expanded imaging techniques such as staining and narrow band imaging, as well as autofluorescence endoscopy, seem to work in special disorders such as inflammatory bowel disease [53–55], but not in a general colonoscopy setting, although the latter has not been tested.

New Colonoscopes

Development is taken a step further by colonoscopes with entirely new design which may indeed widen the spectrum and finally facilitate colonoscopy for patients and physicians. The endoscope with the seemingly greatest similarity is the NeoGuide colonoscope (fig. 1); it is an intelligent scope with sensors memorizing the colonic curves during introduction and keeping these curves on further instrument proceeding ('follow the leader'). Testing on a colon model showed significantly less looping and tension forces [56]. First clinical results on 11 patients (3 screening and 8 diagnostic indications, mostly pain and diarrhea) excluding one further case with poor bowel preparation showed a 100% cecal rate in a median time of 20.5 min. Patients were however sedated with midazolam (mean 4.2 mg) and propofol (mean 96.8 mg) without further specification. However, sedation was not one of the primary endpoints in this first of its kind clinical feasibility study [57]. Based on the data of the computerized algorithm of the shape and path of the scope in vivo, the system generates and displays a real-time, three-dimensional (3D) image of the shape of the colon. This 3D real-time imaging seems to be helpful for evaluating the position of the scope, for detecting and straightening loops, and for anatomical correlations of pathological findings. In addition, due to the unique technology of the system

and by replacing the handle of the scope with a joystick, it could be less tiring for GIs and reduce repetitive stress injuries on the colon wall.

The Cathcam colonoscope (fig. 2) is a soft endoscopy tube (11 mm in diameter, 180 cm long) which is introduced over a soft guidewire with a kinked tip. This guidewire serves the function of path finding and guiding the way of the Cathcam. Bench tests also showed decreased tension force [58]. At the first clinical evaluation of 14 patients with failed conventional colonoscopy, one examination was terminated due to sigmoid stenosis, and in the remaining 13 cases, the cecum was finally reached in 12. Sedation was with 2.5–5 mg midazolam. The first four Cathcam colonoscopies were performed after the principle described above; in the remaining cases, the guidewire was inserted via a partially introduced colonoscopy and then the Cathcam was introduced over this wire. The total examination time was a mean of 24 min (range 5–105), and decreased to a mean of 15 min with the second technique [59].

The last two new endoscopes best fulfill the expectation of a self-moving/self-propelled scope, both were designed with different intentions: The Aer-O-scope^{TM} (fig. 3) is a single-use, purely diagnostic (no working channel) endoscope with an interesting endoscopic viewing mechanism generating a forward and lateral round view. A rectal introducer balloon is placed into the rectum and the balloon is inflated; through this introducer the colonoscope tube with a camera and a specially designed balloon at the tip is introduced. Both balloons are inflated and CO_2 is insufflated into the space between the balloons. Once the pressure between the two balloons exceeds the pressure in the colon lumen in front of the scope, the scope is moving into the colon. The pressures induced are obviously quite low (mean of 34 mbar), and the pressure is measured by sensors and limited to 40 or (adjustable) 50 mbar. Following feasibility and safety studies in pigs [60], first tests in 12 young volunteers (mean age 30 years) confirmed cecal instrument position (monitored by X-ray) in 10/12. Two of the volunteers had to receive sedation by morphine. The mean time to reach the cecum (radiologically confirmed) was 14 min in the 10 successful cases [61]. In the meantime, the optical roundview system has been incorporated into the scope, potentially providing even better overview than with conventional scopes, and tested in vitro and in vivo in animals [62].

The other instrument, the Invendo colonoscope (fig. 4), is a single-use, motor-driven and handheld-controlled colonoscope with a working length of 160 cm, now extended to 200 cm; the colonoscope has a 10-mm inner sheath. A sleeve is pulled over this inner sheath and inverted at each of the respective ends (at the biopsy port and just below the endoscope deflection) and attached to a propulsion connector. The connector is then locked into an endoscope driving unit and the examination is started. Under handheld control by the physician, eight drive wheels in the endoscope driving unit start to move in the selected direction. The wheels grip onto the inner side of the inverted sleeve, causing the inverted sleeve and inner sheath to drive either forward or backwards. The endoscope tip can be deflected electrohydraulically 180° (at body temperature) in any direction by moving a joystick on the handheld device. Due to the inverted sleeve technology, the colonoscope 'grows' at a position just 10 cm below the distal end, where the colonoscope is connected to the endoscope tip/intermediate section. Otherwise, the colonoscope was designed in a similar way to

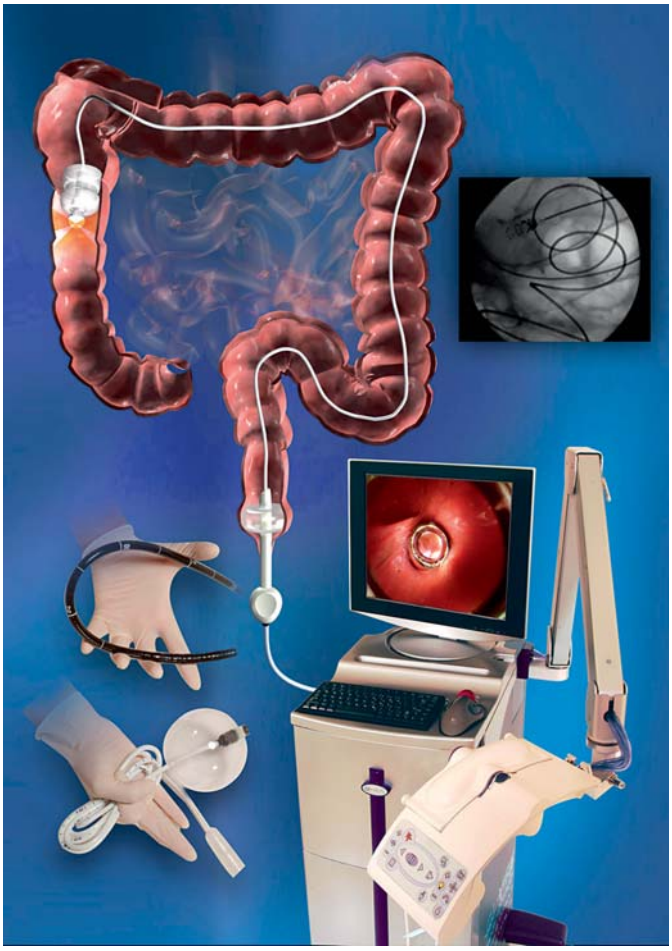


Fig. 3. Aeroscope.

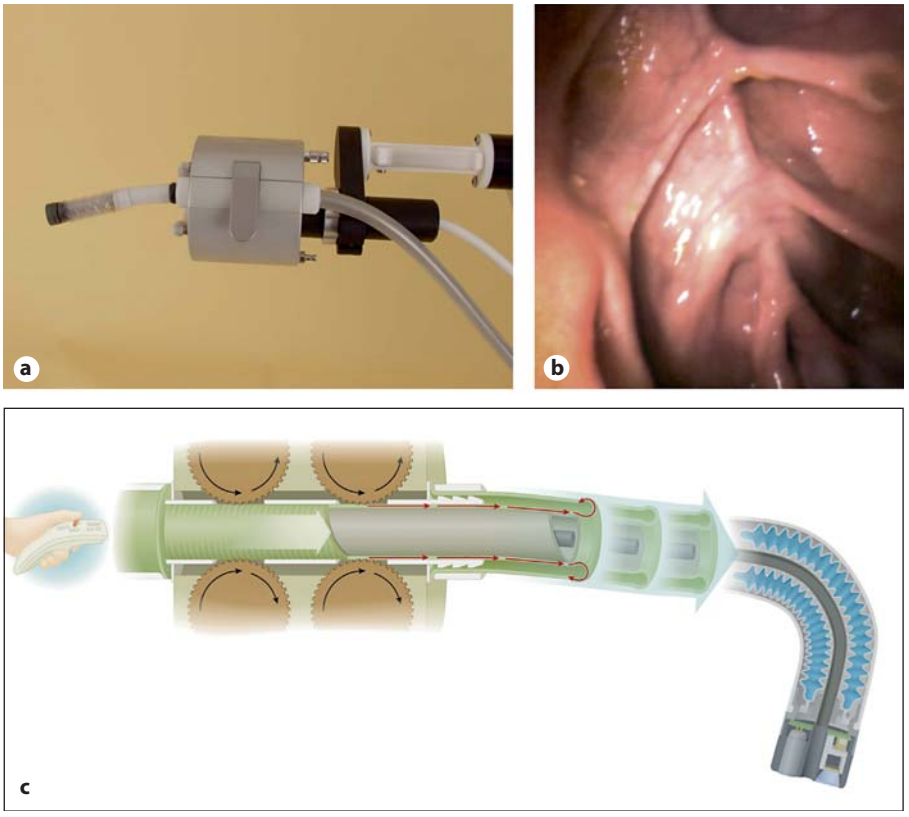


Fig. 4. Invendoscope with driving motor (**a**), an endoscopic image showing the cecum (**b**) and a schematic drawing explaining the principle of expelling the endoscope tip (**c**).

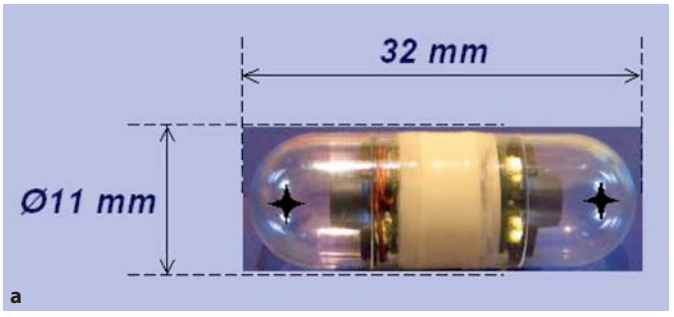
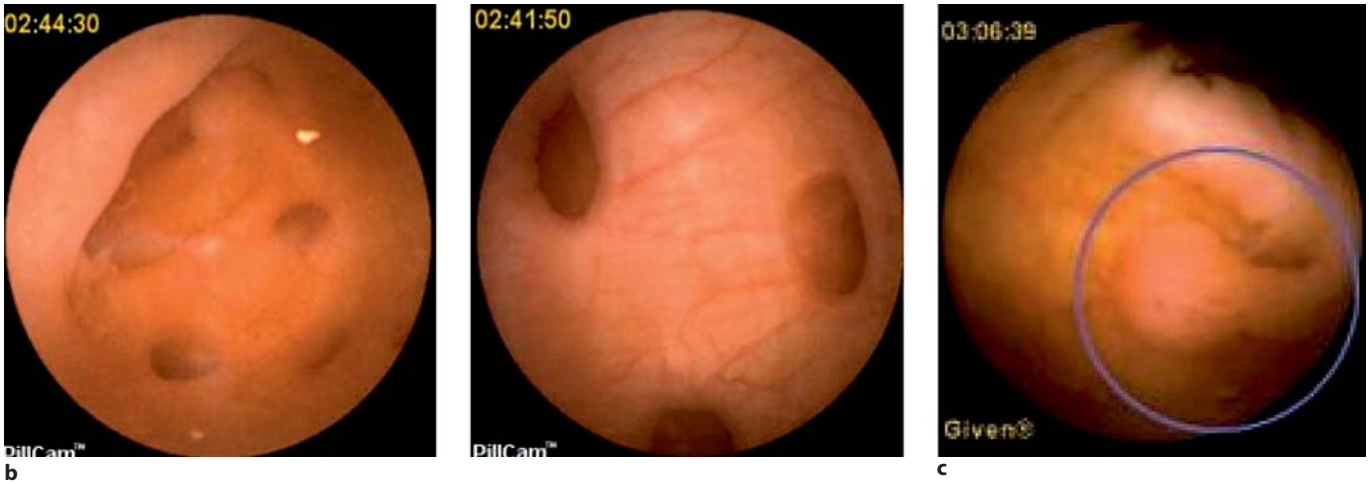


Fig. 5. Example of the colon capsule (**a**) and views of a normal colon with diverticula (**b**) as well as a pedunculated colon adenoma (**c**).



conventional endoscopes, allowing for insufflations, rinsing, and suction. It also has a 3.2-mm working channel. The scope is moving forward, passing any loops without losing much its driving force. In a first pilot volunteer study (n = 28) published in abstract form [63], 4 cases had to be excluded due to instrument dysfunction in the early phase. Of the remaining 24 volunteers, the cecum was reached in 79%, and two of the failures were due to pain, leading to termination of the examination in the sigmoid colon, since no sedation was foreseen in any of the volunteers. The mean time to the cecum was 26 min.

Capsule Colonoscopy – Super-FOBT or Easy to Use Self-Colonoscopy?

The final solution concerning patient acceptance may be the colon capsule (fig. 5), but concerns with respect to deficiencies in lesion detection rates remain. Based on the small bowel and esophageal capsule concept, a two-camera capsule is activated 2 h after swallowing and runs for several more hours. After a complicated preparation regimen including later boosts with laxatives, the capsule was excreted after 10 h in 78% of volunteers [64]. Two studies (multicenter in Israel and single center in Brussels) compared the capsule with subsequent colonoscopy in a total of 132 patients. Blinded reading of capsule results was a bit complicated in the Israeli study since it involved three rounds of assessment (main examiner, external reading service/group of experts), during which sensitivity increased steadily (56/69/76%), as did specificity (69/81/100%) [57]. In Brussels, only one blinded reading was done, with a positive and negative predictive value of 36 and 86% for significant polyps (<6-mm or ≥3 polyps) [65]. No complications were encountered.

The ultimate goal of the colon capsule might be to replace endoscopy, but the benchmark concerning adenoma detection rates is rather high and has recently at least theoretically been improved by modern imaging techniques. If this is the aim, negative predictive values around 90% should finally be achieved. There is also room for improvement in the preparatory regimen, since results are expected to deteriorate if used broadly. If these two problems are not solved to a degree expected, the colon capsule might remain a super-FOB test, more sensitive, but also much more expensive. Since the colon capsule is only at its beginning, it is probably justified to hope for better performance and bowel preparation.

Conclusions

Several considerations have to be made in view of the above preliminary results especially with the new scopes and the colon capsule:

- Minor modifications of conventional endoscopes (more flexible tip, cap, etc.) do not offer large benefit and will probably not be incorporated into clinical routine, especially since at least the cap may be associated with an increased risk of perforation. Other tricks such as a magnetic image localizer do not make the lives of experienced physicians easier; some benefit was evident by variable stiffness scopes. These modifications have mostly been tested in prospective randomized trials.
- More innovative scopes of intelligent, guidewire-, motor- or air-driven scopes have only been tested in animals and in small groups of volunteers and are mostly still under development. Thus, they represent work in progress, although most of the underlying concepts are quite appealing.
- Capsule endoscopy has been tested in a fairly large number of patients in two pilot trials. Results concerning sensitivity are fair at best, but further work is expected and hoped not only to maintain these results in broad-based applications, but also improve them, perhaps with the help of extended imaging techniques (molecular imaging).

The above-mentioned endoscopes as well as the colon capsule may fulfill different expectation in different ways:

Pain- and Sedationless Colonosocopy

All new colonoscopes as well as the capsule claim, to a different degree, reduction or abolishment of pain and discomfort. Whereas this is not doubted for the capsule, only preliminary and very limited experience is present for the other scopes, and only two of the instruments (Aeroscope and Invendo colonoscope) had no sedation in general or only in few cases in their pilot studies.

Easy Colonoscopy

This outcome parameter was not part of any of the studies, only subjective judgment by the physicians (of very limited scientific value) was mentioned in a few papers. Given the small case number and the potential learning curve with new instruments, this question cannot be answered as yet. The colon capsule and to a large extent also the Aeroscope primarily work independent of medical personnel, and can therefore be considered to probably reach this aim.

Sufficient Lesion Detection Rate

This has not been examined in any of the studies with the new scope, but for capsule endoscopy (see above). Most of the new scopes have more or less conventional optical fields, so they should be tested for equity with conventional colonoscopy. The Aeroscope with its round view holds the potential of a higher lesion detection rate, but this has to be shown in appropriate clinical trials.

Single-Use Instruments

The Aeroscope and the Invendoscope (and, of course, the colon capsule) are single-use instruments. The principal decision of reusable versus single-use instruments is however beyond the scope of this overview.

Performance of Biopsy and Therapy

The Neoguide, the Cathcam and the Invendo colonoscope have both a working channel. The other scopes and the capsule do not, but they follow different concepts of a 'filter test' to select patients for subsequent conventional colonoscopy for tissue acquisition and polypectomy or other forms of endotherapy.

At the moment we are at an early, although still very exciting stage of development of new colonic imaging methods. We hope that in the future, high-quality prospective comparative studies looking at outcomes will be available so that the best or a combination of the best will win the game.

Disclosure Statement

T. Rösch holds a consultant contract with Invendo Medical, Ltd., R. Eliakim with Given Imaging, Ltd., and N. Arber with GI View, Ltd.

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derstanding of molecular mechanisms of carcinogenesis have resulted in a rapid development in the field of chemoprevention of CRC.

Chemoprevention

Chemoprevention is defined as the use of natural or synthetic substances to reduce the risk of developing cancer, or to reduce the chance that cancer will recur. Michael Sporn [1] coined the term back in 1976 based on the realization that cancer development was not a 1-stage event. Rather it is a multistep, evolving phenomenon of transformation of normal cells through progressive stages of dysregulated growth due to changes in molecular makeup of the genetic material in the cells, modulated by the interplay of genetic predisposition and environmental factors. The basic concept of chemoprevention is to inhibit the development of epigenetic and genetic alterations that are part of the process by which clonal proliferation of cells with abnormal genetic contents cascades into dysplastic and then malignant cells. Also as various steps are involved, agents that act at different stages of the carcinogenesis pathway may be combined for improved efficacy.

Eric Fearon and Bert Vogelstein [2] came up with a genetic model for colorectal tumorigenesis. This model provided a good working base for understanding how normal colorectal mucosa transforms into cancer via several steps of hyperproliferative epithelium to small adenoma to large adenoma, each step being the result of ≥ 1 genetic changes in an environment of trigger factors.

Subsequently several additions have been made to the basic model and also it has now been recognized that there are alternative pathways of colorectal carcinogenesis [3], especially in patients with inflammatory bowel disease (IBD) [4].

Overview of Molecular Mechanisms in Colon Carcinogenesis

The integrity of the normal mucosa is dependent on the balance of cell division/differentiation and apoptosis. In susceptible cells, in the presence of certain trigger factors, the genetic makeup changes to a state where the normal balance is lost. The changes may be genetic or epigenetic and this may result in loss of function of growth-controlling genes, activation of growth-enhancing genes, over-expression of genes for growth-promoting factors or under-expression of genes promoting apoptosis.

Colon cancer may be sporadic, hereditary or on the background of IBD. Also patients with a previous CRC are at an extremely high risk of developing further malignancy and are the most attractive population to be offered chemoprevention trials.

The majority of sporadic CRCs occur in adenomas due to local imbalance of growth regulation arising out of alteration of proto-oncogenes, loss of tumour suppressor gene activity and abnormalities in genes involved in DNA mismatch repair [5]. These defects result from somatic mutations and are thus more localized with only few foci developing the abnormality due to clonal proliferation of possibly a single mutated crypt stem cell, even though the whole colorectum is exposed to the environmental triggers.

In hereditary CRC syndromes like familial adenomatous polyposis (FAP), hereditary non-polyposis colon cancer (HNPCC) and other less common syndromes there are inherited genetic mutations in either tumour suppressor genes (APC gene in FAP) or genes associated with DNA mismatch repair function (hMSH group of genes in HNPCC). This widespread presence of susceptible genetically defective cells all through the colorectum leads to a field change in growth regulation and thus multiple and often numerous polyps develop. In FAP, as the main defect is in the tumour suppression gene, there are numerous foci of clonal proliferation leading to hundreds of polyps but subsequent cancer transformation is not accelerated.

In HNPCC on the other hand, there is defect in DNA repair and this results in progressive increase in mutated clones of cells with abnormal gene pool and accelerated cancer transformation even without associated polyp formation.

IBD-associated cancer is thought to represent an inflammation-dysplasia-carcinoma sequence. Inflammation induces a cascade of changes in the colonic epithelium, which in turn affects the apoptotic and regenerative activity of the epithelial cells, which is associated with cytogenetic alteration of pro- and anticarcinogenetic influences. Progressive DNA aneuploidy, chromosomal instability, microsatellite instability and molecular alteration in the cytosine-phosphate-guanosine island methylator phenotype have all been implicated in the development of IBD-associated CRC. The high oxidative stress burden in the inflamed mucosa leads to an array of alteration in mediators of cell regulation and apoptosis. Reactive oxygen and nitrogen species produced by macrophages and

neutrophils in the vicinity of colonic epithelial cells can directly mediate damage to DNA, leading to genetic and epigenetic changes, DNA strand breaks and shortening of telomeres, and indirectly affect DNA methylation status. These alterations cause loss of tumour suppressor gene function, gain of oncogene function and loss of genetic stability. The hyperproliferation of cells in the inflammation-associated damage-regeneration cycle contributes to the fixation of genetic and epigenetic alterations and promotes the development of colorectal dysplasia and carcinoma [6].

End Point Selection in CRC Chemoprevention Trials

Since the process of carcinogenesis is a protracted one over several years, large and appropriately powered, long-term, randomized controlled studies in chemoprevention with the gold standard end point of cancer incidence are extremely costly and logistically difficult. The long period of such trials will inevitably be fraught with compliance issues and attrition of study population, and thus translational scientists have resorted to using surrogate end points in most of the studies relating to chemoprevention.

Biomarkers related to cancer can be defined as phenotypic or genotypic characteristics that are altered during carcinogenesis and/or during response to chemoprevention or therapeutic intervention. Ideal biomarkers should be able to substitute for clinical end points such as reducing cancer incidence, progression of precancerous lesions, retarding recurrence after initial definitive therapy and prolonging survival (prognostic biomarkers) [7]. Biomarkers that either appear or transform during the various phases of carcinogenesis can indicate the efficacy of chemoprevention techniques. Biomarkers that indicate how well a particular chemoprevention agent will work are termed predictive biomarkers.

However, the only real way of knowing whether a proposed biomarker is really a true indicator of response to chemoprevention is to validate them in prospective, randomized controlled, long-term human studies. And here lies the difficulty in putting the theoretically attractive chemoprevention strategies into widespread use in the population as there is really no validated biomarker that has stood the test of time to accurately predict the outcome of chemoprevention [8].

Colonic adenomas have been used for some years as a surrogate marker for chemoprevention studies. Large-scale studies specially using aspirin and other non-steroidal anti-inflammatory drugs (NSAIDs), calcium and vitamin supplements have been done with the reduction in recurrence of adenomas after polypectomy and/or new adenoma incidence as end points. However, it has to be kept in mind that, though a significant number of CRCs arise within adenomas, only a few of all adenomas ever turn malignant. Also most of these studies have assessed adenoma recurrence and/or colorectal carcinoma development in adenomas over periods of only between 2 and 5 years, whereas the natural history of adenoma-carcinoma transformation may occur over 10–20 years. In addition, if the putative agent in question exerts its cancer chemopreventive effect at a stage after polyp formation, these effects will not have been picked up. Also it may happen that an agent may reduce the rate of polyp formation, but may have an accelerating effect on transformation of adenomas to cancer. In this latter case, if the end point of studies evaluating such an agent was just the adenoma recurrence rate and not actual rate of cancer formation, then a very wrong evaluation of its chemoprevention effect would have been reported.

Chemoprevention in Practice

Over the past 3 decades there has been a concerted effort to develop chemoprevention agents to reduce the development of various cancers and CRC has been an important area of research in chemoprevention. Observational studies in man, animal model studies, ex vivo cell line studies and more recently the development of long-term, large randomized controlled studies often with multiple arms and combination agents have explored the possibility of finding the ideal agent which would fulfil the major criteria for chemoprevention. First, it has to be effective against ≥ 1 step in carcinogenesis and this should have a mechanistic basis for its action. Second, it should be safe in the short- and long-term use. Other attributes include ease of administration, cost-effectiveness, acceptability in the general population and low risk of escape phenomenon or resistance development. In this latter case it may well be that combinations of agents with differing modes of action have to be used. In terms of safety issues, it is probably much easier to evaluate existing drugs with proven efficacy and safety over years of clinical use for their chemoprevention effects [8]. Although, with the rapid development of molecular biology of cancer initiation and progression, newer targets for chemoprevention will be emerging and a newer, more targeted approach for chemoprevention will be adopted in the next few years (fig. 1).

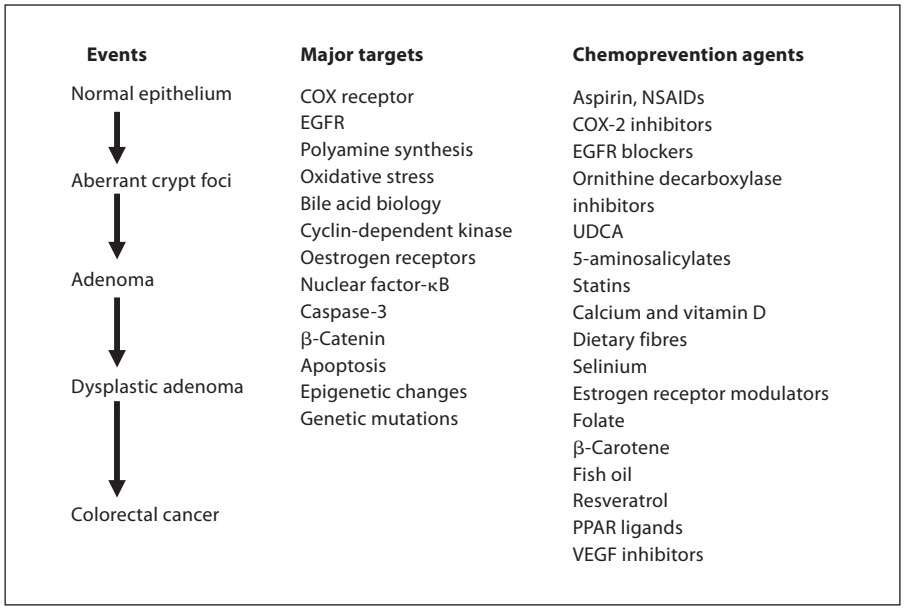

Fig. 1. Events in colorectal carcinogenesis, major chemoprevention targets and agents.

Aspirin and NSAIDs

Apoptosis in the colonic epithelium appears to be progressively inhibited during colonic carcinogenesis [9]. Evidence is now growing that the induction of apoptosis is one of the ways in which aspirin and NSAIDs prevent cancer, and they may well exert their chemopreventive effects in the colon by restoring a normal frequency of apoptosis in the colonic mucosa [10].

Epidemiological studies have shown significantly lower rates of CRC in individuals reporting the regular consumption of aspirin and other NSAIDs [11, 12]. Retrospective and prospective studies have reported between 30 and 50% reductions in the rates of CRC in humans with a regular intake of aspirin or NSAIDs.

Among a group of >600,000 adults enrolled in an American Cancer Society study, the mortality in regular users of aspirin was about 40% lower for cancers of the colon and rectum. In a report from the Health Professionals Follow-Up Study of 47,000 males, regular use of aspirin (at least 2 times per week) was associated with a 30% overall reduction in CRC, including a 50% reduction in advanced cases [13]. In a Women's Health Study randomized 2 × 2 factorial trial of 100 mg of aspirin every other day for an average of 10 years, similar rates of breast, colorectal or other site-specific cancers were observed in both the aspirin and placebo arms [14]. In a report from the Nurses' Health Study involving 82,911 women followed for 20 years, the multivariate relative risk (RR) for colon cancer was 0.77 [95% confidence interval (CI) = 0.67–0.88] among women who regularly used aspirin (≥2 standard 325-mg tablets per week) compared with non-regular use. Significant risk reduction was not observed, however, until >10 years of use. The benefit appeared to be dose-related. In the Physicians' Health Study, 22,000 men aged 40–84 years were randomly assigned to receive placebo or aspirin (325 mg every other day) for 5 years. There was no reduction in invasive cancers or adenomas at a median follow-up of 4.5 years [15]. In a subsequent analysis over a 12-year period, both randomized and observational analyses indicated that there was no association between the use of aspirin and the incidence of CRC. The low dose of aspirin and the short treatment period may account for the negative result [16].

A randomized controlled study of 635 patients with a previous history of CRC, comparing 325 mg of aspirin daily against placebo, found a significantly reduced risk of development of an adenoma in the aspirin-treated group [17]. The RR of a new adenoma being found at colonoscopy in the aspirin-treated group was 0.65 (95% CI = 0.46–0.91). In addition, the time to detection of a first adenoma was also found to be longer in the aspirin-treated group. Though a clear protective effect of aspirin was noted, adenomas still developed in some patients in the aspirin-treated group, and therefore aspirin cannot be viewed as a replacement for surveillance colonoscopy.

Another randomized placebo-controlled trial of 1,121 individuals with a recent history of colorectal adenoma, comparing placebo to 81 mg of aspirin daily or 325 mg of

aspirin daily, noted a moderate, but significant, reduction in the risk of adenoma formation in the group that received 81 mg of aspirin compared with placebo (RR = 0.81; 95% CI = 0.69–0.96), but curiously the RR of adenoma formation in the group receiving 325 mg of aspirin was only 0.96 (95% CI = 0.81–1.13) and not statistically significant [18].

Another study was done on 238 patients with a history of colorectal adenomas in a randomized controlled trial of 160 or 300 mg of lysine acetylsalicylate against placebo with colonoscopy evaluation a year after enrolment [19]. The RR for at least 1 recurrent adenoma with aspirin treatment was 0.73 (95% CI = 0.52–1.04; p = 0.08), and the RR for at least 1 adenoma of >5 mm with aspirin treatment was 0.44 (95% CI = 0.24–0.82, p = 0.01) [20]. The protective effect was higher in the 300-mg group (25% 1-year adenoma recurrence rate) than in the 160-mg group (35% adenoma recurrence rate), though the study lacked adequate power to draw any conclusion on this point.

It has been estimated that 1,250 individuals with no previous history of colorectal neoplasia would have to be treated with aspirin for 10–20 years or longer to prevent 1 death from CRC. However, giving aspirin as chemoprevention to 800 individuals over a period of 4–6 years would result in at least 1 major gastrointestinal haemorrhage and 1 haemorrhagic stroke [20]. This has been reflected in the recent guidance issued by the American Association of Family Physicians. In the Aspirin Esomeprazole Chemoprevention Trial (ASPECT), aspirin is being combined with a proton pump inhibitor and so GI bleeding may be minimized.

In a study of >11,000 men and women in Sweden with rheumatoid arthritis (and presumably ingesting NSAIDs), colon cancer incidence was 37% lower and rectal cancer was 28% lower than predicted from cancer registry data [21]. Several studies have demonstrated that sulindac reduces the size and number of adenomas in familial polyposis [22, 23].

Selective Cyclo-Oxygenase Inhibitors

Cyclo-oxygenase-2 (COX-2) receptors are over-expressed in most CRC, which is an event noted very early on in the carcinogenesis pathway. The stimulation of these receptors leads to a complex array of intracellular and intercellular modulation of functions including angiogenesis, cell proliferation and inhibition of apoptosis [24].

In a randomized double-blind placebo-controlled study of 77 patients with FAP, patients receiving 400 mg of celecoxib twice a day had a 28.0% reduction in the mean number of colorectal adenomas and a 30.7% reduction in the polyp burden which were statistically significant, as compared with non-significant reductions of 4.5 and 4.9%, respectively, in the placebo group and 11.9 and 14.6%, respectively, in the group receiving 100 mg of celecoxib twice a day [25]. Celecoxib has now been approved by the FDA for the reduction of polyp numbers in patients with FAP in conjunction with endoscopic surveillance or surgery.

The randomized, placebo-controlled, double-blind study, Prevention of Colorectal Sporadic Adenomatous Polyps involving 1,561 subjects who had had adenomas removed before enrolment, compared celecoxib (n = 933) to placebo (n = 628) daily, after stratification according to the use or non-use of low-dose aspirin, from 107 centres in 32 countries. The cumulative rate of adenomas detected through year 3 was 33.6% in the celecoxib group and 49.3% in the placebo group (RR = 0.64; 95% CI = 0.56–0.75; p < 0.001). The cumulative rate of advanced adenomas detected through year 3 was 5.3% in the celecoxib group and 10.4% in the placebo group (RR = 0.49; 95% CI = 0.33–0.73; p < 0.001). Adjudicated serious cardiovascular events occurred in 2.5% of subjects in the celecoxib group and 1.9% of those in the placebo group (RR = 1.30; 95% CI = 0.65–2.62) [26].

However, the major drawback of using COX-2 inhibitors for the chemoprevention of CRC, at present, is the recent findings of the cardiovascular risks associated with COX-2 inhibitors. Rofecoxib (Vioxx, Merck), a potent inhibitor of COX-2, was hypothesized to reduce rates of tumour recurrence in the randomized, placebo-controlled trial, Vioxx in Colorectal Cancer Therapy: Definition of Optimal Regime trial of patients who had undergone potentially curative surgery for CRC. However, the recruitment for the trial had to be stopped in September 2004, when Merck withdrew the drug worldwide after a significant increase in confirmed cardiovascular thrombotic events had been noted in another large multicentre trial, Adenomatous Polyp Prevention on Vioxx. An excess of vascular events was also found in the Adenoma Prevention with Celecoxib polyp-prevention trial of celecoxib. In the Adenoma Prevention with Celecoxib study evaluating placebo (679 patients) or 200 mg (685 patients) or 400 mg (671 patients) of celecoxib twice daily. The estimated cumulative incidence of the detection of ≥1 adenomas by year 3 was 60.7% for patients receiving placebo, as compared with 43.2% for those receiving 200 mg of celecoxib twice a day (RR = 0.67; 95% CI = 0.59–0.77; p < 0.001) and 37.5% for those receiving 400 mg of celecoxib twice a day (RR = 0.55; 95% CI = 0.48–0.64; p <

0.001). Serious adverse events occurred in 18.85 of patients in the placebo group, as compared with 20.4% of those in the low-dose celecoxib group (RR = 1.1; 95% CI = 0.9–1.3; p = 0.5) and 23.0% of those in the high-dose group (RR = 1.2; 95% CI = 1.0–1.5; p = 0.06). As compared with placebo, celecoxib was associated with an increased risk of cardiovascular events (RR for the low dose = 2.6, 95% CI = 1.1–6.1; RR for the high dose = 3.4, 95% CI = 1.5–7.9) [27].

Evidence from well-designed, randomized trials, and their meta-analysis, provided support for a moderate increase in vascular event rates associated with the use of COX-2 inhibitors, and a recent report in the *New England Journal of Medicine* found an increased frequency of adverse cardiovascular events among patients with a median study treatment of 7.4 months' duration in patients receiving rofecoxib to reduce rates of recurrence of CRC [28]. Celecoxib administration was also associated with a dose-related increase in death from cardiovascular cause, myocardial infarction, stroke or heart failure in a sporadic adenoma prevention trial (n = 2,035) that extended over 3 years [29].

Also the potential cost-effectiveness of CRC chemoprevention with COX-2 inhibitors was not favourable. As an adjunct to screening in patients over the age of 50 years, chemoprevention increased the average number of life years saved, but at costs exceeding USD 400,000 per life year saved, even in those individuals with 2 affected first-degree relatives [30]. The use of a COX-2 inhibitor alone was both less effective and more costly than screening alone. Also on comparing COX-2 inhibitor against surveillance colonoscopy in average-risk postpolypectomy patients there was a very marginal increase in the number of life years saved compared with colonoscopy, but at higher overall costs [31].

Natural COX-2 Inhibitors

Several substances occurring naturally in animal and plant sources have been identified with COX-2 inhibitory properties. The natural COX-2 inhibitors identified include curcumin and its related compounds, resveratrol and the omega-3 fatty acids found in oily fish [32]. Curcumin is the active ingredient derived from turmeric, a spice which has been a staple part of Indian culinary culture. It has been noted that CRC incidence is much lower in the population from the Indian subcontinent. In animal and ex vivo cell line studies it has been shown to inhibit the growth of colorectal carcinoma cells [33]. Though it has been proposed as a safe, non-toxic chemopreventive agent for CRC in humans based on epidemiological findings, the effective dose and frequency of dosing are yet to be found.

Eicosapentaenoic acid, an omega-3 fatty acid present in oily fish, has also been shown to inhibit the proliferation of human CRC cells in vitro [32]. Also low-dose omega-3 fatty acid supplementation appears to reduce abnormal rectal epithelial cell proliferation patterns in patients with sporadic colorectal adenomas. Diets rich in omega-3 fatty acids have shown up to 90% inhibition of tumour growth, relative to diets containing purely omega-6 fatty acids, in human colon carcinoma xenografts in athymic mice [34]. Phase III clinical trials of a mixture of omega-3 fatty acids have been initiated in patients with adenomatous polyps, using adenoma recurrence as an end point.

Nitrous Oxide Donating COX Inhibitors

The major drawback of aspirin and other NSAIDs as a chemopreventive agent for general use is the high risk of haemorrhagic side effects including haemorrhagic stroke and gastrointestinal bleeding. In recent years there has been an attempt to try and reduce this problem by using synthetically developed nitrous oxide donating compounds from the base agents. Moreover, animal and in vitro cultured human cancer cell line studies with these agents are showing promising results. Human studies are awaited [35].

5-Aminosalicylic Acid Agent Compounds

Several studies have focused on a host of possible candidates for chemoprevention of colorectal cancer in IBD. The best studied and most promising agents appear to be the 5-aminosalicylic acid agents (5-ASAs). There are several retrospective case-control studies to assess the RR reduction in IBD patients following 5-ASA treatment [36, 37].

In a retrospective analysis of a cohort of 175 ulcerative colitis (UC) patients followed for 10 years it was found that patients with UC who were not on long-term sulphasalazine or 5-ASA therapy were significantly more likely (31%) to develop CRC than their compliant counterparts (3%; $\chi^2 = 20.2$, $p < 0.001$) [37]. In another case-controlled retrospective study (n = 102 in each group), regular 5-ASA therapy was shown to reduce cancer risk by 75% (OR = 0.25, 95% CI = 0.13–0.48; $p < 0.00001$) and after adjusting for other variables, taking mesalazine regularly reduced risk by 81% (OR = 0.19, 95% CI = 0.06–0.61; p = 0.006) [38]. Similar findings were noted in a study from Chicago [39]. Conditional logistic regression, adjusted for disease duration, age at diagnosis and family

history of CRC, showed that aminosalicylate use of ≥1.2 g/day was associated with a 72% reduction in the risk of dysplasia and CRC (OR = 0.28, 95% CI = 0.09–0.85). As the total dose of aminosalicylates increased, the risk of dysplasia and CRC decreased (p = 0.056).

However, some recent studies have failed to find such a protective effect, including a population-based case-control study of large, well-established cohorts of IBD patients in Europe and the USA [40], and an observational study based on insurance database records [41].

The mechanism by which 5-ASA compounds act as chemopreventive agent is probably multifactorial. It is known to induce apoptosis and reduce cell proliferation. The mechanism of apoptosis induction by mesalazine has been shown to be via caspase-3 activation rather than by alteration in levels of B cell lymphoma-2 family proteins [42]. Mesalazine also has been shown to inhibit tumour-necrosis-factor-α-mediated effects on intestinal cell proliferation and activate mitogen-activated protein kinase and nuclear factor-κB [43].

If mesalamine exerted its chemopreventive effect by its anti-inflammatory activity, then other medications that reduce colitis activity also should possess chemopreventive properties. However, in a recent study, proportional hazards analysis assessing 6MP/AZA use as a time-changing covariate was performed to evaluate the effect of 6MP/AZA on: (1) progression to any neoplasia (low-grade dysplasia, high-grade dysplasia or CRC), and (2) progression to advanced neoplasia (high-grade dysplasia or CRC). In UC patients with no initial history of dysplasia, 6MP/AZA use appears to have little or no effect on the rate of neoplastic transformation in the colon. Importantly, the use of 6MP/AZA did not increase malignant transformation in UC.

5-ASA compounds are also being used in chemoprevention studies in non-colitic patients [44].

In a large multicentre placebo-controlled trial in sporadic adenomas, 598 patients were randomized to 1 g/day of mesalazine or placebo. In those with low risk (1–2 adenomas) there was no observed benefit, whereas in those with >3 adenomas, there was a non-significant trend towards reduction in recurrence of adenomas [45].

In another small study in patients with small rectosigmoid polyps there was no reduction in size or number of polyps over a 6-month period [46]. However, given the low doses of drug used and short duration of study, it is premature to establish that 5-ASA compounds really do not have chemopreventive effects in non-colitic patients.

Folic Acid

The case for folic acid in terms of CRC chemoprevention mainly comes from observational studies on large cohorts of healthy volunteers enrolled for trials with very different end points. In the Nurses' Health Study, dietary intake between 1980 and 1994 was analyzed in 88,756 women who were free of cancer at inception and had provided updated dietary assessments [47]. Women who had regularly taken multivitamins (containing folic acid) for at least 15 years showed the greatest reduction in the risk of developing colonic cancer, with a RR of 0.25 (95% CI = 0.13–0.51; p = 0.0003), though the effect did not hold for risk reduction of rectal cancer (RR = 1.27; 95% CI = 0.67–2.46). When the data were further analyzed for subgroups of those with and without family history of CRC, the age-adjusted RR of colon cancer for those who consumed ≤200 μg of folic acid per day versus those consuming >400 μg/day was 0.81 (95% CI = 0.62–1.07) in women without a family history of CRC and 0.48 (95% CI = 0.28–0.83) in women with a positive family history of the disease (p = 0.02).

A prospective cohort study observed that higher energy-adjusted folate intake in the form of multivitamins containing folic acid was related to a lower risk for colon cancer (RR = 0.69; 95% CI = 0.52–0.93) for intake of >400 μg/day compared with intake of ≤200 μg/day after controlling for age, family history of CRC, aspirin use, smoking, body mass, physical activity, and intakes of red meat, alcohol, methionine and fibre [47].

There are methodological problems in interpreting the true contribution of folic acid in the risk reduction and any conclusion has to be taken with caution. The same also holds for the subgroup analysis comparing folate intake in 295 cases of CRC and 5,334 randomly selected controls from 56,837 women enrolled in the Canadian National Breast Screening Study [48]. Folate intake was found to be inversely associated with CRC risk, there being a 40% lower risk amongst women in the highest compared with the lowest quintile level of folate intake. However, this reduced risk did not reach statistical significance (incidence rate ratio = 0.6; 95% CI = 0.4–1.1; p = 0.25) [48]. As only 6.2% of the individuals assessed were multivitamin users, these results may indicate that a high intake of folic acid from dietary sources alone may possibly be associated with a lower risk of colonic cancer. A large European case-control study also found a significantly reduced risk of CRC when comparing the highest versus the lowest intakes of folic acid [49].

However, there is conflicting evidence for the exact role of folate in carcinogenesis. It is becoming increas-

ingly evident that folate possesses dual modulatory effects on colorectal carcinogenesis depending on the timing and dose of folate intervention [50]. Folate deficiency has an inhibitory effect, whereas folate supplementation has a promoting effect on the progression of established colorectal neoplasms. In contrast, folate deficiency in normal colorectal mucosa appears to predispose it to neoplastic transformation, and modest levels of folic acid supplementation suppress, whereas supraphysiologic supplemental doses enhance, the development of cancer in normal colorectal mucosa [51]. Several potential mechanisms relating to the disruption of 1-carbon transfer reactions exist to support the dual modulatory role of folate in colorectal carcinogenesis including increased chromosome instability, gene mutations and aberrant DNA methylation. In an in vitro study using 4 types of human colon cancer cell line, it was shown that folate deficiency affects the expression of key genes that are related to cell cycle control, DNA repair, apoptosis and angiogenesis in a cell-specific manner. Cell specificity in gene expression changes in response to folate deficiency is likely due to significant differences in molecular and phenotypic characteristics, growth rates and intracellular folate concentrations among the 4 cell lines [52].

Corroborative evidence for the variable effect in humans comes from a recent study within the Netherlands Cohort Study on diet and cancer, investigating the associations between dietary folate intake and CRC risk with (APC+) and without (APC–) truncating APC mutations, accounting for hMLH1 expression and K-ras mutations. In total, 528 cases and 4,200 subcohort members were analyzed for a follow-up period between 2.3 and 7.3 years after baseline. Although relatively high folate intake was not associated with overall CRC risk, it reduced the risk of APC– colon tumours in men (RR = 0.58, 95% CI = 0.32–1.05, p trend = 0.06 for the highest vs. lowest tertile of folate intake). In contrast, it was positively associated with APC+ colon tumours in men (highest vs. lowest tertile: RR = 2.77, 95% CI = 1.29–5.95, p trend = 0.008) and was even stronger when the lack of hMLH1 expression and K-ras mutations were excluded (RR = 3.99, 95% CI = 1.43–11.14, p trend = 0.007). Such positive associations were not observed among women; nor was folate intake associated with rectal cancer when APC mutation status was taken into account. These opposite results may indicate that folate enhances colorectal carcinogenesis through a distinct APC-mutated pathway [53]. Also, in the Melbourne Colorectal Cancer Study looking into the dietary factors associated with CRC risk in 715 incident cases compared with 727 age/sex frequency-matched randomly chosen community controls using a quantitative assessment of all foods eaten, it was found that for folate there was significant protection for rectal cancer in the second and third quintiles of consumption but not for colon cancer, and this was similar for methionine consumption [54].

Currently available evidence from epidemiologic, animal and intervention studies does not unequivocally support the role of folate in the development and progression of CRC. However, critical analysis of the available portfolio of evidence from these studies overall supports the inverse association between folate status and CRC risk [51]. Nevertheless, the potential tumour-promoting effect makes it premature to support routine folic acid supplementation as a chemopreventive measure against CRC at present.

Vitamins

In a prospective cohort study of 35,215 Iowa women, an inverse association between the risk of colon cancer and vitamin E intake was found; the RR for the highest compared with the lowest quartile was 0.3 (95% CI = 0.19–0.54) [55]. The Women's Health Study, however, showed no relationship between CRC in women and the use of vitamin E. In a meta-analysis of 14 randomized trials of supplemental antioxidant vitamins encompassing 170,025 individuals, no evidence of prevention of colorectal adenomas or cancer was found [56].

After a systematic review of published observational studies that provide sufficient data to calculate the dose-response relationship of serum 25-hydroxyvitamin D or oral intake of vitamin D with risk of CRC it was suggested that a daily intake of 1,000 IU of vitamin D – half the safe upper limit for intake established by the National Academy of Sciences – and a concentration of serum 25-hydroxyvitamin D of 33 ng/ml were each associated with 50% lower risk of CRC [57].

An inverse relationship between vitamin D intake and risk of CRC was found in a population-based case-control study as well.

Calcium

Calcium has been evaluated as a possible chemopreventive agent on the basis of its bile-acid-binding capacity and possible direct action on intracellular metabolism by modulating processes involved in cell proliferation and differentiation. In epidemiological studies diets high in animal fats and red meat have been found to be associated with an increased risk of colonic adenomas and CRC [58]. Various explanations have been proposed including

higher concentration of oxidative stress in the lower bowel due to higher concentration of nitroso compounds, associated constipation due to lifestyle changes (frequent association with excess alcohol and sedentary lifestyle), and also to the increased concentrations of secondary bile acids within the colon, which may increase cell proliferation in the colonic mucosa, and have been found to be carcinogenic in animal models [59].

In a study to investigate whether calcium supplements could prevent the development of colorectal adenomas, 930 patients with a history of colorectal adenomas were randomly assigned to receive either daily supplementation with 3 g of calcium carbonate or placebo [60]. Serial endoscopic examination, 1 and 4 years after the start of the study, showed a moderate but significant reduction (RR = 0.85; 95% CI = 0.74–0.98; p = 0.03) in the development of further adenomas in the group receiving calcium supplements [60]. The protective effect of calcium was observed as early as 1 year after commencing supplementation. It would appear, therefore, that calcium acts very early in the pathway of colonic carcinogenesis, in keeping with its proposed mechanism of action. A European study on 176 patients followed up for 3 years found a modest but statistically non-significant (RR = 0.66; 95% CI = 0.38–1.17) reduction in adenoma recurrence in individuals given 2 g of elemental calcium daily [61].

Recently, a higher calcium intake was found to be associated with a significantly lower risk of distal but not proximal colonic cancer in a combined analysis of the Nurses' Health Study and the Health Professionals' Follow-Up Study [62]. It is important to note that the dose of calcium salt administered may be significant; the usual daily doses in trials have ranged from 1,250 to 2,000 mg of calcium.

In a randomized, double-blind, placebo-controlled trial involving 36,282 postmenopausal women, the administration of 500 mg of elemental calcium and 200 IU of vitamin D3 twice daily for an average of 7.0 years was not associated with a reduction in invasive CRC (hazard ratio = 1.08; 95% CI = 0.86–1.34; p = 0.051) [63]. The relatively short duration of follow-up, considering the latency period of CRC of 10–15 years and suboptimal doses of calcium and vitamin D, may account for the negative effects of this trial, though other factors may also be responsible [64].

Dietary Fibre, Vegetables and Fruit

Higher intake of dietary fibre has been shown to be associated with a lower incidence of CRC in observational studies. The mechanisms by which dietary fibre could reduce the risk of CRC include increasing the stool bulk (diluting potential carcinogens and decreasing transit time), binding potential luminal carcinogens like secondary bile acids, lowering faecal pH and promoting a favourable colonic microflora. Fermentation of dietary fibre and resistant starch by colonic bacteria generates short-chain fatty acids, such as butyrate, an important energy source for colonocytes and shown to have anticarcinogenic properties [65].

Epidemiologic studies have examined the relationship between fruit and vegetable intake and the incidence of colon and/or rectal cancer with considerable variation in findings. A prospective study [66] that examined dietary intake data based on food frequency questionnaires from 88,764 women in the Nurses' Health Study and 47,325 men in the Health Professionals Follow-Up Study included a total of 1,743 645 person-years of follow-up. After adjusting for numerous covariates, the authors found no association in women or men between overall fruit and vegetable consumption and risk of colon or rectal cancer. Neither were associations observed when the data were examined for subgroups of fruits or vegetables (with the exception of legumes, which were associated with an increased risk of colon cancer in women) or individual fruits or vegetables (with the exception of prunes, which were associated with an increased risk of colon cancer in men). For women and men combined, the covariate-adjusted RR of colon cancer associated with 1 additional serving of fruits and vegetables per day was 1.02 (95% CI = 0.98–1.05); the comparable RR for rectal cancer was 1.02 (95% CI = 0.95–1.09).

Analysis of data from previous case-control studies of dietary practices found a significantly reduced risk of CRC when comparing the highest (>31 g/day) against the lowest (<10 g/day) intake of dietary fibre (OR = 0.53; 95% CI = 0.47–0.61) [67]. Meta-analyses of case-control studies suggested, on average, a 50% reduction in the risk of development of CRC between the 2 groups. However, the published large prospective cohort studies showed equivocal findings [68–70], with the largest published study analyzing data on a study population of 19,541 with 16 years of follow-up showing no protective effect of dietary fibre against the development of CRC (RR = 1.08, 95% CI = 0.9–1.29) [71]. Similar findings were also obtained rom another trial using 958 subjects with 36 months of follow-up (RR = 1.00, 95% CI = 0.9–1.12).

Six case-control studies and 3 cohort studies have explored potential dietary risk factors for colorectal adenomas. Four of the 9 found an association of fibre, carbohydrates and/or vegetables with reduced risk. In 1 study,

cases with moderate or severe dysplasia had a significantly lower intake of cruciferous vegetables than those with mild dysplasia. No significant protective effect on adenoma recurrence was found in a randomized controlled trial of high-fibre cereal supplements over a 3-year period on 1,303 individuals. Similar results were observed in a multicentre randomized controlled trial evaluating a diet low in fat (20% of total calories) and high in fibre (18 g of dietary fiber/1,000 kcal) and fruits and vegetables (3.5 servings/1,000 kcal)

The European Prospective Investigation into Cancer and Nutrition evaluated 519,978 individuals aged 25–70 years recruited from 10 European countries. On a follow-up consisting of 1,939,011 person-years (average = 4.5 years) an inverse relation between dietary fibre intake to the incidence of large bowel cancer was found with the adjusted RR for CRC for the highest versus the lowest quintile of fibre intake being 0.75 (95% CI = 0.59–0.95). Examined separately, the protective effect was significant for colonic but not rectal cancer, the adjusted RR for colonic cancer being 0.72 (95% CI = 0.54–0.97) and 0.80 (95% CI = 0.53–1.22) for rectal cancer [72].

As a subgroup analysis amongst participants in the Prostate, Lung, Colorectal and Ovarian Cancer Screening Trial [73] comparison was made between the dietary practice of patients who were found to have adenomas on screening flexible sigmoidoscopy to those who did not. There was a significantly reduced risk of distal colorectal adenomas when comparing the highest quintile with the lowest quintile of fibre intake (OR = 0.73; 95% CI = 0.62–0.86). Interestingly again a difference was noted with respect to risk reduction in distal colon compared to rectal adenomas (OR = 0.70, 95% CI = 0.58–0.85 vs. OR = 0.93, 95% CI = 0.65–1.33) [73].

In a prospective cohort study of a low-risk population, an inverse association was found with legume intake and the risk of CRC (RR for >2 times/week vs. 1 time/week = 0.53; 95% CI = 0.33–0.86, p for trend = 0.03) [74].

An inverse association between total fruit and vegetable consumption and CRC risk was also found in a prospective Swedish study conducted in 61,463 women aged 40–74 years with an average follow-up period of 9.6 years with a RR for developing CRC of 1.65 (95% CI = 1.23–2.2; p trend = 0.001) in those with low daily intake of fruit and vegetables (>1.5 servings) compared to those with higher intake (>2.5 servings) [75].

Dietary Protein and Fat

In Japan, an increased risk of colon cancer with increased frequency of meat consumption was observed in the group with infrequent vegetable consumption among a group of 265,000 men and women. In Norway and the Netherlands an increased risk for processed meat only was found. A prospective study among female nurses showed an increased risk of colon cancer associated with red meat consumption (beef, pork, lamb and processed meat) and also with the intake of saturated and monounsaturated fat, predominantly derived from animals [58].

A randomized controlled dietary modification study was undertaken among 48,835 postmenopausal women aged 50–79 years who were also enrolled in the Women's Health Initiative. The intervention promoted a goal of reducing total fat intake by 20%, while increasing daily intake of vegetables, fruits and grains. The intervention group accomplished a reduction of fat intake of approximately 10% over the 8.1 years of follow-up. There was no evidence of reduction in invasive CRCs between the intervention and comparison groups with a hazard ratio of 1.08 (95% CI = 0.90–1.29) [71].

Explanations for the conflicting results regarding whether dietary fat or meat intake affects risk of CRC [76] include (a) the validity of dietary questionnaires used; (b) differences in the average age of the population studied; (c) variations in the methods of meat preparation (in some instances, mutagenic and carcinogenic heterocyclic amines could have been released at high temperatures [77]), and (d) variability in the consumption of other foods such as vegetables. In addition, some epidemiological studies have reported lower incidence rates of colon cancer in populations with high intakes of both fat and fibre, compared with populations with high levels of fat but low levels of fibre consumption [78]. High fat intake has been found to increase the risk of adenoma recurrence following polypectomy [79].

Statins

Originally approved to prevent heart disease, statins are now also thought to combat rheumatoid arthritis, Alzheimer's disease, multiple sclerosis and most importantly cancer. Studies of the mechanisms of statins and observations that cardiovascular benefits are experienced even in subjects with a normal level of cholesterol led to the recognition that the actions of statins extend beyond their cholesterol-lowering properties. Statins have been extensively used in large cardiovascular risk reduction studies with low adverse side effect and dropout rates over the past couple of decades. A secondary outcome from these studies has been the finding of lower incidence of all cancers in most but not all studies [80]. The

inconsistency of the results relating to cancer prevention from epidemiological studies may well be due to methodological problems including lack of power of these studies in relation to cancer prevention, though they were powered enough to study cardiovascular events. Also these primarily cardiovascular-risk-related studies were not of sufficient length to adequately evaluate the longer duration needed for carcinogenesis risk reduction.

In animal models and CRC cell line studies, statins have been shown to modulate tumour growth by inhibition of proliferation, induction of apoptosis and suppression of angiogenesis, thus leading to the hypothesis that statins may also reduce the risk of cancer. Also several studies in animal models and human colon cancer cell line studies have shown synergistic action of statins and COX inhibitors, both selective COX-2 inhibitors like celecoxib [81], and NSAIDs like sulindac [82] in negative modulation of biomarkers of carcinogenesis and up-regulating apoptosis.

In 2 large clinical trials with HMG-R inhibitors that were designed to study the outcomes in patients with coronary artery disease, there was a 43% [83] and 19% [84] reduction in the number of newly diagnosed cases of colon cancer during a 5-year follow-up period in patients receiving pravastatin and simvastatin, respectively. In a recent large case-control study from Israel among 1,953 patients with CRC and 2,015 controls, the use of statins for at least 5 years (vs. the non-use of statins) was associated with a significantly reduced RR of CRC (OR = 0.50; 95% CI = 0.40–0.63). This association remained significant after adjustment for the use or non-use of aspirin or other NSAIDS; the presence or absence of physical activity, hypercholesterolaemia and a family history of CRC; ethnic group, and level of vegetable consumption (OR = 0.53; 95% CI 0.38–0.74). The use of fibric acid derivatives was not associated with a significantly reduced risk of CRC (OR = 1.08; 95% CI = 0.59–2.01) [85].

Overall, evidence indicates that statin use neither increases nor decreases the incidence or mortality of CRC. Although some case-control studies have shown a reduction in risk, neither a large cohort study [86] nor a meta-analysis of 4 randomized controlled trials [87] found any effect of statin use. A very recent meta-analysis of 18 studies involving >1.5 million participants found no evidence of an association between statin use and risk of CRC either among randomized controlled trials (RR = 0.95; 95% CI = 0.80–1.13; n = 6) or among cohort studies (RR = 0.96; 95% CI = 0.84–1.11; n = 3). However, statin use was associated with a modest reduction in the risk of CRC among case-control studies (RR = 0.91; 95% CI = 0.87–0.96; n = 9) [88]. Clearly the current epidemiologic data are not sufficient to recommend use of statins as a chemopreventive agent, but with statins being used by >10% of the adult population, and 25% of the population over the age of 60 years, it is definitely worth monitoring its possible chemoprevention effect and assess its safety profile further.

Selenium

Selenium compounds have also been shown to inhibit the development of adenocarcinomas in animal models of colorectal carcinogenesis, and there is evidence from epidemiological studies showing an inverse relation between cancer mortality and selenium content in diet.

In a pooled analysis [89] of data from 3 randomized trials that tested the effects of various nutritional interventions for colorectal adenoma prevention (the Wheat Bran Fibre Trial, the Polyp Prevention Trial and the Polyp Prevention Study) in subjects that had recently undergone adenoma removal, it was shown that the subjects with baseline serum or plasma Se in the highest quartile (median = 150 ng/l), when compared with those in the lowest quartile (median = 113 ng/l), had a significantly lower risk of adenoma recurrence (OR = 0.66, 95% CI = 0.50–0.87).

A chemoprevention trial in 1,312 patients with the primary end point being skin cancer development used 200 μg of selenium daily (n = 653) versus placebo. Although selenium did not reduce the incidence of skin cancers, there was a significantly reduced risk of developing CRC in the selenium group versus placebo (RR = 0.42; 95% CI = 0.18–0.95; p = 0.03) [90].

There has been no proof that CRC develops in subjects with low selenium levels in serum compared to those with adequate levels.

In addition, a large multicentre cohort study, the Prevention of Cancer by Intervention with Selenium Trial [91], is being performed to investigate further whether selenium supplementation can reduce the cancer risk as seen in previous smaller studies [90].

Ursodeoxycholic Acid

Patients with IBD have been shown to be at a higher risk of developing CRC and a subgroup with a particularly high risk is those with concomitant primary sclerosing cholangitis. A prospective randomized controlled trial with ursodeoxycholic acid (UDCA), in 52 patients with UC and primary sclerosing cholangitis, found a RR of 0.26 (95% CI = 0.06–0.92; $p < 0.03$) for the development

of colorectal dysplasia or cancer in the UDCA-treated group [92]. This has also been supported by an observational study showing a significant risk reduction of adenoma recurrence in patients with primary biliary cirrhosis undergoing colonoscopic surveillance and taking long-term UDCA therapy, when compared with age- and gender-matched controls from a cohort of patients undergoing polypectomy [93]. A major multicentre phase III, double-blind placebo-controlled trial of UDCA to evaluate its ability to prevent colorectal adenoma recurrence found a non-statistically significant 12% reduction in the adenoma recurrence rate related to UDCA treatment, compared with placebo treatment. However, UDCA treatment was associated with a statistically significant reduction ($p = 0.03$) in the recurrence of adenomas with high-grade dysplasia (adjusted OR = 0.61, 95% CI = 0.39–0.96) [94].

Postmenopausal Female Hormone Supplements

In the Women's Health Initiative Trial, 16,608 postmenopausal women aged 50–79 years, randomized assigned to a combination of conjugated equine oestrogens (0.625 mg/day) plus medroxyprogesterone (2.5 mg/day) or placebo, there were 43 invasive CRCs in the hormone group and 72 in the placebo group (OR = 0.56; 95% CI = 0.38–0.81, $p = 0.003$). The invasive CRCs in the hormone group were similar in histologic features and grade to those in the placebo group but with a greater number of positive lymph nodes (mean ± standard deviation = 3.24 ± 4.1 vs. 0.8 ± 1.7; $p = 0.002$) and were more advanced (regional or metastatic disease; 76.2 vs. 48.5%; $p = 0.004$) [95].

Also there is some epidemiologic evidence that the hormone treatment reduces the risk of colon cancer but has no or possibly a negative chemopreventive effect in terms of rectal cancer.

Epidermal Growth Factor Receptor Inhibitors

Tyrosine kinase activation leads to signal transduction, with activation of pathways downstream of the epidermal growth factor receptor (EGFR), causing cell proliferation, differentiation, migration, adhesion, protection from apoptosis, enhanced survival and gene transcription. The EGFR is a transmembrane glycoprotein that has a tyrosine kinase activator role. Several ligands, including epidermal growth factor and transforming growth factor-α, are highly expressed in many human colon cancer lines and bind to EGFR and appear to play an important role in the growth of colon cancer [96]. Also, over-expression of EGFR occurs at a very early stage in premalignant lesions and 65–70% of colonic carcinomas have been shown to over-express EGFR.

EGFR inhibition has potential in both the treatment and prevention of solid neoplasia. EGFR tyrosine kinase inhibitors have the same antitumour activities as anti-EGFR antibodies but are active orally and potentially lack the dependence on high levels of EGFR for inhibitory activity. Gefitinib (ZD1839, Iressa) is an orally administered, selective and reversible inhibitor of EGFR that competitively inhibits kinase activation. ZD1839 has produced potent inhibition of the in vitro growth of a variety of human tumour cells, including colonic tumour cell lines [97]. In vivo studies have shown dose-dependent ZD1839 antitumour activity against human colon carcinoma xenografts in mice. Results from phase I and II clinical trials have suggested clinical efficacy and good tolerability of ZD1839 in patients with advanced colorectal disease, with further trials ongoing.

Based on murine studies a combined approach of using EGFR inhibitors with NSAIDs has been proposed as a strategy for the chemoprevention of colonic neoplasia in humans, with the potential of using NSAIDs at lower, potentially less toxic, doses [98].

Purified recombinant EGFR-related protein, when exposed to human colonic cancer cell lines, was found to cause a marked inhibition of proliferation and is a potential target chemoprevention agent under study [33].

α-Difluoromethylornithine

The activity of ornithine decarboxylase (ODC) has been found to be significantly elevated in the normal-appearing areas of colonic mucosa in patients with FAP and in the rectal mucosa of patients with the APC gene mutation, compared with unaffected family members, prior to the onset of polyposis. A number of studies in humans have also found significantly elevated ODC activity in the mucosa of sporadic colorectal carcinomas and adenomas compared with the normal surrounding mucosa. ODC is involved in the production of polyamines within proliferating cells which are necessary for cell proliferation.

α-Difluoromethylornithine is an enzyme-activated, irreversible inhibitor of ODC, which results in the depletion of intracellular levels of putrescine and its derivative spermidine. In dose-seeking studies for chemoprevention trials, when given at doses of 0.20–0.40 g/m^2, α-difluoromethylornithine suppressed the polyamine content of rectal mucosa in patients with a history of colorectal adenomas for 12 months, with relatively few side effects [99]. In animal studies, a significant reduction in development of adenomas and subsequent cancer devel-

Table 1. Major ongoing phase II/III CRC chemoprevention trials

Trial	Agents and main end points
CAPP-1 and CAPP-2	Aspirin and resistant starch in FAP and HNPCC, respectively
AspECT	Aspirin and proton pump inhibitors for prevention of oesophageal cancer (and colon cancer)
FAB2	Folate and riboflavin in adenoma and resected CRC
Uk CAP	Folate ± aspirin in adenoma prevention
Vitamin D/Calcium Polyp Prevention Study	Vitamin D ± calcium in adenoma prevention
CASE	Calcium, aspirin, selenium in adenoma prevention
Celecoxib in Preventing Colorectal Cancer in Young Patients with a Genetic Predisposition for FAP	Celecoxib in CRC prevention in FAP
Celecoxib with or without Eflornithine for the Prevention of Colorectal Cancer in Participants with FAP	Celecoxib ± eflornithine in prevention of recurrence of polyp
Study of the Effects of Selenium on Adenomas	Celecoxib ± selenium for prevention of adenoma recurrence
Aspirin/Folate Prevention of Large Bowel Polyps	Aspirin ± folate in adenoma prevention
Colon Cancer Prevention Trial	Sulindac + eflornithine in adenoma prevention
Women's Health Study	Aspirin ± vitamin E in CRC incidence
Selenium in Treating Patients with Adenomatous Colorectal Polyps	Selenium in recurrence of adenoma prevention
Colotech combination treatment for chemoprevention of colorectal adenomas	Aspirin, vitamin D and calcium carbonate for prevention of recurrence of adenomas
Curcumin for the chemoprevention of CRC	Curcumin in colorectal mucosal modulation
Curcumin in the Lower Gastrointestinal Tract in FAP Patients	Curcumin in regression of polyps in FAP
Atorvastatin versus Oligofructose-Enriched inulin (Raftilose Synergy 1) versus Sulindac in Patients at Increased Risk of Developing Sporadic Colorectal Neoplasia	Atorvastatin vs. modified inulin vs. sulindac in ACF modulation
Sulindac and Probiotics on the Development of Pouch Adenomas in Patients with FAP	Sulindac and/or VSL3 – inulin in treating or preventing adenoma development in the ileal anal pouch in patients with FAP

opment was shown with combination of α-difluoromethylornithine and piroxicam [100]. Phase II/III chemoprevention trials are awaited with this promising agent.

Conclusion

The evolving science of chemoprevention is a major step in the fight against the burden of cancer especially in the colorectum. The rapidly increasing knowledge base of the processes involved in the transformation of normal epithelial cells to cancer allows for developing mechanisms based on and targeted at the development of agents that can modify and retard the multistep process of carcinogenesis [3–5]. The availability of well-established animal models and human colon cancer cell lines has allowed testing of >200 agents in an attempt to find the ideal candidate(s). However, these models are severely limited and hence only a few of them have made it to the stage of human trials. Currently, there is not enough validated scientific evidence for any of the agents to allow their widespread practical implementation in chemopreventive strategies. There are several ongoing phase II and III trials of single and combined prospective agents (table 1) and it is expected that with these well-conceived, long-term, randomized, controlled studies with adequate power, we will soon have an answer to this major health problem [8]. Till then lifestyle modification, cancer screening and surveillance for secondary prevention of cancer is the mainstay of fight against cancer-related

mortality [31]. Already celecoxib has been given accelerated approval for use in the high-risk group of FAP patients to try and reduce the burden of adenomas. Postmarketing surveillance for its efficacy is paramount to assess the true benefit of the intervention and evaluate the safety of such agents [101]. With the realization of increased cardiovascular risk associated with most of the COX-2 inhibitors [28, 29], there is a clear warning that whatever agent is promoted as a chemoprevention, the strategy has to be well scrutinized, as only the ones with the minimal toxicity or side effects can be accepted for 'treating' the healthy but at risk population. Also there is increasing recognition that the multistep process of carcinogenesis allows the development of a combination chemoprevention strategy. Synergistic effects of agents working at different steps of the pathway may be used at lower and safer doses, yet achieving additive chemopreventive effect [81, 82, 98]. Several ongoing studies are evaluating such combinations. The other major implications from laboratory studies on animal models of a varied number of cancers are that there are common steps involved in carcinogenesis in various organs and that a combination of several agents, like aspirin, folic acid, selenium, tyrosine kinase inhibitors and calcium, may actually allow a single pill for multiple cancer prevention strategies. Moreover, recognizing that not only carcinogenesis but many degenerative and inflammatory pathways involve common steps like increased COX-2 receptor expression, oxidative stress, free-radical-mediated damage and downregulation of apoptosis, it may be that some agents like aspirin, statins and folic acid are also able to give positive health benefits in relation to most of the major causes of morbidity and mortality in the present-day population. This will require close coordination between translational scientists, clinical trialists, technical infrastructure developers and clinical networks and significant increase in funding of chemoprevention research [8]. Our main hope, however, is that integrated national cancer prevention programmes are set up to investigate these issues urgently.

Disclosure Statement

J.J. is a consultant to AstraZeneca. J.J. is also chair of the Advisory Gastroenterology Group to National Institute for Clinical Excellence, UK.

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el purge, nontrivial adenoma and cancer miss rates, and relative unavailability in some areas due to manpower considerations, colonoscopy is for now the 'gold standard' for CRC screening in 'average risk', i.e. Western populations over age 50. While colonoscopy must compete with traditional measures such as FOBT, flexible sigmoidoscopy, and barium enema in average-risk groups, most authorities agree that for patients at increased risk, colonoscopy is the preferred approach [4].

Groups at increased risk include those with a personal history of CRC or adenoma, patients with long-standing inflammatory bowel disease, and persons with a significant family history of CRC. This discussion will be limited to this last category. My comments will address two main topic areas, endoscopic risk reduction by means of colonoscopy, including endoscopic therapies, and chemoprevention.

Colonoscopy

In contrast with average risk populations for whom such measures as FOBT may be appropriate for screening, the very high prior probability for neoplasia in patients with familial adenomatous polyposis (FAP), hereditary nonpolyposis CRC (HNPCC), Peutz-Jegher and juvenile polyposis syndromes renders these conditions particularly appropriate to colonoscopy. Clinical practice guidelines adopted by a variety of professional organizations support early, aggressive endoscopic evaluation. Guidelines for average- and high-risk subjects have been adopted by the American Cancer Society [6], the National Comprehensive Cancer Network (at www.NCCN.org), the combined gastrointestinal societies [4], and the American Society of Colorectal Surgery [7], and the list is by no means exhaustive. The US Preventive Services Task Force, a generally conservative group that insists on a robust evidence-base before recommending a particular screening measure, remains uncommitted as to the role for colonoscopy in average-risk populations [8]. Unlike the other groups cited above, the USPSTF has not really critically considered the matter of high-risk groups.

A variety of adjuncts to conventional colonoscopy are on the horizon, mainly having to do with new approaches to imaging that might enable recognition of more and more subtle lesions. Other techniques are intended to discriminate between polyps that are merely hyperplastic from those adenomas with low, moderate and high degrees of dysplasia [9–11]. Approaches involving 'virtual' colonoscopy (CT colography) show considerable promise in average-risk populations, whose prior probabilities of neoplasia, importantly, are low. Enthusiasts for this technique concede the absence of data in high-risk groups, including HNPCC. The very early, flat adenomas that the colonoscopist is eager to find may be less well seen with even the best available CT technology. Molecular tests for mutated DNA in epithelium retrievable from stool samples also show promise in early validation studies [11]. Efforts are being made on behalf of subjects being screened for HNPCC-related GI malignancies through the development of microsatellite instability (MSI)-related DNA targets. As with CT colography, reservations must be expressed with the use of mutated DNA tests in carriers of mismatch repair gene mutations, since the early, flat lesions in such patients may be more likely missed due to lesser exfoliation of surface epithelium. Large-scale investigations of these technologies in HNPCC would likely face the same challenges and limitations that exist in the design of chemoprevention trials, noted below.

Familial Polyposis

The role of endoscopic evaluation and therapies in the lower GI tract varies with the circumstances of the patient. It depends on: (1) the severity of FAP, that is 'classic' as opposed to 'attenuated'; (2) whether the patient has undergone prophylactic resection, and if so, whether the resection was a colectomy with ileorectal anastomosis (IRA) or proctocolectomy with ileostomy, or more recently, ileal J-pouch-anal anastomosis (IPAA); (3) patient desires.

For so-called classic FAP, in which diffuse polyposis occurs by the mid-teen years, one may evaluate either by means of flexible sigmoidoscopy or colonoscopy. This ideally is performed pursuant to informative, positive genetic predisposition testing showing an *APC* gene mutation. Genetic test-based management has in general been suggested by modeling studies to be more cost-effective than purely empiric screening. Flexible sigmoidoscopy is of course less expensive than colonoscopy, may be conducted without an oral preparation of the bowel, and can be done without sedation. This approach is favored in many countries and institutions. Because the proximal colon is not evaluated, the assumption must be that prophylactic colectomy will be performed within a few months to at most a few years from the time of diagnosis of multiple adenomas, in order to minimize the chance of malignancy in the unexamined proximal colon. De-

tailed comment regarding the extent of adenomas in the rectum will guide the surgeon in planning the optimal operation. Use of indigo carmine dye spray may provide a more sensitive estimate of the true adenoma burden.

Colonoscopy is preferred in many institutions, including our own. Although more expensive and requiring a full bowel prep and sedation (we universally employ anesthetist-administered total intravenous anesthesia, typically utilizing propofol), young children seem to tolerate this at least as well as sigmoidoscopy. Full colonoscopy provides the most accurate and reassuring estimate of adenoma burden. It is ideally suited to the situation in which parents wish to delay surgery for as long as possible. Removal of larger polyps, combined with use of a chemopreventive agent such as sulindac or celecoxib may allow a year-to-year reassessment of polyp burden and rate of progression. However, it must be conceded that there are virtually no data on the long-term efficacy and risks of such an approach. Individual tailoring is appropriate, ideally in the hands of an expert. Any consideration of such an approach requires extensive discussion with the child and parents regarding the pros and cons of expectant endoscopic/chemopreventive management versus immediate surgical intervention. If the surgeon that will ultimately be carrying out the resection is performing endoscopic assessments, such discussions are straightforward. If a medical endoscopist is doing the surveillance, very close partnership with the surgeon is essential. In any event, it is essential that the family understand that until a more fundamental paradigm shift occurs on the basis of medical (chemopreventive/gene therapy) breakthroughs, current endoscopic management for the typical young patient with classic FAP can be no more than a temporizing measure. One clinical trial employing sulindac failed to show a clear treatment benefit in *APC* carriers who had not yet developed adenomas [12].

Decision-making regarding the approach to prophylactic colectomy or proctocolectomy is principally based on rectal adenoma burden. There are data indicating a genotype-phenotype correlation, such that certain mutations are predictive of heavy rectal adenoma burden. But while genotype is a factor to consider, observed phenotype is generally determinative of the type of surgery. The surgeon planning such surgery must be experienced in the performance of restorative proctocolectomy (IPAA).

If a colectomy with IRA is performed, endoscopic management of the remaining rectum becomes paramount. All concerned will be keen to avoid a subsequent proctectomy if it can be avoided. Patients with residual polyps after colectomy may experience the phenomenon of spontaneous regression of polyps, though they usually recur after an interval of several years. Hence, a trivial adenoma burden for an interval of years following resection should not lead to a false sense of security-surveillance needs to continue. When adenomas persist and/or recur, ablation can be accomplished by means of traditional measures, including hot or cold forceps biopsy or snare polypectomy. For numerous, small (<6–8 mm) polyps, thermal ablation by means of YAG laser, or, more recently, argon plasma coagulation may be preferred on the basis of ease, efficiency, and rapidity. Because such ablation destroys the polyp without the opportunity for histologic examination, any large or confluent lesion should at least be sampled for pathology. As with nonfamilial adenomas, the potential does exist for the various lift and cut approaches to endoscopic mucosal resection of large, flat or confluent lesions [13]. However effective these measures may be, it is usually helpful to consider use of chemopreventive agent, discussed below.

The goal of restorative proctocolectomy is to eliminate risk of rectal cancer, an important goal since rectal cancer was historically one of the most common causes of death in FAP patients that had undergone colectomy with IRA. If an ileal IPAA has been constructed, there are two key issues that bear on adenoma, and thus cancer risk, in addition to the well-known concerns about functional outcome. Although it was once thought (hoped?) that ileal pouches were free of adenoma and cancer risk, this is now known not to be the case. Over time, a majority of patients will develop adenomas in the pouch proper by 15 years of observation [14]. Most behave in a relatively indolent fashion, but severe dysplasia and cancer may occur, presumably due to insufficiently aggressive surveillance and polypectomy.

Completeness of distal rectal mucosectomy varies considerably from patient to patient undergoing IPAA, varying with surgical technique (hand-sewn vs. stapled anastomosis) and experience of the operating surgeon. Because most patients undergoing restorative proctocolectomy for FAP do so because of relatively severe underlying involvement of the rectum in the first place, the amount of residual rectal, as opposed to ileal mucosa, becomes a factor in risk of subsequent polyposis and cancer in the stump. Awareness of this should foster great care in assessing the residual rectal mucosa (fig. 1).

Attenuated FAP

Attenuated FAP (AFAP) is an increasingly recognized subset of FAP. Initially thought to perhaps be a distinct entity, mutation analysis has shown that *APC* mutations do occur. Adenomas characteristically occur much later in life than in 'classic' FAP, often in the 5th to 7th decades of life, and carry a peculiar anatomic distribution. While adenomas do occur in the left colon, they are commonly very scattered in this area, sparing the rectum in most cases. However, extensive yet subtle involvement of the right colon is common. Use of indigo carmine dye spray may be very informative in revealing the true extent of adenomatosis in the right colon, albeit involving a preponderance of microadenomas or 'aberrant crypt foci' (fig. 2). The great number of diminutive polyps, commonly >100, does not lend itself to complete endoscopic ablation any more than in the subject with a more typical, juvenile-onset presentation of diffuse polyposis. The overall picture poses real challenges to surgical and endoscopic decision-making. Despite being examples of definite FAP, a patient with AFAP may have been managed for years as a case of sporadic adenoma and thus accustomed to periodic colonoscopy and polypectomy. He or she may have a course of disease that is very slowly progressive. Once a definite diagnosis of AFAP is made, there may still be a reluctance to consider colectomy due to mutual patient and surgeon concern about various medical comorbidities and their implications for surgical risk. Although the risk of such comorbidities generally increases with age, there may be a strong consensus to avoid surgery for as long as possible and to minimize the extent of surgery. Thus, right or extended right hemicolectomy is not uncommon in this patient population and proctectomy is very rarely indicated.

For a given patient with AFAP who wishes to defer colectomy on a year-to-year basis, there may be an important role for chemopreventive medication, so long as there is evidence of response. Our celecoxib trial included a subset of subjects with AFAP and intact colons. Their response rate was similar to that of classic FAP subjects that had undergone colectomy and whose rectal polyps were the focus of investigation. We follow about 10 subjects with AFAP on an expectant basis, combining endoscopic removal of larger (>8–10 mm) polyps and chemoprevention, generally with celecoxib. Long-term data on the use of sulindac are limited to subjects with classic FAP after colectomy, but there is no good reason that subjects with AFAP could not have their intact colons treated with sulindac. Concerns with any such nonsurgical approach include patient and physician complacency or uncritical acceptance of the long-term effectiveness of polypectomy/drug treatment. Recent evidence of increased cardiovascular risks of long-term, high-dose COX-2 inhibition has to be reckoned with. In all cases in which such conservative treatment is undertaken, there needs to be ongoing discussion between the surgeon, endoscopist, and patient, with documentation of the surgical alternatives that have been offered or recommended.

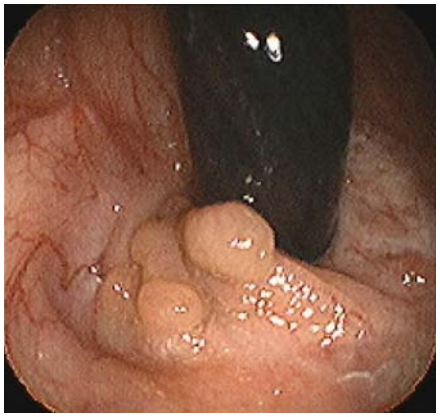

Fig. 1. Retroflex view of rectum. This shows adenoma in distalmost rectum, just below ileal J-pouch-anal anastomosis. Thus, this is arising from rectal mucosa proper rather than ileal pouch. Depending on a variety of technical factors, a greater or lesser amount of residual rectal mucosa will remain following resection.

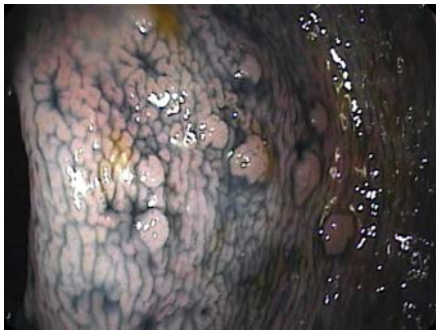

Fig. 2. Indigo carmine stain in right colon. This reveals the presence of a small cluster of relatively flat adenomas, all less than 2 mm in diameter. This is typical of the character of microadenomas seen in AFAP and demonstrates the benefit of indigo carmine in showing the true burden of adenomas in some cases of AFAP.

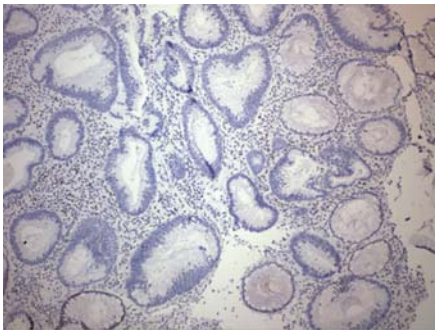

Fig. 3. Photomicrograph of early adenoma in HNPCC. This immunohistochemical stain uses antibody against hMSH2-associated protein. Note the loss of staining in mildly dysplastic crypts, with retention of staining in stromal cells.

Hereditary Nonpolyposis CRC

HNPCC involves early-onset CRC, often several such cancers, but without a significant adenoma count. A variety of extracolonic tumors complete the syndromic tumor spectrum. Colon tumors are frequently right-sided, mucinous, poorly differentiated, and include 'tumor-infiltrating lymphocytes'. Most CRCs in HNPCC display MSI, which is indeed a hallmark of the condition. Immunohistochemistry (IHC) for protein associated with the mismatch repair genes, *hMSH2, hMLH1, hMSH6,* and *hPMS2* commonly shows loss of staining in the tumor, with staining retained in normal mucosa and stromal elements. The informativeness of MSI analysis and/or IHC forms the basis for a commonly employed stepwise approach to genetic workup of potential HNPCC subjects: (1) recognize presenting features, as above, with or without family history of same, i.e. the presence of Bethesda guidelines; (2) perform MSI/IHC; (3) perform germline mutation testing when MSI/IHC informative [15]. Although sometimes clinical circumstances are sufficiently compelling as to warrant germline mutational testing without the intermediate step of tumor evaluation by means of MSI/IHC, clinical practice guidelines largely accept the important role of such tumor evaluation. Among the criteria for considering testing of tumor tissue for MSI are the so-called Bethesda guidelines [16, 17]. Some controversy has existed over the primacy of reliance upon MSI [18], as opposed to use of IHC. Several population studies have examined the role of these methods in screening unselected cases of CRC [19, 20]. One fairly detailed set of guidelines for evaluating and managing suspected HNPCC, including the role of MSI testing can be found through the US National Comprehensive Cancer Network website at www.NCCN.org.

The precursor lesion to CRC in HNPCC is the adenoma, as it is in nonfamilial CRC. These polyps tend to be flat and located in the right colon in patients with HNPCC. For this reason, locating such lesions at an early stage can be challenging. Use of indigo carmine to serve as a mucosal contrast agent can facilitate recognition of flat lesions [9]. I routinely employ indigo carmine administered through a spray catheter. This requires an additional 3–5 min of scope withdrawal time. An excellent prep is essential. Part of the gain achieved through use of indigo carmine may simply be the additional time employed in carefully inspecting the mucosa. The recent introduction of narrow band imaging may serve as a suitable alternative to indigo carmine [10].

Surveillance, mainly by means of colonoscopy, has been shown to be of benefit in reducing cancer incidence and mortality in HNPCC [21–23]. Mortality reduction might certainly have been achieved through identification of early malignancies, but reduction in cancer incidence likely is attributable to removal of premalignant adenomas.

Once an adenoma is identified, its removal is accomplished in the same fashion as nonfamilial adenomas. However, one's threshold for considering surgery for lesions that are difficult to safely and/or completely remove should be lower than for corresponding lesions in the average risk population. Patients with HNPCC will, on average, be younger and therefore better surgical candidates. By virtue of the presentation with a challenging lesion, further such lesions can be expected at a higher rate than in the general population. Surprisingly few data have been generated regarding the natural history following endoscopic removal of adenomas in HNPCC.

If an adenoma is removed or sampled in a subject suspected, but not known to have HNPCC, how informative is it to subject the tissue to MSI analysis or IHC for loss of MMR-associated protein (fig. 3)? As techniques for laser-based microdissection have improved, a substantial majority of adenomas from patients with known HNPCC show evidence of MSI. As with invasive cancers, MSI in adenomas is highly correlated with MMR protein loss [24, 25]. What is not known are the positive and negative predictive values for these tests with respect to germline mutation detection. Nevertheless, the Bethesda Guidelines for MSI testing in HNPCC include the presence of adenoma before age 40 [16, 17].

Table 1. Evolving approaches to colorectal prophylaxis in FAP

Decade	Surgical	Endoscopic	Medical
Pre-1980	colectomy with ileorectal anastomosis or proctocolectomy with end ileostomy	proctoscopy	none
1980s	continent ileostomies; early use of ileal pouch-anal anastomosis	flexible scopes	none
1990s	evolving selection of IPAA candidates	use of indigo carmine, magnification; ablation with lasers; argon plasma coagulation	trials, clinical use of sulindac
2000s	laparoscopic-assisted colectomy/proctocolectomy	new imaging modalities – narrow band imaging; spectroscopy; endoscopic mucosal resection	trials, clinical use of COX-2 inhibitors
2010s	transanal resections?	endoscopic mucosal dissection	gene therapy? tailored drug therapy based on genetics of drug metabolism?

Chemoprevention and Risk Reduction

Considering the 'strong' effect of the underlying genetic susceptibility in FAP and HNPCC, the notion that natural agents or drugs could prevent or regress adenomas and cancer appears at first impression somewhat unlikely. Indeed, a fully effective medical management prevention strategy employing such agents remains elusive. Nevertheless, considerable progress has been made in recent years, gradually increasing the role of nonsurgical measures in FAP (table 1).

Because FAP presents with such a striking adenoma phenotype and since the adenomas lend themselves to quantification, it continues to be the model system for evaluating new drug treatment strategies. The early interventions employing natural agents were largely unsuccessful in regressing or preventing adenomas. Thus, antioxidant vitamins were ineffective in reducing adenomas, and may have contributed to some pessimism regarding prospects for effective drug treatment [26].

The first steps toward potentially effective drug therapy in FAP came with the recognition that the nonsteroidal anti-inflammatory drug (NSAID) sulindac induced regression of FAP polyps. Initially, this entailed anecdotal case reports and uncontrolled trials [27]. There followed a number of controlled clinical trials and relatively long-term observational studies. These confirmed at least a partial, temporary regression of adenomas in FAP, mainly in subjects that had already undergone colectomy and had recurrent rectal polyposis [28–31]. These have been reviewed by several others [32, 33]. Strategies for long-term administration have shown reasonable effectiveness in diminishing adenoma burden [30, 31]. Such studies properly emphasized the variable response to treatment and the need for close endoscopic monitoring. The opportunity to adjust the dose of sulindac in relation to observed response provided a chance to minimize potential toxicity, and further underscored the importance of tailoring treatment to individual patient circumstances. Doses generally have ranged from 150 to 400 mg/day. In the series by Winde et al. [31], sulindac was administered in suppository form to subjects with recurrent rectal adenomas following colectomy and IRA. This rectal route of administration does not appear to have been widely adopted, but remains interesting as it appears to have enabled use of doses as low as 50 mg/day. However, sulindac cannot be administered uncritically, as cases of invasive cancer have been described in patients while receiving sulindac [34]. This of course raises the interesting question regarding the nature of drug resistance – do adenomas become resistant once they reach a certain size or degree of dysplasia or might certain patients be resistant, due to their metabolism of sulindac.

Because of the known GI and other toxicities of NSAIDs such as aspirin and sulindac, agents were developed that selectively inhibited the COX-2 enzyme. Because COX-1 was associated with much of the GI toxicity and antiplatelet effects of NSAIDs, and because COX-2 was implicated in neoplasia, it seemed appropriate to investigate selective COX-2 inhibitors or 'coxibs' in FAP. If

efficacious in the model system of FAP, it would then appear reasonable to conduct trials of COX-2 inhibitors in nonfamilial or sporadic adenoma chemoprevention. The coxibs comprised two agents investigated in FAP trials, celecoxib and rofecoxib. In the first published study [35], celecoxib at a dose of 400 mg, orally, twice a day, reduced baseline adenoma burden by an average of about 30%, compared with placebo. A lower dose, 100 mg, reduced adenomas by a nonsignificant 12%. The study duration, 6 months, was similar to that of the sulindac trials. One difference from the earlier sulindac trials was the inclusion of a substantial proportion of subjects with intact colons. No significant toxicities were observed. Based on these results, celecoxib was the first drug approved by the US Food and Drug Administration (FDA) for use as a chemopreventive agent in FAP.

As a condition of FDA approval, follow-up studies were mandated, including a long-term observational 'registry trial' which is ongoing at several centers around the world. Because the approval was really based more on proof of principle rather than demonstrated clinical efficacy, another trial confirmatory of clinical efficacy was mandated. Such a trial, involving children with *APC* mutations but few or no adenomas, is getting under way. Carriers age 10 and older will undergo baseline colonoscopy and eligible subjects will have fewer than 20 adenomas, with such adenomas being ablated in order that all subjects will enter the trial with a 'clean colon'. The dose employed will follow the 400-mg BID schedule used in the origin adult trial, adjusted for body mass (approximately 16 mg/kg/day). A preliminary phase I trial in 18 subject aged 10–14 showed no significant adverse events at this dose. Another celecoxib trial, nearing completion at 3 centers, adds difluoromethylornithine, an ornithine decarboxylase inhibitor, to celecoxib. The comparison arm is celecoxib alone, since use of placebo was felt to be inappropriate, given the noted activity of celecoxib and the FDA indication for its use.

Rofecoxib has also been shown, in smaller trials, to induce regression of or prevent adenomas in FAP [36]. In this small trial from Israel, a rather interesting and clinically appealing design was employed. Prevalent adenomas were removed/ablated. Thus, patients entered the trial essentially free of polyps. Rofecoxib 25 mg/day was administered and rates of recurrence assessed. The actual results may be moot as the cardiovascular toxicities of rofecoxib render its future doubtful (see below). Nevertheless, the notion of combining endoscopic ablation with chemoprevention represents a clinically worthwhile approach.

Initiated before the Israeli rofecoxib trial, a similarly designed trial employed sulindac sulfone, a derivative of sulindac that does not carry appreciable COX-2 inhibitory activity. Although the preliminary work showed some promise [37], the multicenter phase III trial was terminated early and sulindac sulfone failed on initial review to demonstrate statistically significant efficacy compared with placebo. Reanalysis did suggest a benefit but was never reported beyond abstract form.

Unfortunately, the future of COX-2 inhibitors in chemoprevention appears clouded at present. Three well-known sporadic adenoma trials, one with rofecoxib and two with celecoxib, despite demonstrating significant efficacy in reducing risk of recurrent adenomas [38–40], also showed significant cardiovascular toxicity [41, 42]. In response to this, rofecoxib was removed from the market, and indications for use of celecoxib were withdrawn in some countries. So-called 'black box' warnings regarding cardiovascular safety issues have been added for celecoxib, and the cardiovascular safety of nonselective NSAIDs has been newly called into question.

Given the widespread use of aspirin and its low cost, it is perhaps surprising that so little attention has been devoted to its chemopreventive potential in FAP. The CAPP1 trial [43] conducted mainly in Europe contained 4 arms, aspirin 600 mg/day, resistant starch, both, and neither. Preliminary reports suggested a modest effect of aspirin, but no significant synergy with or independent efficacy of resistant starch. Full results are expected soon.

Currently, for clinical treatment of subjects with FAP and rectal polyps postcolectomy or for those with colorectal adenomas in the intact colon, one may cautiously consider the use of celecoxib or sulindac [33]. As the FDA approval statement for celecoxib clearly indicated, use should be considered adjunctive to standard endoscopic and surgical measures. This must be stressed to patients undertaking such a course, as there may be a temptation to rely on the supposed benefit of drug treatment. The patient cannot fail to schedule or report for endoscopic surveillance. Patients must be discouraged from postponing colectomy or further surgery (completion proctectomy or duodenectomy) due to the belief that drug treatment, abetted by endoscopic polypectomy, can indefinitely avoid resection when there is clear evidence of unmanageable polyp progression.

There has been much less activity to date with respect to clinical trials in HNPCC. A key challenge to HNPCC trial development has been, until fairly recently, the inability to confirm mutation carrier status. Unlike FAP, in which adenoma regression could be measured quantita-

tively, a meaningful endpoint in an HNPCC trial would have to be the occurrence or recurrence of adenomas. Although HNPCC patients develop adenomas earlier than 'sporadics', sample size for a trial would have to akin to that of such sporadic adenoma studies, on the order of 1,000 subjects. Given the relative rarity of HNPCC, accrual to a trial of this size has only recently been attainable. The CAPP2 trial, very similar in design to the CAPP1 trial, enrolled subjects with mismatch repair gene mutations or a history of qualifying HNPCC tumors. Drug assignment was similar to CAPP1 and subjects were to have been followed for up to 5 years. Data are due to be reported soon [Burn, pers. commun.]. At present, no agent is recommended for use in HNPCC chemoprevention.

Conclusion

Much progress can be reported in the prevention of cancer in FAP and HNPCC. Keys to successful management include:

(1) Sensitivity to the clinical features of the conditions, particularly the subtleties of AFAP and HNPCC;
(2) Comprehensive genetic counseling whenever possible, laying the proper foundation for genetic predisposition testing, with attention to clinical surveillance strategies;
(3) Regular endoscopic assessment by gastroenterologists and surgeons experienced in the management of these conditions;
(4) Effective communications between gastroenterologists, surgeons, genetic counselors, patients and their families;
(5) Thoughtfully considered use of chemopreventive agents that have shown demonstrated promise, along with a willingness to encourage patients to participate in clinical trials.

Clinical investigators will continue to be challenged to develop improved endoscopic imaging modalities as well as noninvasive screening measures, perhaps including CT colography and tests for altered DNA in exfoliated colorectal epithelium collected from the stool. Imaginative clinical trials to evaluate new drugs and drug combinations should be encouraged.

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