ENCODE
IDEAS

Epigenomics AG
INITIATION REPORT

June 17, 2020

Encode Ideas, L.P.
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FINANCIAL SUMMARY TABLE

Symbol	ECX.DE ECX.F EPGNF
Exchange	XETRA Frankfurt OTC
Current Price	€1.19 ECX.DE $1.32 EPGNF
52 week High - Low	€0.80 - €1.99 $0.97 - $2.28
O/S	~47.13mm
Market Cap	€56.08mm** $62.21mm**
Average Volume (30D)	~48k ~6k
Cash	€11.035mm* $12.42mm*

* as of 3/31/2020 ** as of 6/17/2020

KEY CATALYST DATES

Aug 28, 2020	CMS Issues Proposed Decision Memo for Epi proColon
Nov 28, 2020	Formal publication of National Coverage Decision for Epi proColon by CMS

KEY DISCLOSURES

All Encode Ideas partners own stock in the covered company; Encode Ideas, L.P. is currently engaged to provide research coverage and investor awareness. Encode partners intend to continue transacting in the securities covered therein, and we may be long, short, or neutral thereafter.

HIGH CONVICTION INVESTMENT IDEA

Encode Ideas is initiating coverage on Epigenomics, AG (ECX.DE, OTC: EPGNF) as a high conviction investment idea. There is tremendous upside for investors by owning Epigenomics ahead of, what we expect to be, a positive CMS reimbursement decision on August 28th.

Epigenomics has the first and only FDA-approved blood-based test, Epi proColon (SEPTIN9), for the detection of colorectal cancer. The American Cancer Society set a goal for 80% colorectal screening rate for patients >50 years of age, yet the screening rate for eligible patients in the U.S. has been mired in the mid-60% range for years. Being up to date on screening substantially decreases the risk of colorectal cancer death. A retrospective analysis, published in 2018, of 1,750 colorectal deaths in the Kaiser Permanente system found 76% of the patients were not up to date in their colorectal screening. Current screening modalities are effective when used, but adherence is problematic due to the invasiveness (colonoscopy) or unpleasantness (stool-based) of the test. It is clear that in order to close the screening gap, from the current mid-60% to the goal of 80%, which represents approximately 32mm people in the U.S., a more convenient test is needed. Epi proColon, a simple blood test performed annually, has the effectiveness and convenience to narrow and ideally close the screening gap. However, in order for Epi proColon to address the 32mm unscreened, it requires the same broad reimbursement the other screening modalities enjoy. Epigenomics is expecting a reimbursement decision for Epi proColon from the U.S. Centers for Medicare & Medicaid Services (CMS) by August 28th. Medicare is estimated to represent 50% of the colorectal cancer screening market and big commercial payers like Aetna, UnitedHealth, and Cigna often follow Medicare reimbursement decisions. This CMS decision is a critical milestone for the company, and one we think will be favorable for Epigenomics.

We believe there is tremendous upside for investors by owning Epigenomics ahead of a positive CMS decision. Epigenomics plans to commercialize Epi proColon through the existing CLIA lab system which is dominated by LabCorp (NYSE: LH) and Quest Diagnostics (NYSE: DGX). Epi proColon has already been added to CMS's Clinical Laboratory Fee Schedule for 2019-2021 at a reimbursement rate of $192. This is a lucrative rate that regardless of how you slice the economics back to Epigenomics, with CMS reimbursement in place, the company should print money. The addressable market is huge, as we highlighted above, the unscreened population is 32mm. Quest, LabCorp, and the other CLIA labs, will be highly incentivized to sell Epi proColon, given the simplicity of the test, large market, and huge margin potential. With the push to increase screening rates in the U.S., and the ease and convenience to both patients and labs of a blood-based test, we believe the uptake of Epi Procolon will be swift. Quest, LabCorp, and the other big diagnostic lab companies already have huge sales and marketing teams promoting other blood-based tests, adding Epi proColon should be quick and seamless. It took Exact Sciences (Nasdaq: EXAS) about four years to get to 1mm / annually for their stool-based DNA test Cologuard, and they built their own sales organization from the ground up. We believe Epi proColon could get there even faster. If we assume Epigenomics sells the test to the labs at $100 / test, a million tests a year brings in $100mm in revenue to Epigenomics. Making some other simple assumptions for COGS ($10 /test), SG&A ($25mm), and a small amount of future dilution (additional 10mm shares, i.e. pro-forma 57mm O/S), assuming a positive CMS reimbursement

decision, we think it's possible Epigenomics could have EPS of ~$1.15 in a few years. Apply a 20x earning multiple, and the equity could be worth $20.

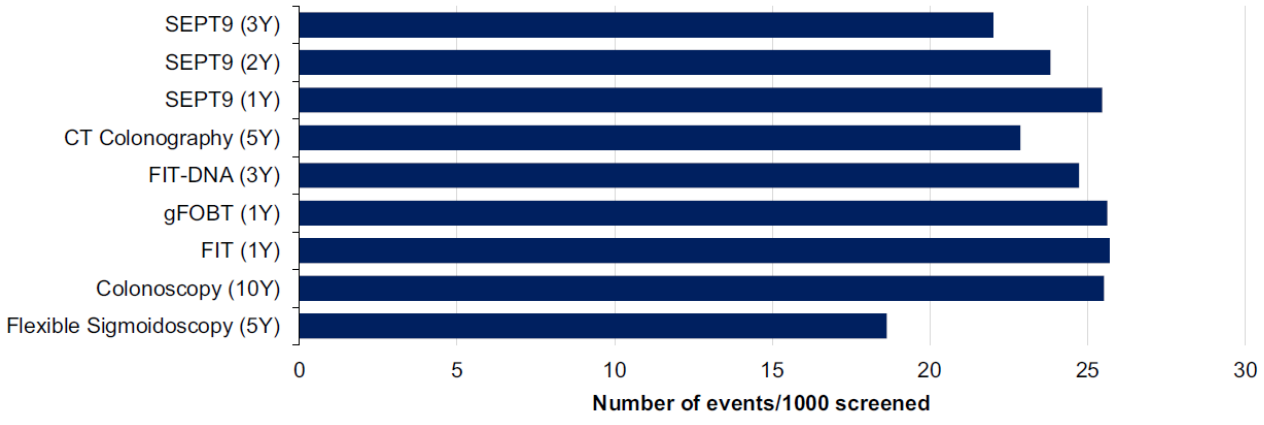
CMS reimbursement will also raise the probability of M&A for Epigenomics. In 2017 shortly after the FDA approval for Epi proColon, Epigenomics received a takeover bid from Cathay Fortune International for €7.52 / share. At the time this valued Epigenomics at ~US$200mm. Although Epigenomics management and board were in favor of the transaction, the takeover did not receive the 75% shareholder consent needed and was rejected. We think the CMS decision will spark renewed M&A interest for Epigenomics, and that management and the board will once again be receptive to offers. It is worth noting that Epigenomics leadership, Greg Hamilton, CEO and Dr. Jorge Garces, President and CSO, have been part of a successful exit in the diagnostic space before. Both were in senior leadership and/or executive positions with Third Wave Technologies when it was acquired by Hologic (Nasdaq: HOLX) for $580mm in 2008. They remained with Hologic through a transition period, while Third Wave's CEO, Kevin Conroy, left and shortly thereafter became the CEO of a small, development stage, colorectal cancer screening company - Exact Sciences.

The CMS Process

CMS initiated a National Coverage Analysis (NCA) for Epi proColon on February 28th, 2020. CMS will issue a proposed decision memo for the NCA by August 28th, and the NCA will be formally completed by November 28th with a published National Coverage Determination (NCD).

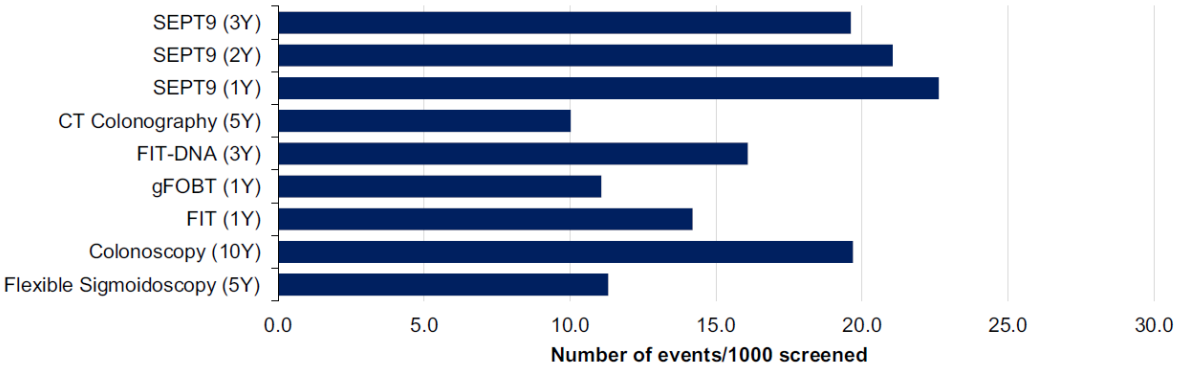
Epi proColon's diagnostic performance, clinical utility and safety, were already established through its premarket approval (PMA) by FDA. CMS's reimbursement decision will be driven by whether Epi proColon is necessary and reasonable. To support the case for reimbursement Epigenomics recently completed a microsimulation study to assess the outcome and benefits of Epi proColon, along with all the other common screening strategies, for detecting colorectal cancer at early stages. Developed by Harvard Medical School and published in Cancer Medicine in October 2019, this microsimulation study demonstrated that annual testing with Epi proColon was equivalent to the most common screening modalities, including colonoscopy every 10-years, stool-DNA testing (Cologuard) every 3-years, and annual fecal immunochemical test (FIT), when assessing colorectal cancer cases averted and colorectal cancer deaths averted.

**CRC Deaths Averted per 1000 Screened (Full Adherence)*



These data alone should get Epi proColon CMS reimbursement, however, the data are even more favorable for Epi proColon when considering adherence. Most microsimulation studies assume 100% adherence for all screening modalities, but real-world experience has demonstrated that adherence for colonoscopy and stool-based tests are suboptimal. When the authors of this microsimulation study applied reported adherence for the various screening modality to their model, annual Epi proColon testing and Colonoscopy every 10-years, were notably superior to all other screening modalities for colorectal cancer cases averted and colorectal cancer deaths averted.

**CRC Deaths Averted per 1000 Screened (Reported Adherence)*



The data from this microsimulation study provide a compelling case for annual Epi proColon testing being equivalent to other screening modalities and arguably superior when adherence is considered. We think these data will lead to CMS reimbursement in a few months, making Epi proColon widely available as a disruptive new screening modality for colorectal cancer.

"Exactly" What the Market Needs - Some Competition

We think a positive CMS reimbursement decision for Epi proColon will cause Exact Sciences to start looking over their shoulder at the emerging competition. Exact, the developer and marketer of Cologuard, the first and only FDA-approved stool-DNA screening test for colorectal cancer, has been a commercial success and capital markets darling. They have basically had the branded colorectal cancer screening market to themselves for the past 6-years, building Cologuard into a $1b annual (and growing) business. To be clear, we are not suggesting Exact will be the least bit concerned about Epigenomics as a commercial threat, but Quest Diagnostics and LabCorp may cause them some pause. Epigenomics plans to commercialize Epi proColon through the "traditional model", working with the established clinical laboratory companies, of which Quest and LabCorp are the two largest. Exact opted not to work with the established lab companies, instead, it built its own sales and marketing infrastructure and its own CLIA lab. A bold approach, that has proven successful, but also drawn the ire of the clinical laboratory establishment, who haven't seen a cent of revenue from Cologuard, while also seeing Cologuard chew into their FIT revenue base. Epigenomics already has an agreement in place with LabCorp to distribute Epi ProColon, and we would expect one with Quest to follow shortly after the CMS decision. A positive CMS decision on Epi proColon could set the stage for an interesting competitive battle between Exact and the big lab companies.

Expanding Epi proColon Market & Pipeline Opportunities

In 2019 Exact Sciences was successful in getting a broader label for Cologuard from FDA to include standard risk patients 45-49 years of age. This label expansion opened up an additional 20mm patients to Cologuard's addressable market. Epi proColon's current label is for average risk patients 50-75 who have refused colonoscopy and FIT. Following Exact's lead, Epigenomics also plans to run a study to support a 45-49 FDA label expansion, which they estimate will take 12-months and about $3mm. Beyond Epi proColon, Epigenomics has a blood-test for liver cancer in development, and it is estimated to be about 3-years away from a potential FDA-approval.

Notable Risks

The most notable risk for Epigenomics is a negative CMS reimbursement decision. The CMS decision is binary, positive and Epigenomics should fly, negative and it will likely be cut in half. Epigenomics does have options if the CMS decision is negative; they can go through a reconsideration process with CMS, or they can pursue a legislative path through the U.S. Congress. We would also highlight that the risk of a delay in the CMS decision due to the COVID-19 situation has already been addressed by Epigenomics. In their 1Q20 filings from May, the company stated that they fully expect CMS to meet the August 28th and November 28th deadlines for a preliminary and final decision respectively on the NCD for Epi proColon.

Financial Considerations

Epigenomics, founded in Germany, is listed on the Frankfurt and Xetra exchanges, ticker ECX. In the U.S. there is a 1:5 OTCQX ADR listing, ticker EPGNY, and a 1:1 OTC Pinks listing, ticker EPGNF. The German Xetra listing has the best liquidity, but for those wanting to buy in the U.S. the EGPNF is an option. There is no liquidity in the ADR at this time.

Up until recently Epigenomics was predominantly held by German investors, but we are now starting to see a number of U.S. institutions filing as owners. Bridger Management, 683 Management, and Altium Capital Management are notable U.S. owners, and were the main participants in the March €1.11 / share financing that raised proceeds of €4mm.

As of March 31st, Epigenomics had €11mm of cash, which the company estimates takes them into 1Q21. We would expect the company to raise additional capital after the August 28th CMS decision.

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Technical Summary

Colorectal cancer (CRC) is a type of gastrointestinal malignancy originating from either the colon or rectum and is the third most commonly diagnosed cancer in both men and women in the United States. The American Cancer Society estimates that in 2020 there will be approximately 147,950 new cases.

The pathogenetic features of colorectal cancer make it one of the most preventable and often curable malignancies. However, disease curability entirely depends on early detection. The best method for early detection is screening. Despite many years of effort, United States colorectal cancer screening rates have plateaued well below the national goal of 80%, with a considerable segment of the population remaining unscreened.

The main methods for colorectal cancer screening include imaging-based methods as well as stool- and blood-based testing with the frequency of testing dependent on the type of method used.

Colorectal Cancer Screening Methods

Test Type	Method	Testing Frequency
Imaging-based	Colonoscopy	Every 10 years
	CT Colonography	Every 5 years
	Flexible Sigmoidoscopy	Every 5 years
Stool-based	Fecal Occult Blood Test (gFOBT)	Annually
	Fecal Immunochemical Test (FIT)	Annually
	Stool DNA (Cologuard)	Every 3 years
Blood-based	mSEPT9 (Epi proColon)	Annually
CT = Computer Tomography; DNA = Deoxyribonucleic Acid; mSEPT9 = Methylated SEPTIN9		

Various organizations in the United States have worked on developing American guidelines for colorectal cancer screening. Most guidelines recommend starting CRC screening for average-risk individuals at age 45 to 50. This is based on the steep increase of CRC beginning around age 50. Many guidelines recommend an upper age screening threshold varying from age 70 to 75, based on associated harms potentially exceeding benefits if screening is continued after that point. All guidelines have considered gFOBT, FIT, FS, and colonoscopy as mainstays of CRC screening.

US Colorectal Cancer Screening Guidelines

Association Source	Publication Year	Age	Recommendations
American Cancer Society	2018	45-75	FIT (1 yr) OR High sensitivity, FOBT (1 yr) OR FIT DNA (3 yr) OR Colonoscopy (10 yr) OR CT colonography (5 yr) OR FS (5 yr)
		75-85	Individualize CRC screening decisions
		>85	Discouraged
American College of Gastroenterology	2009	≥ 50	Preferred prevention test: Colonoscopy (10 yr). If not possible or refused by individual: FS (5-10 yr) - OR CTC (5 yr) OR detection test Screening starting at age 45 for African American population Preferred detection test: FIT (1 yr). If not possible: Annual gFOBT (Hemoccult Sensa) OR- Fecal DNA testing (3 yr)
American College of Physicians	2015	50-75	High sensitivity FOBT/FIT (1 yr) OR FS (5 years) OR FOBT/FIT (3 yr) + FS (5 yr) OR Colonoscopy (10 yr)
		≥ 75	Screening not recommended
U.S. Preventive Services Task Force	2016	50-75	gFOBT/FIT (1 yr) OR FIT-DNA (1-3 yr) OR FS (10 yr) + FIT (1year) OR FS (5 yr) OR colonoscopy (10 yr) OR CT-colonoscopy (5 yr)
		76-85	Screening is considered an individual decision
National Comprehensive Cancer Network	2017	50-75	Colonoscopy (10 years) OR gFOBT/FIT (1 yr) OR Fecal DNA test (3 yr) OR FS (5-10 yr) (+/- gFOTB/FIT at year 3) OR CTC (5 yr)
		76-85	Screening should be an individual decision, can be discussed
United States Multi-Society Task Force on Colorectal Cancer	2017	50-75	First-tier (preferred tests): Annual FIT OR colonoscopy (10 yr) Second-tier: CTC (5 yr) OR FIT-fecal DNA testing (3 yr) OR FS (5-10 yr) Third-tier: Capsule colonoscopy (5 yr)
		76-85	Screening should be considered for individuals without prior screening
CRC = Colorectal Cancer; FS = Flexible Sigmoidoscopy; CTC = CT Colonography; FOBT = Fecal Occult Blood Test; gFOBT = Guaiac-based Fecal Occult Blood Test; FIT = Fecal Immunochemical Test; yr = Year			

In 2016 the Food and Drug Administration approved the first blood-based CRC screening method called Epi proColon. The Epi proColon test provides an alternative screening method for the detection of asymptomatic colorectal cancer in average-risk adults aged 50–75 years who have refused colonoscopy. In a prospective study of Epi proColon, population sensitivity (true positive rate) for colorectal cancer was determined to be 68.0% (95% confidence interval 53% to 80%) and specificity (true negative rate) was 80.0% (95% confidence interval 78% to 82%). Epi proColon,the newest of the screening tests, has only begun to be included in CRC screening guidelines, the first being its recent inclusion in the new 2020 NCCN guidelines.

Screening adherence has a large effect on CRC outcomes. The table below lists the one-time CRC screening adherence levels for the various screening methods. The blood-based Epi proColon test was found to have the highest potential adherence level at 85% which is significantly higher than the other currently used screening methods.

Estimated CRC Screening Adherence Levels

Method	Adherence % (Range)
Imaging-based Methods	
Colonoscopy	38 (25 to 55)
CTC	22 ± 10%
FS	35 (34.3 to 35)
Stool-based Methods	
FIT	42.6 ± 10%
gFOBT	33.4 ± 10%
Cologuard	42.6 ± 10%
Blood-based Methods	
Epi proColon	85 ± 10%
CRC = Colorectal Cancer; FS = Flexible Sigmoidoscopy; CTC = CT Colonography; gFOBT = Fecal Occult Blood Test; FIT = Fecal Immunochemical Test	

To assess the effectiveness of colorectal screening methods in terms of incidence and mortality, a microsimulation model was developed at Harvard Medical School, involving men and women 50 years or older under two conditions:

- 100% adherence rates
- Reported adherence rates

Under the ideal conditions of 100% adherence, screening annually with a stool- (FIT or FOBT) or blood-based (Epi ProColon) test produced comparable benefits in terms of cases and deaths averted, to screening with colonoscopy every ten years. Under reported adherence conditions (see table below), screening annually with Epi ProColon or with colonoscopy every ten years produced superior results to CTC, FS and all stool-based methods. Screening with colonoscopy and Epi proColon was predicted to avert more cases and deaths compared to the other screening methods.

Cases and Deaths Averted Based on Reported Adherence Rates

Method	Cases Averted per 1000 Individuals	Deaths Averted per 1000 Individuals
Imaging-based Methods		
CS (every 10 years)	34	20
CTC (every 5 years)	16-25	11-16
FS (every 5 years)	16-25	11-16
Stool-based Methods		
FIT (every year)	16-25	11-16
gFOBT (every year)	16-25	11-16
Cologuard (every 3 years)	16-25	11-16
Blood-based Methods		
Epi proColon (every year)	37	23
CS = Colonoscopy; CTC = Computed Tomographic Colonography; FIT = Fecal Immunochemical Test; FS = Flexible Sigmoidoscopy; gFOBT = High-sensitivity Guaiac-based Fecal Occult Blood Test		

To estimate the cost and clinical implications to health plans, including the clinical and fiscal implications of the use of Epi proColon, FIT, and Cologuard, a simulation model was developed to project the 3-year aggregate health outcomes and costs for colorectal cancer screening among average-risk persons who are eligible for screening according to current guidelines and were not screened previously. It was determined that assuming all non-invasive strategies could be applied to improve colorectal cancer screening adherence from 65% to 80% participation over 3 years, analysis estimates the health plan cost and outcomes of each strategy. Epi proColon and FIT achieved similar 3-year outcomes in terms of the number of colorectal cancer cases detected (221 and 216 cases, respectively); Cologuard detected fewer cases (193 cases).

Including the costs of screening, diagnostic testing, and treatment, the per-member per-month impact versus status quo costs were highest for Epi proColon ($1.08), followed by Cologuard ($0.98) and FIT ($0.71), suggesting a modest trade off between cost and the number of cases detected among the screening strategies. Considering only the costs of screening and diagnosis, the costs for Epi proColon and Cologuard were almost the same ($0.67 and $0.69, respectively) but the cost for FIT was lower ($0.33).

At this time, Medicare does not cover the cost of the Epi proColon blood-based test. Epigenomics is currently navigating the Medicare national coverage determination (NCD) process to establish Medicare coverage for its Epi proColon test. The following is a list of the key milestones in the NCD process as well as the current timelines for establishing Epi proColon Medicare coverage:

- FDA approval – 2016 (completed)
- CMS sets final price – 2019 (completed)
- NCD opened – February 28, 2020 (completed)
- Proposed decision memo – August 28, 2020 (ongoing)
- Final decision memo – November 28, 2020 (ongoing)

A rate of $192 per test has already been finalized for Epi proColon and has been fixed for a three-year period (2019-2021).

Increasing adherence to screening is critical to improving colorectal cancer outcomes. Health insurance plans considering ways to improve screening rates among their most reluctant members must weigh many factors, including:

- Costs related to testing,
- Adherence over time,
- Sensitivity and specificity of testing, and
- Rates of diagnostic evaluation among patients who test positive on screening.

Historically emphasis was predominantly on test performance (sensitivity / specificity), but there is growing recognition for the importance of adherence for CRC screening modalities. Blood-based screening approaches such as Epi proColon should have an advantage over other screening methods in that individuals may be more willing to have a blood test than provide a stool sample or undergo an invasive colonoscopy. Blood tests can be completed easily as part of a standard medical office appointment for a wellness check or to take advantage of opportunities to promote screening during scheduled visits to manage chronic illnesses. Blood-based tests may have lower one-time sensitivity compared to colonoscopy and stool-based tests, but the frequency of testing and superior adherence increases the overall probability of cancer detection over time.

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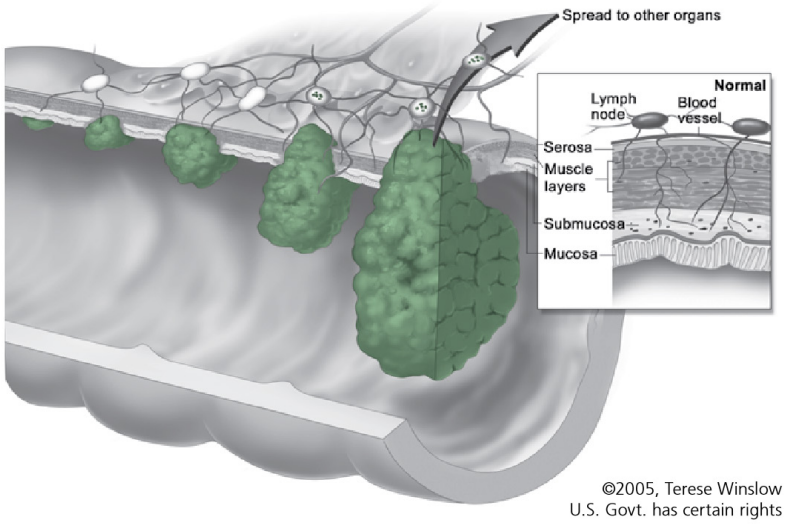
1 Introduction

1.1 Colorectal Cancer

Colorectal cancer (CRC) is a type of gastrointestinal (GI) malignancy originating from either the colon or rectum. Although both forms can be simply defined as colon or rectal cancers, depending on their origin, they are often merged because of their many common biological and clinical features (American Cancer Society, Colorectal Cancer).
CRC usually begins with the non-cancerous proliferation of mucosal epithelial cells. These growths are known as polyps and can grow gradually for 10–20 years before becoming cancerous. The most common form is an adenoma or polyp originating from granular cells, which function to produce the mucus that lines the large intestine (Stryker et al, 1987). Only about 10% of all adenomas progress to invasive cancer, although the risk of cancer increases as the polyp grows larger.
CRCs that grow into the wall of the colon or rectum can penetrate blood or lymphatic vessels, allowing metastasis to distant organs via the blood or to nearby lymph nodes (Figure 1). The extent of invasion determines the staging, and thus the prognosis. *In situ* cancers are polyps that have not yet invaded the colon or rectum wall and therefore are not considered or reported as CRCs. Local cancers are cancers that have grown into the wall but have not yet extended past it. Regional cancers are those that have invaded nearby lymph nodes or tissues, while distant cancers are those that have metastasised, via the bloodstream, to distant organs where they grow, for example in the lungs or liver (Rawla et al, 2019).

Figure 1 Stages of Colorectal Cancer Growth



(American Cancer Society, Colorectal Cancer Facts & Figures 2020-2022)

1.2 Colorectal Cancer Prevalence

CRC is the third most commonly diagnosed cancer in both men and women in the United States (US) (American Cancer Society, Cancer Statistic Center). According to the latest statistics of the International Agency for Research on Cancer (IARC) of the World Health Association (WHO), CRC is also the third most frequent malignant disease found around the world following lung and breast cancers (Table 1) (International Agency for Research on Cancer, Cancer Fact Sheets). The American Cancer Society estimates that in 2020 there will be approximately 147,950 new cases of CRC (104,610 colon cancer and 43,340 rectal cancer) in the US (American Cancer Society, Cancer Statistic Center) and an additional 1.85 million new cases worldwide (International Agency for Research on Cancer, Cancer Fact Sheets).

Table 1 Global Cancer Incidence

Type	New Cases in 2018	% of All Cancers
Total	17,036,901	-
Lung	2,093,876	12.3
Breast	2,088,849	12.3
Colorectal	1,800,977	10.6
Prostate	1,276,106	7.5
Stomach	1,033,701	6.1
Liver	841,080	5.0
Esophagus	572,034	3.4
Cervix uteri	569,847	3.3
Thyroid	567,233	3.3
Bladder	549,393	3.2

(American Institute of Cancer Research)

Overall, the lifetime risk of developing CRC is about 1 in 23 (4.4%) for men and 1 in 25 (4.1%) for women (American Cancer Society, Key Statistics for Colorectal Cancer). The incidence of CRC is highest in Australia and New Zealand, followed by Europe, Eastern Asia and North America. The lowest incidence rates are in Africa and South-Central Asia (Table 2) (Rawla et al, 2019).

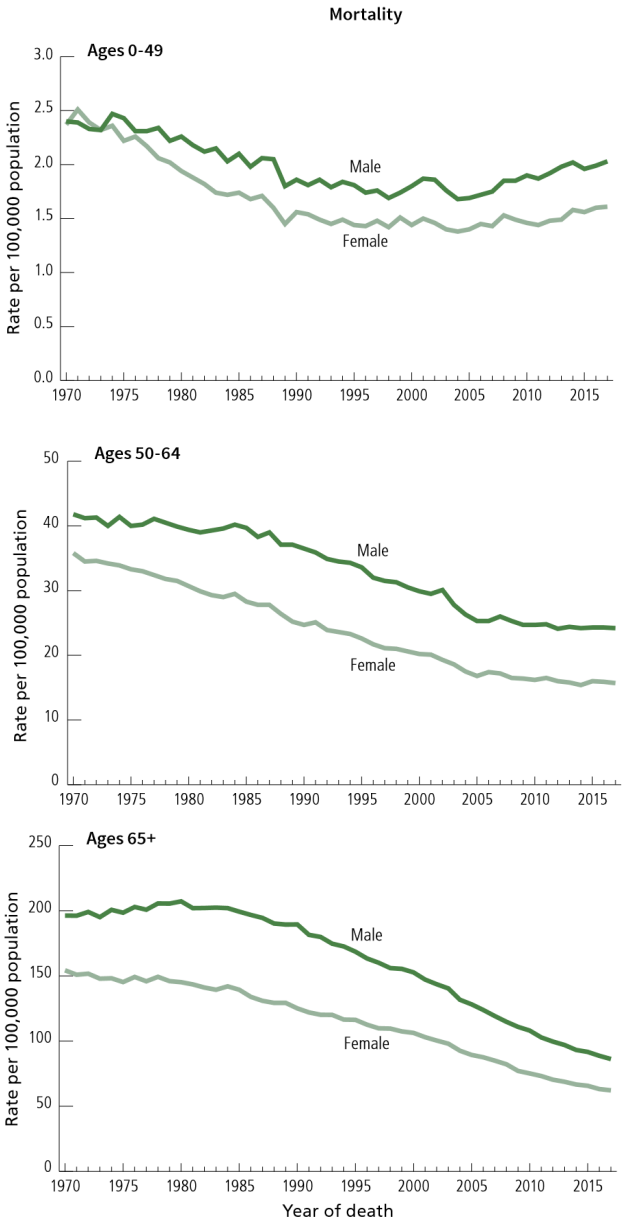
Table 2 Colorectal Cancer Incidences Around the World

Region	Colorectal Cancer Incidence
Australia and New Zealand	36.7 cases per 100,000
Europe	28.8–32.1 cases per 100,000
Eastern Asia	26.5 cases per 100,000
North America	26.2 cases per 100,000
Africa	6.4–9.2 cases per 100,000
South-Central Asia	4.9 cases per 100,000

(Rawla et al, 2019)

Colorectal cancer is the second-leading cause of cancer related death in the US. The American Cancer Society's estimates that in 2020 there will be around 53,200 deaths caused by CRC (American Cancer Society, Cancer Statistic Center). The CRC death rate (the number of deaths per 100,000 people per year) has been dropping in both men and women for the last several decades. However, although the overall death rate has dropped, deaths from CRC among people younger than age 50 have been increasing by about 2% per year from 2007 and 2016 (Figure 2).

Figure 2 Trends in US CRC Mortality Rates by Age and Sex

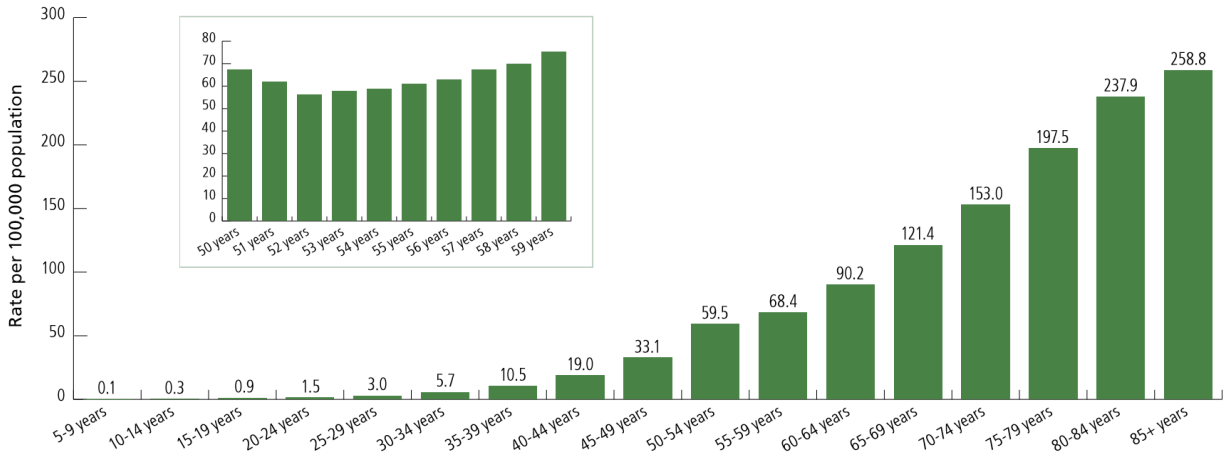


(American Cancer Society, Colorectal Cancer Facts & Figures 2020-2022)

1.3 Colorectal Cancer Risks

For the majority of adults, the most important risk factor for the development of CRC is age (Figure 3). Most cases of CRC occur among adults older than 50 years with a median age at diagnosis of 68 years (Howlader et al, 2013). In the US, those over 65 years are about three times more likely to be diagnosed with CRC than those aged 50–64, and about 30 times more likely to be diagnosed than those 25–49 years old (Rawla et al, 2019).

Figure 3 Age-specific Colorectal Cancer Incidence Rates, US, 2012-2016



Source: Main figure: NAACCR, 2019. Inset: Surveillance, Epidemiology, and End Results (SEER) Program, 2019.

A positive family history (excluding known inherited familial syndromes) is thought to be linked to about 20% of cases of CRC (Lin et al, 2016). About 3% to 10% of the population has a first-degree relative with CRC (Henrikson et al, 2015). Male gender and black race are also associated with higher CRC incidence and mortality (Kim et al, 2015; Howlader et al, 2013; Irby et al, 2006).

Other non-modifiable risk factors associated with CRC include:

- inflammatory bowel disease (IBD) (Olen et al, 2017)
- abdominal radiation (Nottage et al, 2012)
- cystic fibrosis (Yamada et al, 2018)
- cholecystectomy (Zhang et al, 2017) and
- androgen deprivation therapy (Gillessen et al, 2010)

Modifiable risk factors for CRC include:

- obesity and physical inactivity (Karahalios et al, 2016)
- diet (Zhao et al, 2017)
- smoking (Botteri et al, 2008)
- alcohol (Fedirko et al, 2011)
- medications (Rothwell et al, 2010; Chang et al, 2018; Hildebrand et al, 2009; Thosani et al, 2013; Makar et al, 2014)
- diabetes and insulin resistance (Jiang et al, 2011)

When CRC is found at an early stage before it has spread, the 5-year relative survival rate is about 90% (American Cancer Society, Survival Rates for Colorectal Cancer). However, only about 4 out of 10 CRCs are found before cancer has spread to the rest of the body. When cancer has spread outside the colon or rectum, survival rates are considerably lower (American Cancer Society, Survival Rates for Colorectal Cancer).

The pathogenetic features of CRC make it one of the most preventable and often curable malignancies. However, disease curability entirely depends on early detection. CRC detection is not straightforward since clinical symptoms usually only emerge once the disease is already advanced. The latter factor warrants the necessity of active population screening for CRC, since it has been proven that screening can save lives (Brenner et al, 2018).

Colorectal Cancer Screening

Screening is the process of looking for cancer or pre-cancer in people who have no symptoms of the disease. Regular CRC screening is one of the most powerful weapons against CRC. Therefore, US public health officials have invested considerable resources into raising the awareness of CRC and encouraging Americans to participate in CRC screening.

A microsimulation modeling study found that increasing CRC screening prevalence to 80% had the potential to decrease CRC incidence and mortality by 22% and 33% respectively by 2030 (Meester et al, 2015). This would result in 277,000 new cases being averted and 203,000 deaths prevented by 2030, assuming that participants start screening at age 50 years and continue periodic screening as recommended through age 75.

The National Colorectal Cancer Roundtable (NCCRT), was established in 1997 and is dedicated to reducing CRC incidence and mortality in the US by increasing the use of recommended CRC screening tests among adults 50 and older to 80%. Unfortunately, however, approximately one-third of all eligible adults are still not up to date with their CRC screening (Table 3).

Table 3 Percentage of Respondents Reporting Being Up to Date with CRC Screening in 2018

	Age Groups (years)		
	All (50-75) % (95% CI)	50-64 % (95% CI)	65-75 % (95% CI)
Total	68.8 (68.3–69.3)	63.3 (62.7–63.9)	79.2 (78.5–79.8)
Male	67.0 (66.3–67.7)	61.1 (60.2–62.0)	78.2 (77.1–79.2)
Female	70.5 (69.9–71.2)	65.4 (64.5–66.2)	80.1 (79.2–80.9)

(Joseph et al, 2020)

In a study by Cooper at al (2016) participants were asked about CRC screening. The most common reason participants gave for not getting screened for CRC was an aversion to some aspect of colonoscopy (CS), such as preparation, the invasive nature of the test, or the possibility of complications. Many CS-resistant participants lacked awareness of alternative screening options, and those who were familiar with other screening tests generally believed that CS was the only worthwhile test. Other participants indicated that they had not been screened because they did not know that they should be, or because no health care provider had recommended it to them.

Many participants also indicated that they did not feel that screening was necessary because they had no symptoms and were in good health. Some believed they did not need to be screened because they had no family history of CRC. A few participants indicated that the costs and logistics (e.g. taking time off from work) associated with CS prevented them from being screened. Several patients were reluctant to see a health care provider under any circumstance, and a few indicated that they would prefer to die of cancer without it ever being diagnosed. Finally, a few participants attributed their lack of screening to general procrastination and laziness.

2 Discussion

2.1 Methods

The main methods for CRC screening include imaging-based methods (endoscopic), stool-based methods, and blood-based methods. A list of current screening methods and their recommended screening frequency have been provided in Table 4. A more detailed description of each method can be found in the sections below.

Table 4 CRC Screening Methods

Test Type	Method	Frequency
Imaging-based	Colonoscopy	Every 10 years
	CT colonography	Every 5 years
	Flexible Sigmoidoscopy	Every 5 years

Stool-based	Fecal Occult Blood Test	Every year
	Fecal Immunochemical Test	Every year
	Stool DNA (Cologuard®)	Every 3 years
Blood-based	mSEPT9 (Epi proColon®)	Every year
CT = Computed Tomography; DNA = Deoxyribonucleic Acid		

The two primary endpoints for endoscopic CRC screening are finding cancer at an early stage (secondary prevention) and finding and removing precancerous lesions (adenomatous polyps), to reduce the incidence of CRC (primary prevention). The primary endpoint for stool- and blood-based tests is finding cancer at an early stage. Stool-based tests also have some ability to detect adenomatous polyps; therefore, a secondary endpoint of these tests is reducing the incidence of CRC.

2.1.1 Imaging-based Methods

2.1.1.1 Colonoscopy

Full colonoscopy (CS) is regarded as the gold standard diagnostic technique for colorectal tumor detection (Hazewinkel et al, 2011), and is a popular method for primary CRC screening in the US (Hoff et al, 2010; Lieberman et al, 2014; Young et al, 2019). One reason for this trend is that diagnostic CS is usually combined with the simultaneous removal of detected polyps and functions as both a diagnostic and preventive procedure reducing mortality from CRC (Zauber et al, 2012). Nonetheless, CS is an expensive and invasive technique that requires unpleasant bowel preparation and occasionally causes serious complications (Lieberman, 2011).

Moreover, its sensitivity is not perfect, with polyps sometimes being missed (Zhao et al, 2019), the latter problem often depends on the operator's skills (Ladabaum et al, 2020). Although CS as the final (confirmatory) diagnostic step is indisputable, its use in primary CRC screening remains questionable as the indiscriminate application of this method inevitably results in frequent negative outcomes and a large health economic burden (Corte et al, 2016).

2.1.1.2 Computed Tomographic Colonography

Computed tomographic colonoscopy (CTC) refers to the examination of computer-generated images of the colon constructed from data obtained from an abdominal computed tomographic (CT) examination. It provides a non-invasive structural assessment of the colon. The images generated simulate the effect of a conventional CS. Compared with conventional colonoscopy, CTC is sedation-free and has an extremely low risk of bowel perforation (0.005%-0.059%) (Sosna et al, 2006; Berrington de Gonzalez et al, 2010). Furthermore, assessment of the extra-colonic organs can be performed at the same time (Pickhardt et al, 2008). A lower volume of bowel preparation may be used (Zalis et al, 2012) and the radiation risk is negligible (Berrington de Gonzalez et al, 2010). Its main disadvantage is that biopsy is not possible, and the patient may require a second procedure with another bowel preparation, thus imposing additional costs and discomfort to the patient. Its role in CRC screening remains debatable. The American Cancer Society supports screening with CTC every 5 years (Levin et al, 2008). Other guidelines including the National Institutes of Health Asia Pacific Consensus Recommendations do not support its use, citing its lack of evidence as a screening technique in an average-risk population (Steinwachs et al, 2010; Sung et al, 2015).

2.1.1.3 Flexible Sigmoidoscopy

The flexible sigmoidoscope (FS) permits a more complete examination of the distal colon with more acceptable patient tolerance than the older rigid sigmoidoscope. The rigid instrument can discover 25% of polyps, and the 60 cm scope can find as many as 65% of them. The finding of an adenoma by FS may warrant a CS to evaluate the more proximal portion of the colon (Read et al, 1997; Wallace et al, 1998).

The sensitivity of FS depends on the adequacy of mucosal inspection and is operator dependent (Laiyemo et al, 2012). Studies have shown inadequate screening in up to 91.7% of cases, ie <50 cm depth of insertion (Laiyemo et al, 2012). The technique has had relatively low and fluctuating participation rates (20.9%-63.0%) (Denis et al, 2009; Holme et al, 2014).
The impact of FS as a screening tool is well established in the literature and accepted in various screening protocols (Levin et al, 2008). This technique may be included as an alternative for a population-wide screening program, and the shortage of endoscopists could be partially addressed by training specialized nurses in the procedure (Shum et al, 2010).

2.1.2 Stool-based Methods

2.1.2.1 Fecal Occult Blood Test

Fecal occult blood tests (FOBTs) are based on the detection of GI occult blood in the stool (Young et al, 2015; Schreuders et al, 2016). Guaiac FOBT (gFOBT) detects blood using paper impregnated with guaiac, which is extracted from the wood resin of Guaiacum trees, to which hydroperoxidase is added. When it contacts hem (but not exclusively), the hydroperoxidase oxidizes guaiac, leading to a blue color that is evaluated as a qualitative result (positive or negative for the presence of blood).

The standard gFOBT consists of three paper cards, each with two panels, requiring sampling from three separate feces samples (Schreuders et al, 2016). gFOBT can be analyzed with or without rehydration. gFOBT does not detect hemoglobin (Hb) concentrations of less than approximately 600 µg Hb/g feces; when gFOBT is rehydrated, the analytical sensitivity is higher, but more false-positive results are obtained (Tinmouth et al, 2015). One manufacturer has developed a high sensitivity gFOBT (HSgFOBT) with performance similar to that of rehydrated gFOBT (Allison et al, 1996). Results of gFOBT are read with the naked eye, which leads to subjective evaluation. Results are not quantifiable using automated instrumentation and are therefore not suited to high-throughput screening programs.

In gFOBT, any dietary Hb or myoglobin (e.g. from meat, especially if raw or half-cooked) as well as drugs or foods that have peroxidase properties (e.g. some uncooked fruits and vegetables, such as cabbage and green beans) can potentially lead to a positive test result, although there is no consistent evidence that positivity rates differ substantially between gFOBT participants with or without restrictions of those foods (Rozen et al, 1999; Pignone et al, 2001). In contrast, antioxidants in drugs or foods (e.g. vitamin C or vitamin E) have the potential to lead to a negative test result by interfering with the oxidation of guaiac. There is no consistent evidence of medications with anticoagulant properties, such as aspirin, non-steroidal anti-inflammatory drugs, or warfarin, causing positive gFOBT results in individuals without disease (Norfleet, 1983; Greenberg et al, 1996, 1999; Kahi and Imperiale, 2004; Clarke et al, 2006) or altering the positive predictive value of gFOBT (Sawhney et al, 2010; Lee et al, 2012; Gandhi et al, 2013). Finally, the dark-green or black appearance of feces in patients treated with iron supplements, antacids, or antidiarrheal treatments with bismuth can be confounded with the blue color of a positive gFOBT (Laine et al, 1988; Rockey, 1999).

2.1.2.2 Fecal Immunochemical Test

The immunochemical FOBT (iFOBT or FIT) was developed to detect intact human hemoglobin. FIT for Hb was developed in the late 1970s by the clinical pathologist Barrows (Barrows et al, 1978). The method was based on using goat anti-Hb antibodies and demonstrated improved sensitivity and specificity compared with gFOBT in the detection of small amounts of Hb in feces (Barrows et al, 1978). FIT detects the globin moiety of human Hb by immunoassay methodology using different methods. Two of the most widely used methods are lateral flow immunochromatography (qualitative) and immunoturbidimetry (quantitative) (Phalguni et al, 2015). FIT can detect human blood with high analytical sensitivity (Rockey, 1999), which ranges from 1 µg to 300 µg Hb/g feces, depending on the FIT characteristics and the manufacturer. However, FIT does not usually detect small quantities of blood from the upper GI tract (i.e. above the stomach), because it is normally degraded by digestive proteolytic enzymes (Rockey et al, 1999).

Quantitative FIT is becoming the most commonly used stool-based method for CRC screening (Schreuders et al, 2015). Many different quantitative FIT devices are commercially available; they vary in collection method, Hb stability, analytical methodology, polyclonal or monoclonal antibody characteristics, or calibration material. One of the major differences among the FITs from different manufacturers is that they use different fecal sample collection devices, which vary in the amount of stool collected and the volumes of preservation buffers used (Fraser et al, 2012). The observed/apparent discrepancies in the diagnostic performance of quantitative FITs can be largely reduced by adjusting the cut-off level to provide specific positivity rates or defined levels of specificity (Gies et al, 2018).

Manufacturers of automated quantitative FITs provide an internal quality control, and participation in an external quality assessment scheme is particularly important for national screening programs in which different laboratories are involved (Halloran et al, 2012). Another important issue that must be accounted for in the sample quality. The globin moiety (detected with FIT) is less stable than the hem moiety (detected with gFOBT); therefore, proteolysis of globin should be avoided between sample collection and analysis. Samples show good stability at refrigerator temperatures but marked deterioration with rising temperatures. Samples refrigerated at 4 °C showed no significant degradation over a period of 21 days (daily degradation, 0.3% ± 0.4%), whereas with storage at 28 °C a daily degradation of 3.7% ± 1.8% was shown (Vilkin et al, 2005; Rozen et al, 2006; Halloran et al, 2012). A decrease in positivity, a lower detection rate, and a loss of clinical sensitivity have been reported during seasons with high temperatures (van Roon et al, 2012; Doubeni et al, 2016). Manufacturers are investing in the development of new preservation buffers to improve stability, but sample conservation still represents a challenge to the organization of FIT-based screening programs.

2.1.2.3 Cologuard

In 2014, the FDA approved the first stool-DNA CRC screening test (Cologuard) (FDA, 2014). It is a multi-target test that detects the presence of hemoglobin and CRC related DNA mutations in shed abnormal cells using nine biomarkers. The test is repeated once every three years and may reveal the presence of an advanced precancerous lesion from samples sent from the privacy of home. Compared to CS, the most sensitive of all CRC tests, the Cologuard test requires no bowel preparation, dietary changes, or sedation.
Effectiveness of the Cologuard test was established in a clinical trial that screened 10,023 asymptomatic adults between 50 and 84 years of age. The trial compared the Cologuard test to FIT. The sensitivity for detecting CRC using the DNA test and the FIT test was found to be 92.3% and 73.8% ($p=0.002$) respectively. For advanced precancerous lesions sensitivity of the DNA test was 42.4% and for FIT was 23.8% ($p<0.001$). Although with lower specificity, DNA testing had a 27% relative increase in the detection rate of stage I–III CRC and a 78% relative increase in advanced precancerous lesions compared to FIT (Imperiale et al, 2014). However, a positive result with either test should be followed by a diagnostic CS.

2.1.3 Blood-based Methods

2.1.3.1 Epi proColon

The FDA approved Epi proColon, the first blood test for CRC screening, in April 2016 (FDA, 2016). Epi proColon provides an alternative screening test for the detection of asymptomatic CRC in average-risk adults aged 50–75 years who have refused colonoscopy. The Epi proColon test is a qualitative *in vitro* diagnostic test for the detection of methylated SEPTIN9 (mSEPT9) DNA in plasma derived from patient whole blood specimens.

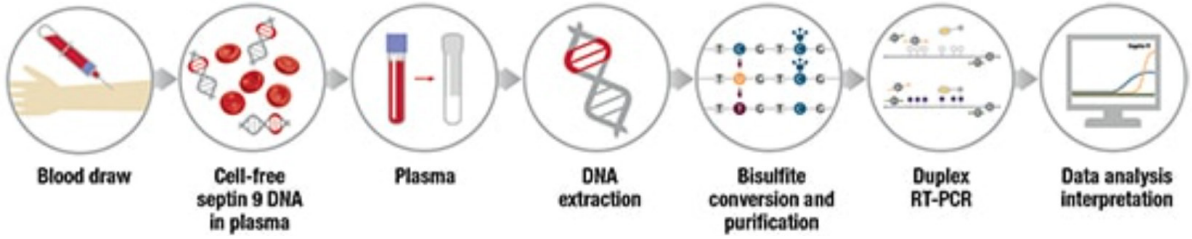
As a normal process, DNA methylation is one of the most commonly occurring epigenetic events and vital components of many genetic processes including gene expression and transcription (Das et al, 2004). Alterations to normal DNA methylation patterns during early carcinogenesis make these events valuable markers for the early detection of cancer (Mikeska et al, 2012; Mikeska et al, 2014). As a highly recognized alteration associated with a variety of human cancers, DNA hypermethylation typically occurs at CpG islands located in the promotor region of a gene, inactivating tumor suppressor genes and silencing transcription (Mikeska et al, 2012; Li et al, 2014; Gyparaki et al, 2013).

The *SEPT9* gene encodes the Septin 9 protein, a member of a highly conserved family of GTP-binding proteins that function in key regulatory and cellular processes (Connolly et al, 2011; Mostowy et al, 2012). Located at chromosome 17q25.3 in human cells, *SEPT9* is the most complex of the 13 septin genes containing 18 distinct transcripts encoding 15 isoforms (Li et al, 2014; Wasserkort et al, 2013). *SEPT9* plays an important role in actin dynamics, angiogenesis, bacterial autophagy, cell motility, cell proliferation, cell shape, cytokinesis, microtubule regulation, vesical targeting and exocytosis (Li et al, 2014; Mostowy et al, 2012; Wasserkort et al, 2013). Abnormal or no expression of the *SEPT9* gene critically affects cytokinesis, a key feature in CRC carcinogenesis (Li et al, 2014; Molnar et al, 2015).

The Epi proColon test is based on the detection of *mSEPT9* as circulating tumor (ct) DNA in plasma using sensitive 'HeavyMethyl' polymerase chain reaction (PCR) technology (deVos et al, 2009). The mSEPT9 test was developed after the discovery of aberrant hypermethylation at an intragenic CpG island within the *SEPT9* gene in ~97% of CRC, whereas methylation was low or absent in normal colorectal mucosa (NCM), peripheral blood lymphocytes (PBL), and other cancer types (Lofton-Day et al, 2008; Wasserkort et al, 2013).

The workflow for the analysis of *mSEPT9* from cell-free plasma DNA has been summarized in Figure 4 below. DNA is isolated from plasma by magnetic particles, then subjected to bisulfite conversion of unmethylated cytosines. In the unmethylated case, a blocker oligonucleotide prevents amplification of the target and the methylation-specific probe binds only to amplified methylated product. The quantitative PCR (qPCR) amplification signal is read and reported as positive or negative.

Figure 4 Epi proColon Workflow



(Potter et al, 2019)

To date, 25 independent trials, mostly case-control or cohort studies, have investigated the diagnostic performance of *SEPT9* gene methylation assay for CRC detection using either research assays or Epi proColon kits (Song et al, 2017). The sensitivity and specificity of the assay were found to be largely dependent on study design, sample size, study population, and type of test (Song et al, 2017).

A meta-analysis of pooled data from diagnostic performance studies of the mSEPT9 test in average-risk populations showed sensitivity to detect CRC (stages I–IV pooled) was 78% and specificity was 84% (Song et al, 2017). In a prospective study, population sensitivity for CRC was 68.0% (95% Confidence Interval (CI) 53% to 80%) and specificity was 80.0% (95% CI 78% to 82%) (Potter et al, 2014). In a case-control study that compared the accuracy of the plasma mSEPT9 test with the FIT test in paired samples from the same people, sensitivity to detect CRC was marginally superior for mSEPT9 at 72.2% (95% CI 63% to 80%) than for FIT at 68.0% (95% CI 58% to 77%). However, specificity at 80.8% (95% CI 75% to 86%) was inferior to FIT at 97.4% (95% CI 94% to 99%) (Johnson et al, 2014). The mSEPT9 test is currently contraindicated for use by those at high risk for CRC, including those with a hereditary cancer predisposition condition since it has not been evaluated in that setting.

2.2 Guidelines

Organizations such as American Cancer Society, United States Multi-Society Task Force on Colorectal Cancer (MSTF), and American College of Radiology (ACR) along with U.S. Preventive Services Task Force (USPSTF), American College of Physicians (ACP), American College of Gastroenterology (ACG) and National Comprehensive Cancer Network (NCCN) have focused on developing guidelines for CRC screening (Bénard et al, 2018). Table 5 lists the current American CRC screening guidelines with their corresponding recommendations.

Table 5 USA Recommendations for CRC Screening

Association Source	Publication Year	Age	Recommendations
ACG (Rex et al, 2009)	2009	≥ 50	Preferred prevention test: Colonoscopy (10 yr) If not possible or refused by individual: FS (5-10 yr) - OR CTC (5 yr) OR detection test Screening starting at age 45 for African American population Preferred detection test: FIT (1 yr) If not possible: Annual gFOBT (Hemoccult Sensa) OR- Fecal DNA testing (3 yr)
American Cancer Society (Wolf et al, 2018)	2018	45-75	FIT (1 yr) OR High□sensitivity, FOBT (1 yr) OR FIT DNA (3 yr) OR Colonoscopy (10 yr) OR CT colonography (5 yr) OR FS (5 yr)
		75-85	Individualize CRC screening decisions
		>85	Discouraged
ACP (Wilt et al, 2015)	2015	50-75	High sensitivity FOBT/FIT (1 year) OR FS (5 years) OR FOBT/FIT (3 yr) + FS (5 yr) OR Colonoscopy (10 yr)
		≥ 75	Screening not recommended
USPSTF (US Preventive Services Task Force, 2016)	2016	50-75	gFOBT/FIT (1 yr) OR FIT-DNA (1-3 yr) OR FS (10 yr) + FIT (1year) OR FS (5 yr) OR colonoscopy (10 yr) OR CT colonoscopy (5 yr)
		76-85	Screening is considered an individual decision
NCCN (NCCN, 2017)	2017	50-75	Colonoscopy (10 years) OR gFOBT/FIT (1 yr) OR Fecal DNA test (3 yr) OR FS (5-10 yr) (+/- gFOTB/FIT at year 3) OR CT colonoscopy (5 yr)
		76-85	Screening should be an individual decision, can be discussed
MSTF (Rex et al, 2017)	2017	50-75	First-tier (preferred tests): Annual FIT OR Colonoscopy (10 yr) Second-tier: CTC (5 yr) OR FIT-fecal DNA testing (3 yr) OR FS (5-10 yr) Third-tier: Capsule colonoscopy (5 yr)
		76-85	Screening should be considered for individuals without prior screening
CRC = Colorectal cancer; FS = Flexible sigmoidoscopy; DCBE = Double contrast barium enema; CTC = CT colonography; FOBT = Fecal occult blood test; gFOBT = Guaiac-based fecal occult blood test; FIT = Fecal immunochemical test; yr = Year			

(Bénard et al, 2018)

In addition to the American guidelines, CRC screening guidelines from other countries and regions have also been published:

- Scotland (SIGN, 2011)
- Germany (GGPO, 2014)
- Spain (Segura et al, 2014)
- Europe (European Colorectal Cancer Screening Guidelines Working Group, 2013; von Karsa et al, 2012)
- South Korea (Lee et al, 2012)
- China (Fang et al, 2014)
- Asia Pacific (Sung et al, 2015)
- Saudi Arabia (Alsanea et al, 2015)
- Canada (Canadian Task Force on Preventive Health Care, 2016)

Most guidelines recommend starting CRC screening for average-risk individuals at age 45 to 50. This is based on the steep increase of CRC beginning around age 50. Many guidelines recommend an upper age screening threshold varying from age 70 to 75, based on associated harms potentially exceeding benefits if screening is continued after that point. All guidelines have considered gFOBT, FIT, FS, and CS as mainstays of CRC screening (Bénard et al, 2018).

Epi proColon, the newest of the screening tests, has only begun to be included in CRC screening guidelines. The new 2020 NCCN guidelines have been updated to include the following statement that although the Epi proColon mSEPT9 blood test is "not recommended for routine screening" it "can be considered for patients who refuse other screening modalities".

2.3 Adherence and Preference

According to the National Health Interview Survey (NHIS), CRC screening in accordance with guidelines increased rapidly among adults ages 50 and older from 2000 (38%) to 2010 (59%), but has increased more slowly over the past decade, topping out at 68% in 2018. Since screening adherence has a large effect on outcomes it is important to understand factors that affect adherence.

Table 6 lists the one-time CRC screening adherence levels for the various screening methods (D'Andrea et al, 2019). For imaging-based methods adherence ranged from 22% for CTC to 38% for CS. For the stool-based methods adherence ranged from 33.4% for gFOBT to 42.6% for FIT. No value was provided for Cologuard but it is assumed to be similar to FIT. The blood-based Epi proColon method was estimated to have the highest adherence levels of all the methods at 85%. This estimate is based on two studies by Adler et al (2014) and Liles et al (2017) which have been described in more detail below.

Table 6 One-time Adherence to CRC Screening Methods

Method	Adherence % (Range)	Literature Reference
Imaging-based Methods		
CS	38 (25 to 55)	Singal et al, 2017
CTC	22 ± 10%	Khalid-de Bakker et al 2011
FS	35 (34.3 to 35)	Khalid-de Bakker et al, 2011
Stool-based Methods		
FIT	42.6 ± 10%	Akram et al, 2017 Jensen et al, 2016

gFOBT	33.4 ± 10%	Akram et al, 2017
Cologuard	42.6 ± 10%	Assumption D'Andrea et al, 2019
Blood-based Methods		
Epi proColon	85 ± 10%	Adler et al, 2014 Liles et al, 2017
CS = Colonoscopy; CTC = Computed Tomographic Colonography; FIT = Fecal Immunochemical Test; FS = Flexible Sigmoidoscopy; gFOBT = High-sensitivity Guaiac-based Fecal Occult Blood Test		

(Modified from D'Andrea et al, 2019)

In the Adler et al (2014) study, they assessed German patients' willingness to use non-invasive stool- or blood-based screening tests after refusing CS. In the study, subjects were recruited during regular consultations and were advised to undergo screening by CS. Subjects who refused CS were offered a choice of non-invasive tests, stool-based or blood-based. Subjects who selected stool-based testing received a collection kit and instructions; subjects who selected blood-based testing had blood drawn during the office visit. Stool samples were tested with the Hb/Hp Complex Elisa test, and blood samples were tested with the Epi proColon® 2.0 test. Patients who tested positive using either test method were advised to have a diagnostic CS.

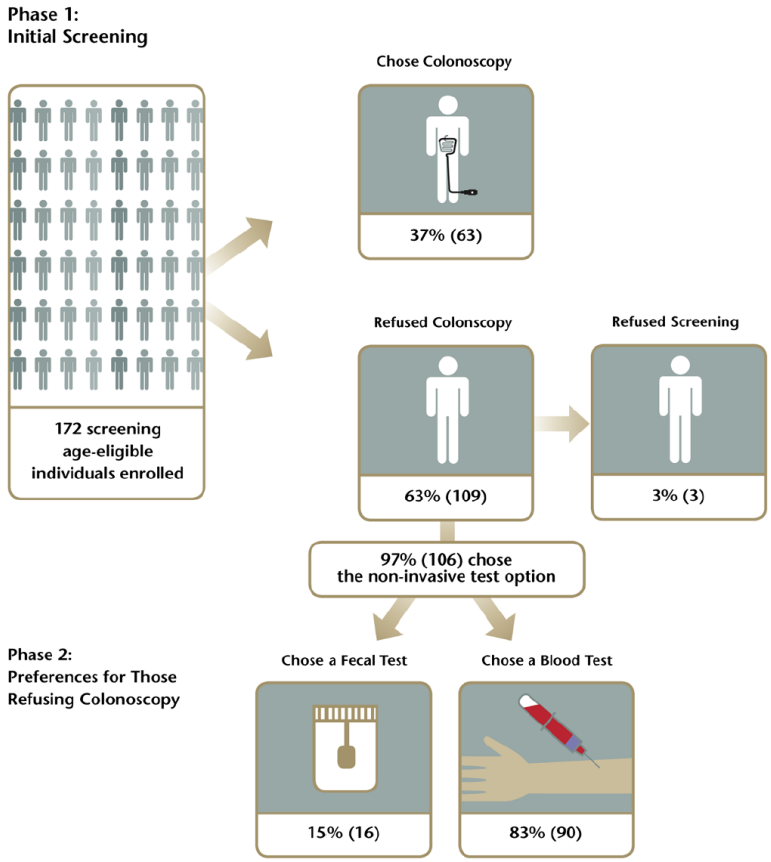
Of the patients enrolled in the study, 63 of 172 subjects were compliant with CS screening (37%). Of the subjects who refused CS, 97% accepted a non-invasive method (106 of the 109). Ninety patients selected the Epi proColon blood test (83%) while 16 selected a stool test (15%). The remaining three subjects refused any test (3%) (Figure 5).

The top three reasons the patients gave for rejecting CS included:
- Being uncomfortable with the bowel preparation (54%),
- Fear of CRC itself (44%) and
- Fear that CS would be painful (32%).

These results were corroborated in a follow-up question asking what would convince subjects to be screened by CS:
- 38% indicated improved bowel preparation,
- 29% indicated cancer prevention by polypectomy and
- 24% indicated that overcoming fears would change their minds.

In addition, when asked why they chose one of the screening tests, 78% and 81% of subjects who had a blood and stool test respectively, indicated ease of getting the test. For those choosing the blood test, primary reasons for not choosing the stool test related to being uncomfortable with specimen handling. For those choosing the stool test, the primary reason related to having used a stool test in the past.

Figure 5 Compliance with CRC Screening



(Adler et al, 2014)

The Liles et al, (2017) study was a small two-site randomized controlled trial (ClinicalTrials.gov, ID NCT02251782) which assigned 413 average-risk adults overdue for screening to one of two arms: o□er of a stool-based FIT versus o□er of a blood-based Epi proColon test for CRC screening. The primary outcome was completion of the o□ered test within six weeks. Secondary outcomes were the proportion of participants with positive test results, and the proportion of participants with positive results who completed CS within 3 months of referral. The results of the study were as follows, 99.5% (95% CI: 97.3%-100%) of participants in the blood test arm and 88.1% (95% CI: 83.0% – 91.8%) of participants in the FIT arm completed the o□ered test, a di□erence of 11.4% (95% CI: 6.9% – 15.9%, p<.001). 16.5% of participants in the blood test arm and 1.7% of participants in the FIT arm had a positive test result. 20 of 30 and 2 of 3 in the blood test and FIT arms, respectively, either scheduled or completed a CS within three months of the positive test result (Table 7).

Table 7 Subject CRC Screening Adherence

Adherence	Epi proColon Test	FIT Test
Yes	202	185
No	1	25
Adherence Rate (95% CI)	99.5% (97.3-100%)	88.1% (83.0% – 91.8%)
Positive Test	16.5%	1.7%
Scheduled CS	20 out of 30	2 out of 3
CI = Confidence Interval; CS = Colonoscopy; FIT = Fecal Immunochemical Test		

(Liles et al, 2017)

2.4 Sensitivity and Specificity

The sensitivity (true positive rate) and specificity (true negative rate) of CRC screening methods indicate the likelihood of false-negative and false-positive results occurring. This is important because false negative results may appear to be normal even though CRC is present and a person who receives a false-negative test result may delay seeking medical care even if there are symptoms. A false-positive result may appear to be abnormal even though no cancer is present. A false-positive test result can cause anxiety and is usually followed by more tests (such as biopsy), which have risks.

The sensitivity and specificity of the various CRC screening methods have been summarized in Table 8. The specificity for the various methods were all similar, ranging from 80% for Epi proColon to 96.4% for FIT. There were, however, significant differences in the sensitivity of the various methods. The imaging-based methods were much better at identifying non-advanced and advance adenomas as well as cancer compared to the stool- and blood-based methods. The stool- and blood-based methods had a similar sensitivity, ranging from 7.5% to 20% for non-adenomas, 12.4% to 42.4% for advanced adenomas and 68% to 92.3% for cancer (D'Andrea et al, 2019).

Table 8 Analytical Characteristics of CRC Screening Methods

Method	Specificity %	Sensitivity		
		Non-advanced Adenomas %	Advanced Adenomas %	Cancer %
Imaging-based Methods				
CS (per lesion)	86	75 (70-79)	85 (80-92)	95 (93.1-99.5)
CTC (per person)	88	57 (48.9-71.6)	84 (75.6-92.4)	84 (75.6-92.4)
FS (per distal lesion)	87	75 (70-79)	85 (80-92)	95 (93.1-99.5)
Stool-based Methods				
FIT (per person)	96.4	7.6 (6.7-8.6)	23.8 (20.8-27)	73.8 (62.3-83.3)
gFOBT (per person)	92.5	7.5	12.4 (10-26.2)	70 (61.5-79.4)
Cologuard (per person)	89.9	17.2 (15.9-18.6)	42.4 (38.7-46.2)	92.3 (84-97)
Blood-based Methods				
Epi proColon	80.0	20 (15-23)	22 (18-24)	68 (53-80)
CS = Colonoscopy; CTC = Computed Tomographic Colonography; FIT = Fecal Immunochemical Test; FS = Flexible Sigmoidoscopy; gFOBT = High-sensitivity Guaiac-based Fecal Occult Blood Test				

(modified from D'Andrea et al, 2019)

Despite the high accuracy of CS and FS, their acceptance rates remain low due to their bothersome bowel preparation, invasiveness and potential for complications (Niu et al., 2017).

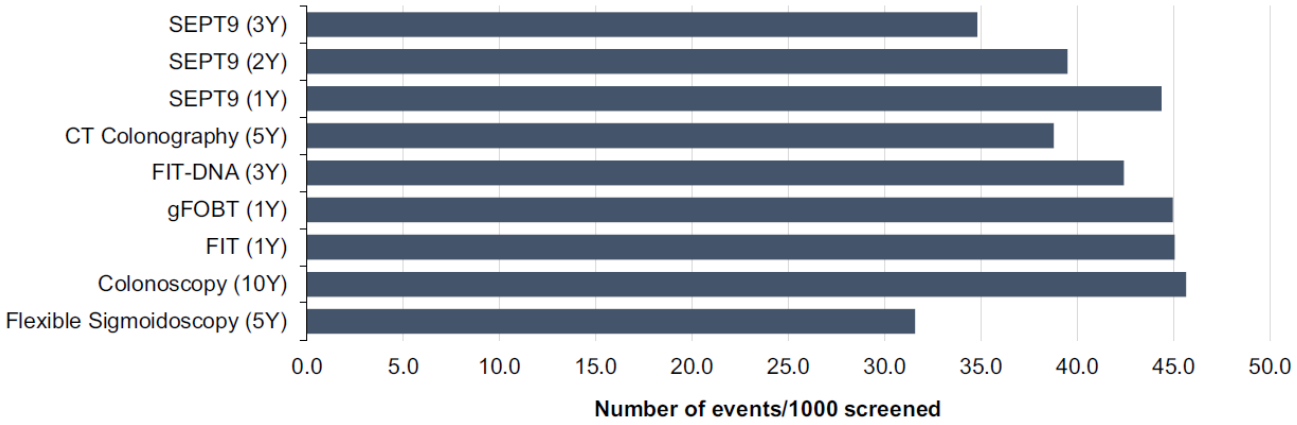
2.5 Incidence and Mortality

D'Andrea et al (2019) developed and validated a microsimulation model to assess the effectiveness of CS, FS, CTC, FIT, HS-gFOBT, Cologuard, and Epi proColon in terms of CRC incidence and mortality, for men and women 50 years or older. The outcomes were assessed under two conditions:

- 100% adherence rates
- Reported adherence rates (see Table 6)

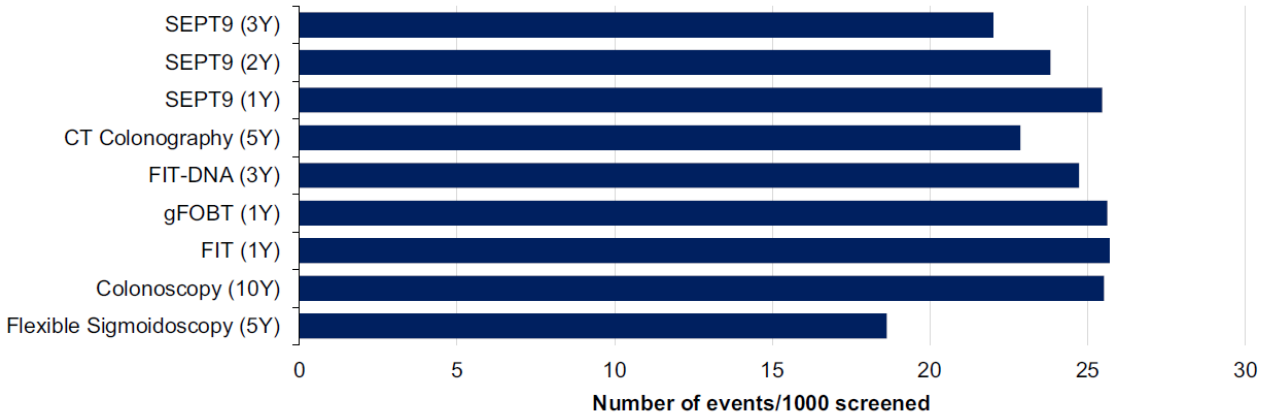
Under the ideal conditions of "100% adherence", screening with annual stool- or blood-based (Epi ProColon) tests produce comparable benefits (cases and deaths averted) to screening with CS every ten years (Figure 6, Figure 7 and Table 9).

Figure 6 CRC Cases Averted per 1000 Screened (Full Adherence)



(D'Andrea et al, 2019)

Figure 7 CRC Deaths Averted per 1000 Screened (Full Adherence)



(D'Andrea et al, 2019)

Table 9 Cases and Deaths Averted Assuming 100% Adherence to CRC Screening Methods

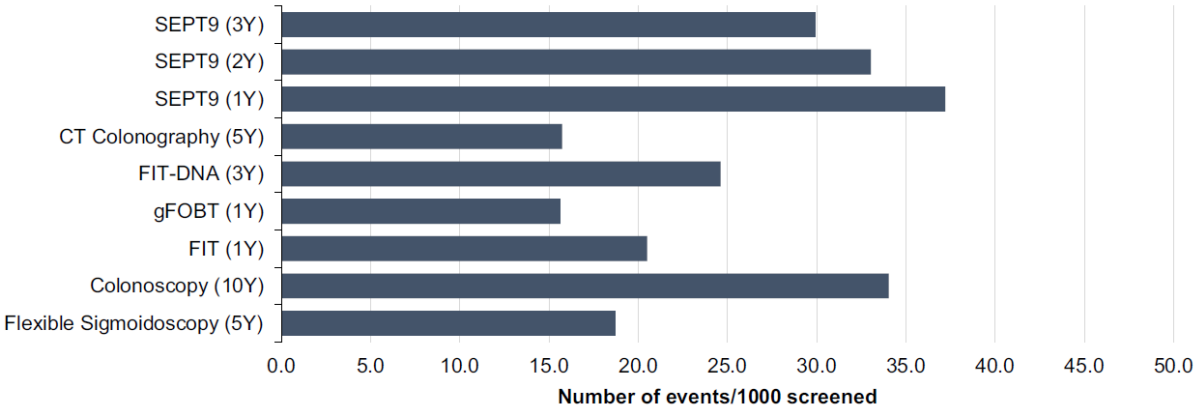
Method	Cases Averted per 1000 Individuals	Deaths Averted per 1000 Individuals
Imaging-based Methods		
CS (every 10 years)	46	26
CTC (every 5 years)	39	23
FS (every 5 years)	32	19
Stool-based Methods		

FIT (every year)	42-45	25-26
gFOBT (every year)	42-45	25-26
Cologuard (every 3 years)	42-45	25-26
Blood-based Methods		
Epi proColon (every year)	42-45	25-26
CS = Colonoscopy; CTC = Computed Tomographic Colonography; FIT = Fecal Immunochemical Test; FS = Flexible Sigmoidoscopy; gFOBT = High-sensitivity Guaiac-based Fecal Occult Blood Test		

(modified from D'Andrea et al, 2019)

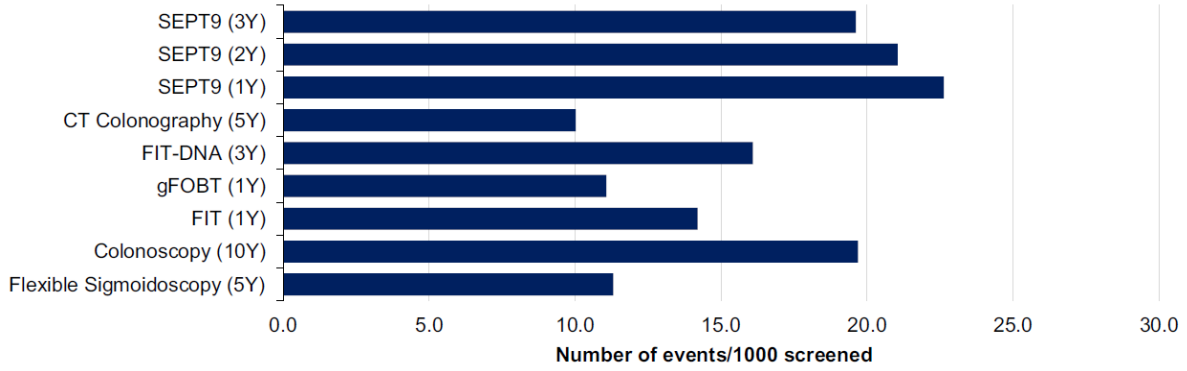
Although stool- and blood-based tests have a substantially lower one-time sensitivity compared to CS, the frequent testing and shorter test interval increases the overall probability of cancer detection over time. Under "reported adherence" conditions, screening annually with Epi ProColon produced comparable benefits to screening with CS every ten years. In addition, screening with CS and Epi proColon averted more cases and deaths compared to the other screening methods (Figure 8, Figure 9 and Table 10).

Figure 8 CRC Cases Averted per 1000 Screened (Reported Adherence)



(D'Andrea et al, 2019)

Figure 9 CRC Deaths Averted per 1000 Screened (Reported Adherence)



(D'Andrea et al, 2019)

Table 10 Cases and Deaths Averted Assuming Reported Adherence to CRC Screening Methods

Method	Cases Averted per 1000 Individuals	Deaths Averted per 1000 Individuals
Imaging-based Methods		
CS (every 10 years)	34	20
CTC (every 5 years)	16-25	11-16
FS (every 5 years)	16-25	11-16
Stool-based Methods		
FIT (every year)	16-25	11-16
gFOBT (every year)	16-25	11-16
Cologuard (every 3 years)	16-25	11-16
Blood-based Methods		
Epi proColon (every year)	37	23
CS = Colonoscopy; CTC = Computed Tomographic Colonography; FIT = Fecal Immunochemical Test; FS = Flexible Sigmoidoscopy; gFOBT = High-sensitivity Guaiac-based Fecal Occult Blood Test		

(modified from D'Andrea et al, 2019)

The findings from this study suggest that adherence rates higher than 65-70% are required for any stool- or blood-based screening method to achieve the benefits similar to CS.

2.6 Benefits and Limitations

Like all screening tests, CS has limitations and potential harms. For example, it can lead to unnecessary procedures, such as the removal of small polyps that would not have progressed to cancer (Levin et al, 2008). A recent study found that although >90% of polyps can be safely removed during CS, elective surgery to remove non-malignant polyps, which has a higher risk of harms, increased by more than 50% from 2000 to 2014 (Peery et al, 2018). Other limitations of CS include a higher risk of complications compared to other screening tests, such as bowel tears and bleeding, especially when a polyp is removed or patients are older (Levin et al, 2008; Peery et al, 2018).

Although side effects are rare, serious bleeding occurs in 1 to 2 of every 1,000 colonoscopies (Bretthauer et al, 2016; Ko et al, 2010; Quintero et al, 2012). In addition, CS sometimes misses adenomas, especially those that are located in the proximal colon; those that occur in high-risk patients; and those that are flat (sessile adenomas), from which 20% to 30% of CRCs are thought to originate (Lieberman et al, 2016; Zhao et al, 2019). The quality of CS, which is variable in the US, is also associated with missed lesions, which sometimes progress to CRC before the next scheduled exam (i.e., interval cancer) (Meester et al, 2015; Corley et al, 2014). Low-quality CS (measured as low adenoma detection rate) is associated with a higher likelihood of interval CRC and CRC death (Corley et al, 2014).

The overall benefits and limitations of the various CRC screening methods have been summarized in Table 11.

Table 11 Benefits and Limitations of CRC Screening Methods

Testing Method	Benefits	Limitations	Testing Interval
Imaging-based Methods			
CS	- Examines entire colon - Can biopsy and remove polyps, Can diagnose other diseases - Required for abnormal results from all other tests	- Full bowel cleansing - Expensive - Sedation required - Patient may miss a day at work - Risk of bowel tears or infection	10 years
CTC	- Examines entire colon - Fairly quick - Few complications - No sedation required - Non-invasive	- Full bowel cleansing - Cannot remove polyps or perform biopsies - Exposure to low dose radiation - CS necessary if result positive - Not covered by all insurance plans	5 years
FS	- Fairly quick - Few complications - Minimal bowel preparation - No sedation required	- Partial bowel cleaning - Views 1/3 of colon - Cannot remove large polyps - CS necessary if result positive - Limited availability	5 years
Stool-based Methods			
FIT	- No bowel cleansing - No sedation - Performed at home - Low cost - Non-invasive	- Requires multiple stool samples - Will miss most polyps - May produce false-positive results - More effective when combined with FS - CS necessary if result positive	Annual
gFOBT	- No bowel cleansing - No sedation - Performed at home - Low cost - Non-invasive	- Requires multiple stool samples - Will miss most polyps - May produce false-positive results - Pre-test dietary limitations - More effective when combined with FS - CS necessary if result positive	Annual
Cologuard	- No bowel cleansing - No sedation - Performed at home - Single stool sample required, Non-invasive	- Will miss most polyps - May produce false-positive results - Higher cost than gFOBT and FIT - CS necessary if result positive	3 years
Blood-based Method			
Epi ProColon	- No bowel cleansing - No sedation - Non-invasive - Single blood sample at doctor's office	- Will miss most polyps - May produce false-positive results - Higher cost than gFOBT and FIT - CS necessary if result positive	Annual
CS = Colonoscopy; CTC = Computed Tomographic Colonography; FIT = Fecal Immunochemical Test; FS = Flexible Sigmoidoscopy; gFOBT = High-sensitivity Guaiac-based Fecal Occult Blood Test			

(modified from American Cancer Society, Colorectal Cancer Facts & Figures 2020-2022)

2.7 Costs and Reimbursement

To estimate the cost and clinical implications to health plans, including the clinical and fiscal implications of the use of blood-based screening with Epi proColon, FIT, and Cologuard, Roth et al (2019) developed a simulation model to project the 3-year aggregate health outcomes and costs for CRC screening among average-risk persons who are eligible for screening according to the USPSTF recommendations (age 50-75 years) and were not screened previously. They focused on the 50- to 64-year-old screening-eligible population because of its relevance to commercial insurers and because this population had the largest screening gap. They determined that assuming all non-invasive strategies could be applied to improve CRC screening adherence from 65% to 80% participation over 3 years, the analysis estimates the health plan cost and outcomes of each strategy. Epi proColon and FIT achieved similar 3-year outcomes in terms of the number of CRC cases detected (221 and 216 cases, respectively); with Cologuard detecting fewer cases (193 cases) (Table 12).

Table 12 Three-Year Clinical Impact of Using Blood- and Fecal-Based CRC Testing

Screening Approach	CRC Detected (N)	Advanced Adenomas Detected (N)	Nonadvanced Adenomas Detected (N)
Status quo	49	0	0
+15% with Epi proColon	221	609	1115
+ 15% with FIT	216	305	1117
+ 15% with Cologuard	193	830	1233
FIT = fecal immunochemical testing; N = Number			

(Roth et al, 2019)

Including the costs of screening, diagnostic testing, and treatment, the per-member per-month (PMPM) impact versus status quo costs was highest for Epi proColon ($1.08), followed by Cologuard ($0.98) and FIT ($0.71) (Table 13), suggesting a modest trade-off between cost and the number of cases detected among the screening strategies. Considering only the costs of screening and diagnosis, the costs for Epi proColon and Cologuard were almost the same ($0.67 and $0.69, respectively) and the cost for FIT was lower ($0.33).

Table 13 Three-Year Economic Impact of Using Blood- and Fecal-Based CRC Testing

Screening Approach	Screening ($)	Diagnostic	PMPM Cost Impact ($)	With Treatment ($)	Total ($)	PMPM Cost Impact ($)
Status quo	-	82,988	reference	5,401,433	5,484,430	-
+15% with Epi proColon	13,564,454	10,663,312	0.67	20,007,434	44,235,199	1.08
+ 15% with FIT	6,563,367	5,428,210	0.33	19,031,752	31,023,328	0.71
+ 15% with Cologuard	17,919,163	6,864,433	0.69	15,890,785	40,674,381	0.98

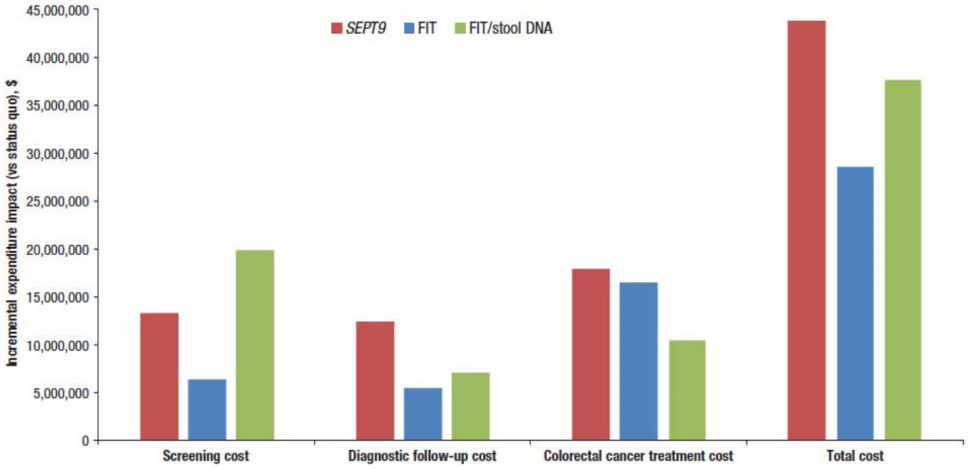
FIT = fecal immunochemical testing; PMPM = per-member per-month impact versus status quo			

(Roth et al, 2019)

The cost associated with blood-based screening with Epi proColon (Current Procedural Terminology [CPT] code 81327, $192) was based on pricing from the Centers for Medicare & Medicaid Services (CMS). The cost of stool-based CRC screening was based on the 2018 CMS reimbursement for FIT (CPT code 82274, $19.64). The cost of Cologuard testing was based on published CMS reimbursement (CPT code 81528, $508.87). The calculations assume that the full cost of the blood- and stool-based screening tests for CRC will be covered by insurers (without cost-sharing) in accordance with the terms of the Affordable Care Act (ACA) regarding the coverage of screening tests with USPSTF grade A ratings (HealthCare.gov) and the CMS national coverage determination for CRC screening (US Preventive Services Task Force, 2016) (Roth et al, 2019).

As illustrated in Figure 10, the costs for screening, diagnosis, and treatments varied for each screening strategy. For Epi proColon and FIT, the screening and diagnostic costs were relatively similar. For Cologuard, the screening costs were higher than diagnostic costs and were similar to the treatment costs.

Figure 10 Direct Medical Cost Expenditures with Blood- and Fecal-based CRC Screening Methods



(Roth et al, 2019)

The Affordable Care Act requires both private insurers and Medicare to cover the costs of CRC screening tests, because these tests are recommended by the United States Preventive Services Task Force. The law stipulates that there should be no out-of-pocket costs for patients, such as co-pays or deductibles, for these screening tests. The ACA doesn't apply to health plans that were in place before it was passed in 2010, which are called "grandfathered plans."

Colonoscopy is covered without cost-sharing for people with Medicare insurance and most commercial insurance plans. However, the required follow-up CS for a positive stool test is often coded as a diagnostic procedure, resulting in out-of-pocket costs for patients. In addition, Medicare still imposes cost-sharing on beneficiaries who have a polyp removed during a screening CS. This has undermined efforts to improve CRC screening, particularly among low-income patients who are at the highest risk for CRC (Doubeni et al, 2016).

Medicare covers the following tests, generally starting at age 50:

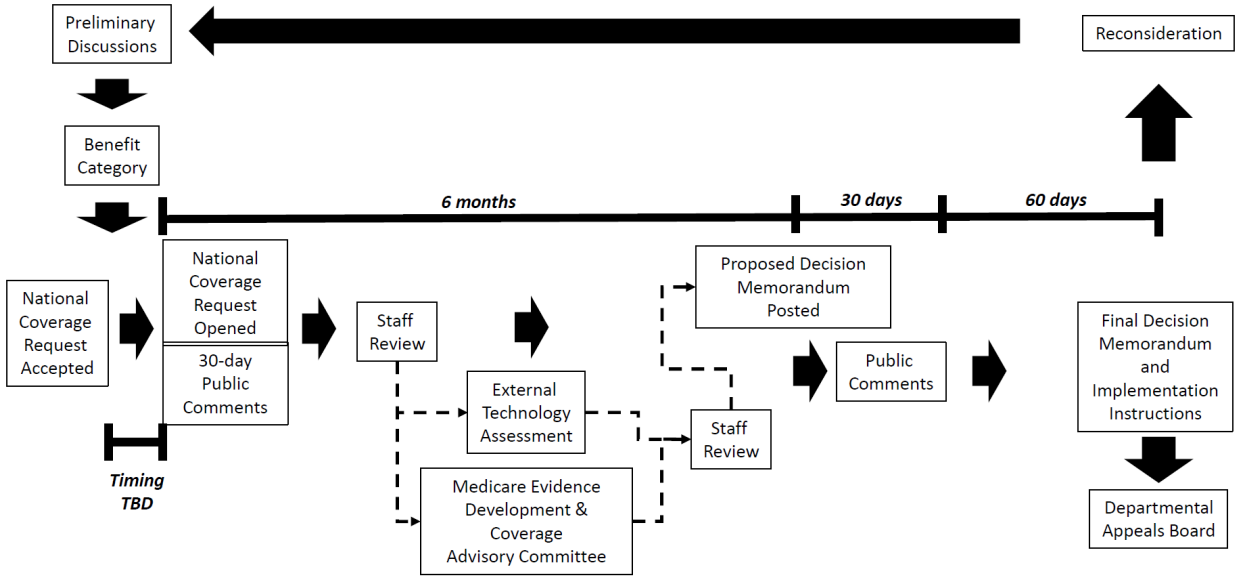
- FOBT or FIT once every 12 months.
- Cologuard every 3 years for people 50 to 85 years old who do not have symptoms of CRC and who do not have an increased risk of CRC.
- FS every 4 years, but not within 10 years of a previous CS.
- Colonoscopy
    - Once every 2 years for those at high risk (regardless of age)
    - Once every 10 years for those who are at average risk

- 4 years after a FS for those who are at average risk

- Double-contrast barium enema if a doctor determines that its screening value is equal to or better than FS or CS:
  - Once every 2 years for those who are at high risk
  - Once every 4 years for those who are at average risk

At this time, Medicare does not cover the cost of CTC or the Epi proColon blood-based test.
Epigenomics is currently navigating the Medicare national coverage determination (NCD) process (Figure 11) to establish Medicare coverage for its Epi proColon test.

Figure 11 Medicare National Coverage Determination Process



The following is a list of the key milestones in the national coverage determination process as well as the current timelines for obtaining Epi proColon Medicare coverage:

- FDA approval – 2016
- CMS sets final price – 2019
- NCD opened – February 28, 2020
- Proposed decision memo – August 28, 2020
- Final decision memo – November 28, 2020
-

A rate of $192 per test has been finalized for Epi proColon and has been fixed for a three-year period (2019-2021).

3 Conclusions

The pathogenetic features of CRC make it one of the most preventable and often curable malignancies. However, disease curability entirely depends on its early detection. The best method for the early detection of CRC is screening.

The US Preventive Services Task Force recommends that adults age 50 to 75 be screened for CRC. There are several recommended methods for CRC screening, including imaging-based methods, which are performed at a health care facility, stool-based methods, which are collected at home and blood-based methods, which are collected at a doctor's office. The decision about which test to use must take into account the following factors:

- The person's age, medical history, family history, and general health
- The potential harms of the test
- The preparation required for the test
- Whether sedation may be needed for the test
- The follow-up care needed after the test
- The convenience of the test
- The cost of the test and the availability of insurance coverage.

There is no single "best test" for any one person. Each test has its own set of advantages and disadvantages. Increasing adherence to screening is critical to improving CRC outcomes. A key component of any screening strategy involves recruiting individuals who have been nonadherent to screening over time. For unscreened individuals who have not received CS, a non-invasive test (blood- or stool-based) may be the best option to reduce the burden of CRC.

Epi proColon has a potential advantage over other methods in that individuals may be more willing to do a blood test than take a stool sample at home. Blood tests can also be completed easily as part of a standard medical office appointment for a wellness check or to take advantage of opportunities to promote screening during scheduled visits to manage chronic illnesses. However, Epi proColon is not covered by Medicare. Epigenomics is currently navigating the Medicare national coverage determination process and is expecting a preliminary decision in August of 2020.

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