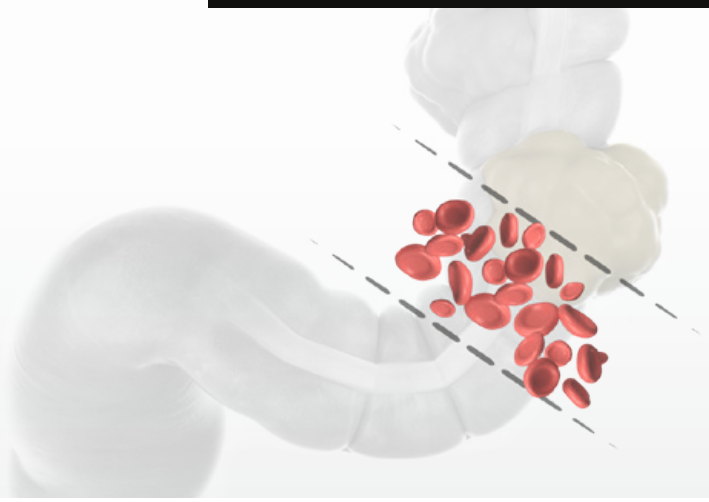


Fecal Occult Blood Testing

Colorectal Cancer Screening

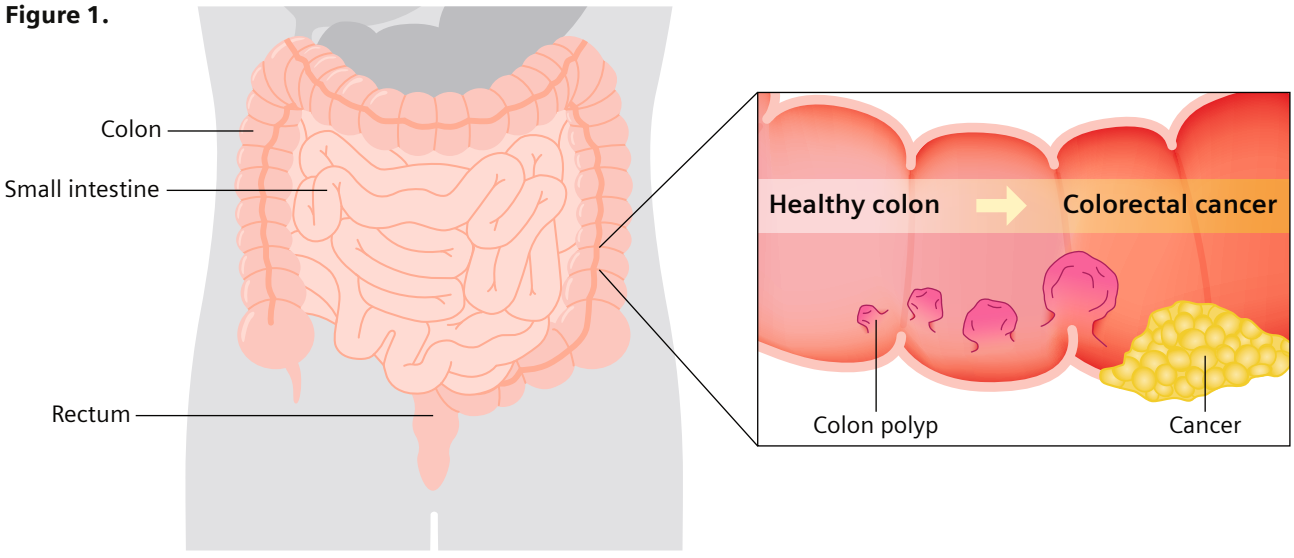
Updated Guidelines and the Power of FIT for Early Detection

Introduction

In 2022, the European Health Union announced a target of 90 percent of the EU population eligible for colorectal cancer (CRC) screenings be offered such testing by 2025.[1] CRC occurs in the tissues of the colon and the rectum (Figure 1) and is the second leading cause of death from cancer in Europe.[2] Early identification is associated with a high rate of treatment success.[3]

Screening programs can lower CRC disease burden, including increased detection and improved outcomes, especially when conducted in targeted populations.[3-5] Data indicate countries with long-standing population screening programs achieve a meaningful reduction in CRC incidence over time.[3]

Figure 1.



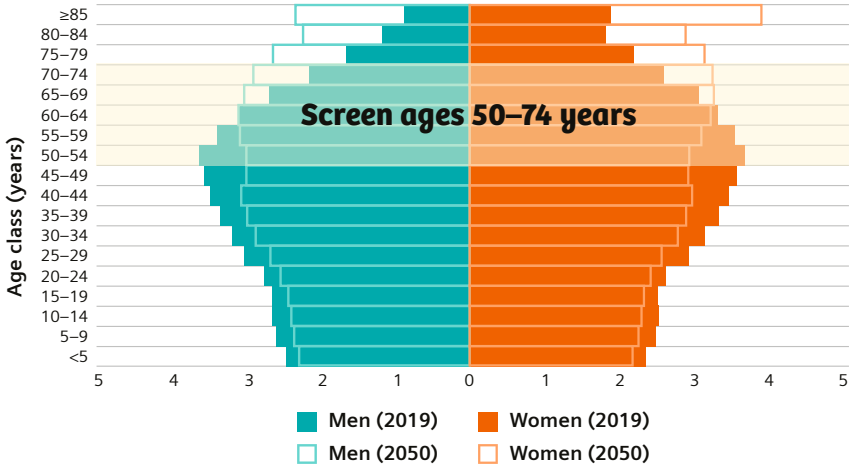
SIEMENS Healthineers

Testing for CRC

Initial testing for CRC typically falls into two categories:

1 Screening targeted to asymptomatic populations (e.g., recommended age-specific testing of 50-74 years).[1,3]

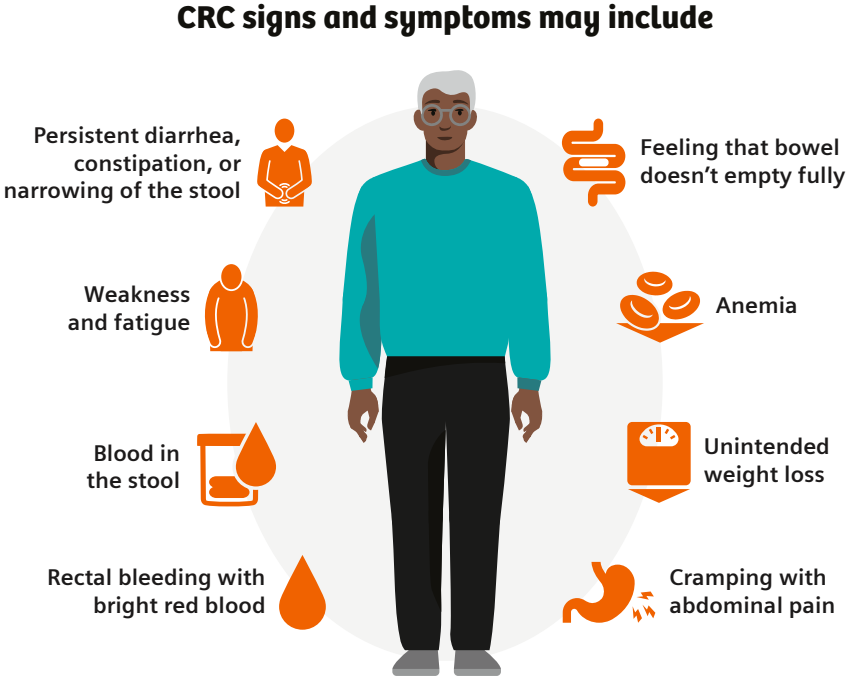
Population pyramids, EU-27, 2019 and 2050
(% share of total population)



Note: all data as of 1 January. 2019: estimates and provisional. 2050: population according to the 2019 projections, baseline variant (EUROPOP2019). Source: Eurostat (online data codes: demo_pjangroup and proj_19np)

Screening in asymptomatic individuals is essential to improved detection, especially as early and more treatable forms often lack signs or symptoms (or may go unrecognized).[7] Currently, the EU recommends CRC screening for all individuals aged 50–74 years[1] in addition to testing for patients who are symptomatic.[6] The large number of tests needed to meet screening targets necessitates assays that are amenable to ease of sample collection for increased uptake and scalable efficient analysis.[5]

2 Testing in a symptomatic patient (signs/symptoms)[6]



Screening methods for CRC

Screening techniques include non-invasive testing or invasive endoscopic procedures (e.g., colonoscopy) (Table 1). Non-invasive faecal tests that detect the presence of hidden (occult) blood in the stool, which could be a sign of bowel cancer or polyps (especially large precancerous polyps), are widely available.[8,9] As blood in the stool is not specific to CRC, positive tests typically reflex to colonoscopy for diagnosis and confirmation.[10]

Colonoscopy is essential to diagnose or exclude cancer or to identify and remove polyps. While colonoscopy also performs well as a screening test, it has several limitations for use in a high-volume testing population.[12]

Table 1. Common methods for CRC screening.[11]

Screening methods include	Type	Benefits/limitations
Guaiac faecal occult blood tests (gFOB)	Non-invasive (requires multiple stool samples–typically three). Qualitative detection of blood in the stool. Positive samples reflex for diagnostic testing (e.g., colonoscopy).[9]	Benefits include no need for bowel prep. Limitations include need for multiple stool collections (typically three) and cross-reactivity to non-human haem and other components in food and medicine, necessitating dietary restrictions prior to sample collections. Assays are not quantitative and most require subjective interpretation (positive or negative) and can be less sensitive compared to other methods.[9,13] Other limitations include reduced sensitivity compared to colonoscopy and reduced detection of advanced polyps.
Faecal immunochemical testing (FIT)	Non-invasive (single stool sample for most assays) Detects blood in stool. Can be qualitative or quantitative. Positive samples reflex for diagnostic testing (e.g., colonoscopy).[9]	Benefits include no bowel prep required and use of a single stool sample collection. Specific for human haem so no dietary restrictions for testing. Data supports improved detection vs. gFOB.[11,13] Reactive rates may be higher compared to gFOB testing and have been associated with increased sensitivity. Multiple FIT assays are quantitative, supporting objective interpretation and application of an optimized threshold in the target testing population.[13,14] Limitations include reduced sensitivity compared to colonoscopy and reduced detection of advanced polyps.
Colonoscopy	Invasive (endoscopic). Can visualize polyps and CRC. Considered the leading standard for diagnosis and an important follow up for positive screens.[9,10]	Benefit includes leading performance for screening and/or diagnosis.[9] Limitations include risks such as bleeding or bowel perforation; bowel prep and sedation are required.[12] The number of procedures that can be performed is limited relative to the number of tests needed and can be associated with long wait times. Patient challenges can include insufficient bowel prep that may hinder accuracy, reticence to undergo the procedure, or limited access to sites performing colonoscopies.

Most commonly recommended/preferred[1,11]

Continued on next page

Continued from previous page

Table 1. Common methods for CRC screening.[11]

Screening methods include	Type	Benefits/limitations
CT colonography ("virtual colonoscopy")	Non-invasive. May not be as sensitive or specific as colonoscopy.[15]	Benefits include minimal risk for bleeding or procedure-related damage and reduced prep compared to colonoscopy. Limitations include radiation exposure and use of an oral contrast agent is typically required. Positive results typically reflex to colonoscopy for diagnosis and confirmation.
Flexible sigmoidoscopy	Considered less invasive than colonoscopy but doesn't visualize the entire colon (principally the rectum and lower colon).	Benefits include reliable performance for detection of CRC and or polyps in the lower portion of the colon and typically requires less bowel prep versus colonoscopy. Limitations include that it can miss some cancers detected by colonoscopy, especially in the upper colon. Positive findings may require a follow-up colonoscopy. Patient access, limited number of procedures, and wait times for the procedure (may be similar to colonoscopy) can challenge use as a screening test.
sDNA-FIT (e.g., "Cologuard")[16]	Non-invasive (stool sample). Detects blood in stool and/or altered DNA that may indicate CRC.	Benefits include use of a single stool sample and detection for both occult blood and abnormal DNA that may link to cancer. Limitations include need for a follow-up colonoscopy with positive results and limited availability of the test in many countries (current use principally limited to the U.S.).

Healthcare economic impact of screening

Prevention or early treatment of CRC is projected to have a substantial impact on healthcare costs.[17-20] Early treatment of CRC is typically less costly while offering an improved quality of life and reducing deaths from CRC. In Europe, the estimated yearly economic burden of colon cancer is >19 billion euros, including ~ten-fold average increase in the cost of treating late vs. early-stage CRC.[18]

Broad uptake of screening recommendations could increase the percent of early cases diagnosed, saving an estimated 130,000 more lives, and producing 3 billion in healthcare savings each year.[19] While testing frequency can impact costs, analysis indicates that even frequent (yearly) screening for CRC could be cost-effective and save more lives throughout Europe if widely implemented in targeted populations.[20]

The European Health Union has specifically identified FIT as the preferred methodology for CRC screening.[1]

The 2022 EU approach recommends FIT as the preferred screening test to improve early detection of colorectal cancer for individuals between 50 and 74 years old.[1]

Multiple European countries have existing population-based CRC screening programs, with many designating FIT as the recommended non-invasive test (some include gFOB), with follow-up colonoscopy for positive tests.[21] Suggested testing frequency can vary by country, often every two years in the targeted asymptomatic population.[21]

FIT's advantages for screening include a high-negative predictive value, good sensitivity, patient uptake (noninvasive, single stool sample), superior performance to gFOB, and the ability to support large testing numbers.[5,13,14]

While screening for CRC in Europe is on the rise, only a few countries show the majority of the eligible population achieving screening targets.[21] Increasing awareness of the FIT test as the preferred screening assay is anticipated to improve utilization as it is noninvasive, widely available, and performs well to differentiate higher risk individuals to prioritize for referral to colonoscopy.

"Throughout the world, the most used approach for colorectal cancer screening is the faecal immunochemical test (FIT)."[11]

Faecal Immunochemical Test (FIT) versus Guaiac faecal occult blood tests (gFOB)

Older guaiac faecal occult blood tests (gFOB) have historically been used and remain in use in some settings. However, these assays have been criticized for lower sensitivity and a requirement for multiple stool collections (typically three).[13,25] False-positive results associated with non-human haem or peroxidase in food occur, necessitating dietary restrictions for accurate results. Some medicines should be discontinued prior to use.[13,14] Typical gFOB tests require a subjective interpretation (e.g., change of color on card with sample). gFOB testing produces a binary (qualitative) result (positive or negative) for the detection of hemoglobin in the stool.[22]

FIT avoids many of the gFOB limitations.

Unlike gFOB's, FIT assays are specific for human haem, have no dietary restrictions, and most require only a single stool sample and can be objectively analyzed directly from the sample collection tube. Data show improved performance for FIT, especially for sensitivity, when compared to gFOB.[13,14,22,25] Many screening programs worldwide are converting from gFOBT-to-FIT-based testing.[13,21] Commonly used FIT assays are quantitative, allowing customization of the positivity threshold (although quantitation is not standardized among manufacturers, so are typically assay-specific).[13]

NEW! Simplified collection and fully automated high throughput testing with the Atellica CH Sentinel FIT Alliance Application

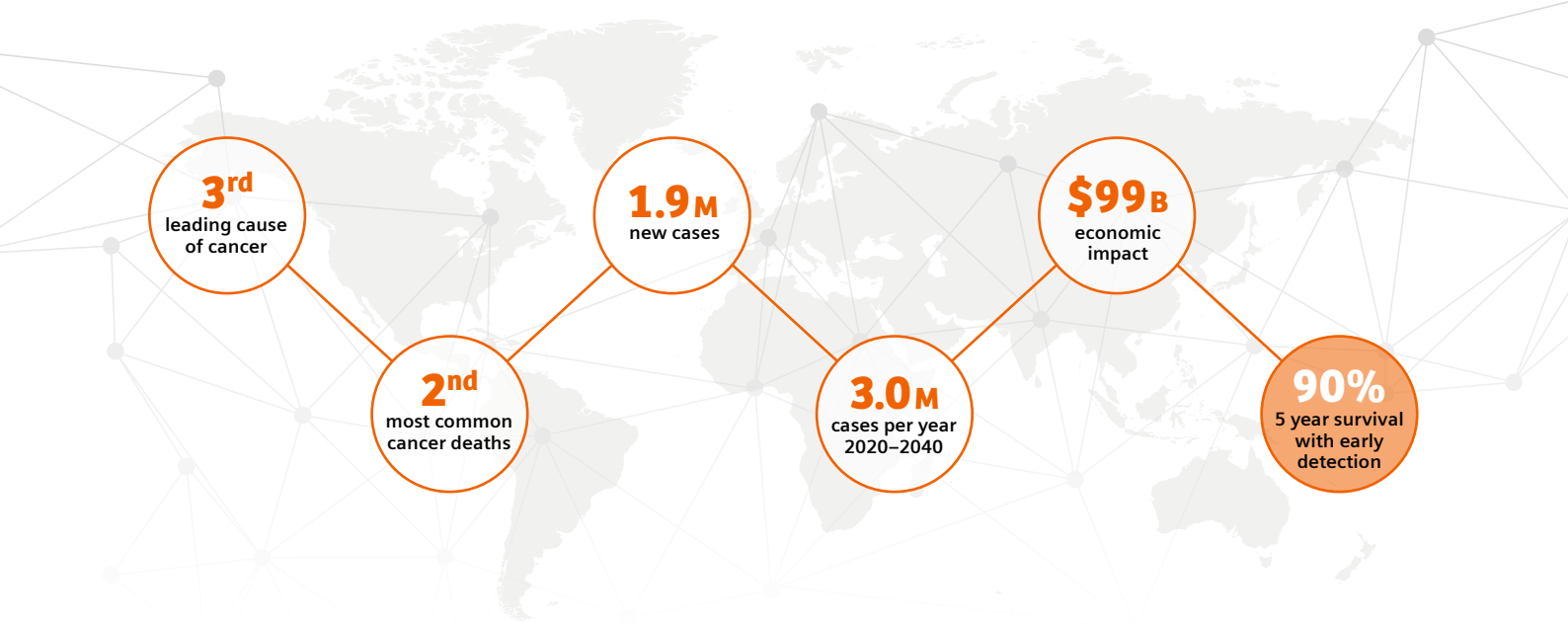
While non-invasive, barriers to both gFOB and FIT testing can include the requirement for a stool sample collection, as well as concerns associated with laboratory operator exposure to the faecal material (especially when manually decapping). While FIT testing has generally simplified collection compared to gFOB, methodology (sample tube and testing modality) can vary between manufacturers.

> **Now, through an alliance with SENTINEL Diagnostics and Siemens Healthineers, FIT samples can be readily collected by the patient using the Sentinel Diagnostics FOB Gold® Tube Screen and analyzed on the Atellica CH 930 Analyzer or fully automated with decapping on the Atellica Solution with Atellica Integrated Automation.[23]**

Operator exposure to the sample is minimized through the programmed auto-decapping of the Sentinel Diagnostics FOB Gold Tube Screen. This partnership mitigates many of the drawbacks associated with a user-defined method, as the Sentinel FIT alliance application on the Atellica CH 930 analyzer is fully validated and supported by Siemens Healthineers.

Use of an existing **Atellica Solution with Atellica Integrated Automation** eliminates the need for additional specialized equipment, minimizes operator risk of sample exposure, and fully integrates automated FIT testing into routine chemistry workflow.

Colorectal Cancer (CRC) overview



Bray F, et al. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin 2018;68:394–424. doi:10.3322/caac.21492. American Cancer Society/cancer.org – Colorectal Cancer Early Detection, Diagnosis, and Staging
International Agency for Research on Cancer (IARC/WHO) 2023, Colorectal cancer awareness 2023

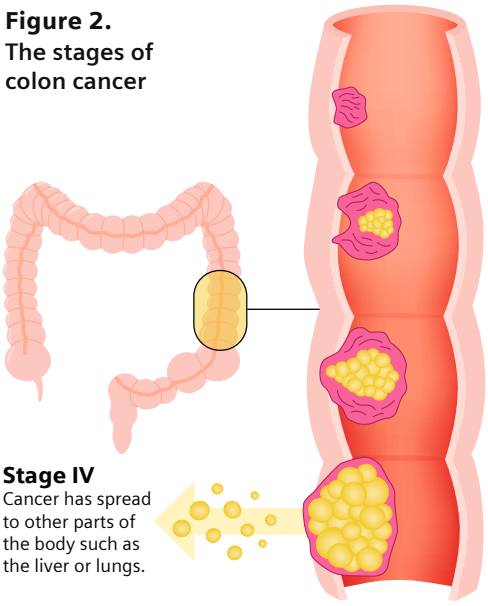
CRC incidence and mortality

Colorectal cancer (CRC) accounts for approximately 10 percent of deaths from cancer globally.[24] The majority of cases (>90%) occurs at age 50 years or greater, a population targeted for CRC screening.[1,21] However, a clear trend in CRC has been observed in many countries in a younger population,[26,27] and some countries (notably the U.S.) have reduced the recommended age of screening as a result.[27] CRC is also linked to other conditions such as ulcerative colitis or Crohn's disease, as well as dietary and genetic factors.[28,29]

CRC stages

Cancer occurs in the colon or rectum and is often asymptomatic, especially in the early (and more treatable) stages.[28,29] Development of CRC is usually slow and spreads from the inner wall of the colon outward with the extent of spread defined by histopathological stages[30] (Figure 2).

Figure 2.
The stages of colon cancer



CRC and polyps

CRC typically begins with small polyps (growths) that may or may not develop into precancer/cancer.[28] Polyps tend to appear/increase with age and can occur as different types (Table 2).

Up to 80 percent of CRC develops from colonic adenomas (commonly over five to 20 years), but only about 10 percent of all adenomas progress to CRC within 10 years as the remainder stabilize or regress.[28,31] Identification and removal of polyps can be performed during colonoscopy to reduce CRC occurrence.[32] While adenomas and serrated polyps have a higher risk of becoming cancerous, most polyps are benign.[29,33]

Table 2.

Polyp types include	Association with cancer
Adenomas (three types: tubular, villous, and tubulovillous)	Common. Larger adenomas and adenomas with a villous growth pattern are more likely to contain cancer cells.
Hyperplastic or inflammatory	Typically, not precancerous.
Serrated	Less common but may have a higher likelihood of developing into cancer.

Adapted from https://www.mountsinai.org/health-library/diseases-conditions/colorectal-polyps#:~:text=Symptoms,by%20losing%20blood%20over%20time

Colonoscopy, Polyps, and CRC

Since polyps can take years to become cancerous, a significant window of opportunity exists for prevention or early diagnosis.[32] While an optical colonoscopy (Figure 3) is required to definitively identify and remove polyps or to diagnose precancer/cancer, it is not ideal as the primary screening methodology. Reasons include invasiveness, need for a thorough bowel prep (and associated compliance challenges), site/clinician access, risks such as bleeding or perforation, and the inability to expediently test the large number of individuals recommended for screening.[9,12,27,32]

Screening programs that utilize non-invasive testing to identify patients more likely to benefit from a colonoscopy can decrease unnecessary referrals, reduce patient wait times for the procedure, and avoid unnecessary risk. Importantly, a positive FIT test should be followed up with a diagnostic colonoscopy, as positive results are linked to a higher prevalence of CRC and advanced adenomas.[10]

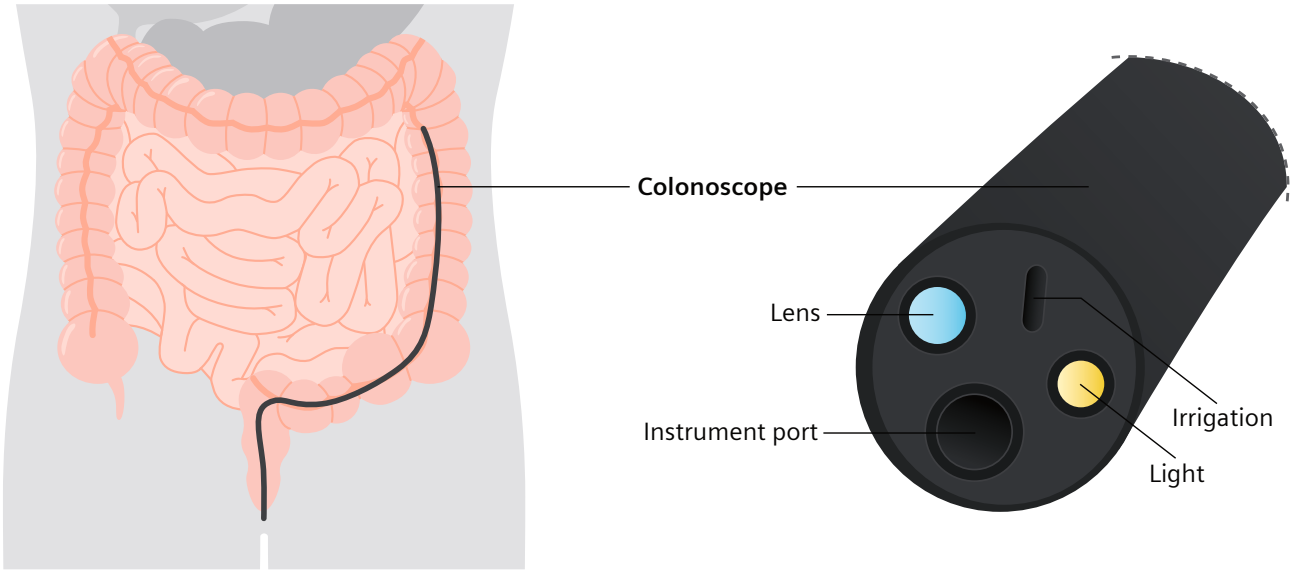
Colonoscopy advantages

Can detect and allow removal of polyps/precancerous polyps and identify CRC. Positive non-invasive screening tests should be followed up with colonoscopy to diagnose CRC and/or remove polyps.

Risks and limitations include

Bleeding, risk of colonic perforation or infection, clinician/site access, sufficient bowel prep required by patient, sedation complications, limited number of procedures that can be performed cannot meet screening demand.

Figure 3. Colonoscopy



FIT as a routine screening tool in symptomatic and asymptomatic populations.

While a colonoscopy remains the primary method of identifying polyps/CRC, population-based screening necessitates a method capable of scalability and large testing numbers using a minimally invasive, "patient friendly" approach with good sample stability for transport and testing.[4,5,34] FIT testing meets these criteria with proven performance for both sensitivity and specificity.[4,5]

Abundant data supports FIT as an effective method of screening in both symptomatic and asymptomatic populations, although percent of cases detected can be impacted by the cut-point used.[4,5,6,8,12-14,22,25,34-40]

FIT testing in asymptomatic populations

In asymptomatic populations, faecal occult blood may be the only indication of precancerous polyps or CRC (although not all polyps, including advanced adenomas, or even cancers, will bleed).

According to many European guidelines, individuals between 50 and 74 years old should be screened with a FIT test for CRC (with repeat testing commonly performed every two years).[1,21] One large population-based study found that completing even just one or more FIT screenings within the prior five years was associated with a 33 percent lower risk of death from CRC.[36]

While trace blood in the stool may be a sign of cancer or polyps, it is not a diagnosis of cancer. Other conditions including hemorrhoids and inflammatory bowel disease can produce bleeding.[41] A CRC diagnosis requires visualization and tissue removal for histopathology. So, positive screens should be referred for colonoscopy or other additional investigation.[9,10]

FIT testing in symptomatic patients

While offering high utility for asymptomatic screening, FIT performs as well or better in symptomatic patients, including those characterized with high-versus-low-risk CRC symptoms.[6,42-45]

Guidelines for patients with signs/symptoms of CRC recommend FIT to assist triage into an urgent "suspected cancer" pathway for additional investigation.[6] FIT can help identify those at lower risk who may potentially be managed in primary care, helping prioritize referrals for those at higher risk.[6,44,45]

A significant benefit of FIT is to support identification of those majority of patients unlikely to benefit from an invasive colonoscopy and reassure that CRC is unlikely. A large study in England in symptomatic patients found a negative FIT test produced a rule-out accuracy of >99%.[42]

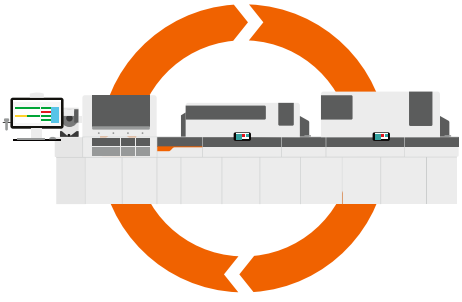
NEW! "Hands-free" FIT testing on Atellica Solution with Atellica Integrated Automation

Routine FIT testing using the FOB Gold Tube Screen sample collection tube can now be fully automated on existing equipment (Atellica CH 930 analyzer or Atellica Solution with Atellica Integrated Automation) used for chemistry testing in labs worldwide. Table 3 describes some of the benefits for both patient and sample analysis.

Table 3. Benefits of FIT testing using FOB Gold patient collection tube on the Atellica Portfolio

Sample collection	Sample transport	Automated testing
The patented 2-in-1 sample collection-dilution tube offers an easy to use, hygienic, and non-invasive solution for at-home sample collection.† With just a single sample required and no patient pre-preparation provides a seamless and private experience for the patients. Data indicate ease of patient collection is similar or superior to other commonly used FIT methods.*	By dissolving and diluting the patient sample in the buffer solution upon re-insertion of the collection stick, the process ensures the sample is properly prepared for easy and efficient transport to the testing site.	The patient collection tube is loaded directly onto the **Atellica Solution with Atellica Integrated Automation**, which automates decapping and testing workflow reducing operator hands-on time.
The patented design of the patient collection tube ensures consistent sample volume,† optimizing accuracy and reliability for analytical testing.	The patient collection tube extracts and preserves hemoglobin from the stool sample, ensuring its stability across a broad temperature range, allowing for accurate testing upon transport to the laboratory.‡	The Atellica CH Sentinel FIT test integrates seamlessly into routine chemistry workflows, enabling labs to perform FIT testing with their routine chemistry tests. The Atellica Solution delivers results in 10 minutes and supports high throughput, improving efficiency and minimizing turnaround time.

*Data on file with Sentinel Diagnostics
†Sentinel Diagnostics FOB Gold Tube Screen IFU 11561H-5.0/02, 2023/11/09
‡Sentinel Diagnostics FOB Gold NG Wide IFU REF 1156009-5.0/02, 2023/09/21 and reference 43



Ease of Use
Enhances patient compliance, preserves samples, and reduces laboratory hands-on time

Trust in Results
Proven assay design, fully supported by Siemens Healthineers

Operational Efficiency
Streamlining screening, reducing unnecessary procedures, and focusing resources on high-risk patients

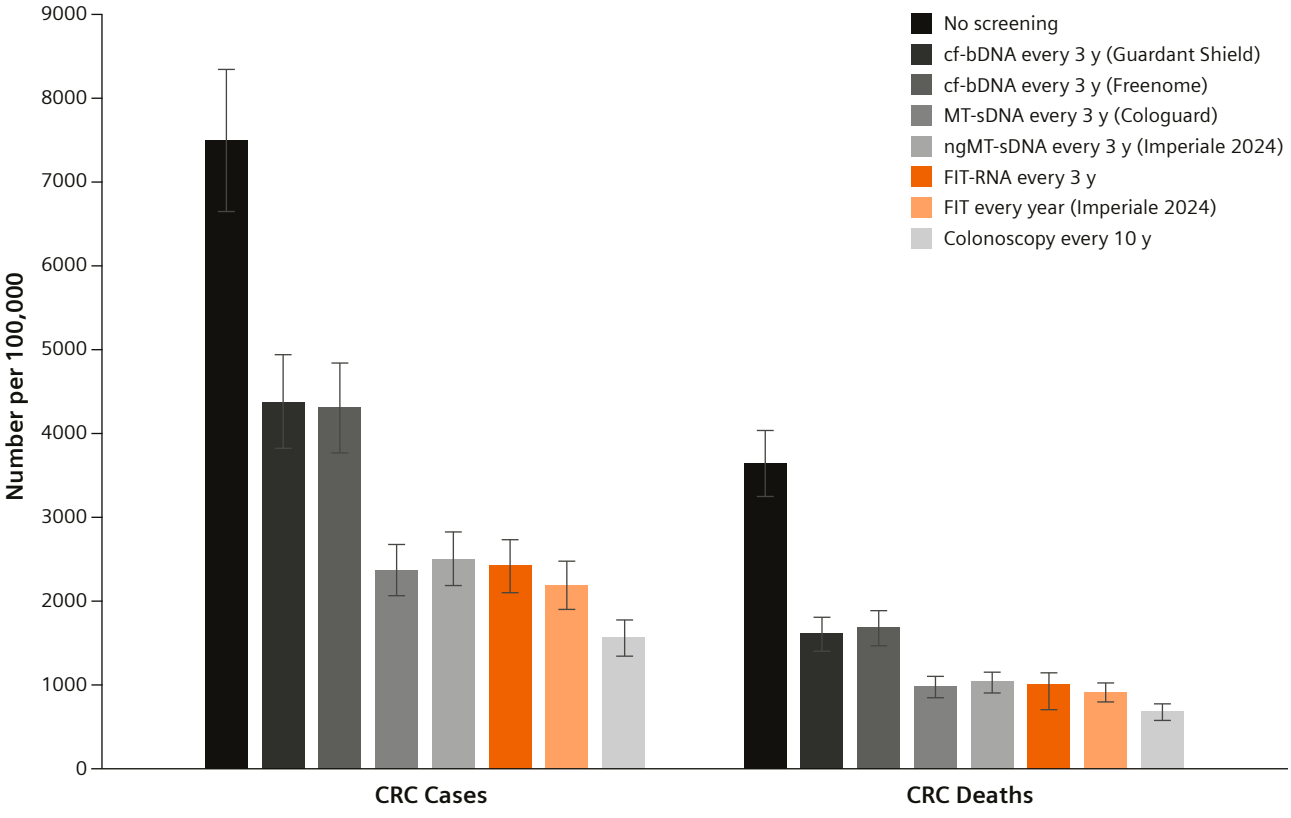
Newer non-invasive testing methodologies versus FIT

Emerging technologies include testing from blood/stool that include molecular markers (DNA or RNA) alterations that may be associated with CRC.[35] Some combine molecular markers with faecal occult blood detection in stool samples. These tests are often associated with a significantly higher price point vs. FIT testing and may not currently outperform existing approaches.[35]

A study published in 2024 modeled various CRC screening methods that included emerging technologies and found that FIT followed by colonoscopy would reduce incidence of CRC by 70 percent and cut mortality by 75 percent versus no screening.[35] Similar or inferior performance was observed for the alternatives to FIT and colonoscopy (Figure 4).

Overall, stool testing was found to be superior to molecular testing using a blood sample. While new data or tests may emerge that improve detection or further simplify sample collection, currently, FIT testing of stool and colonoscopy offers an established benefit for improved CRC detection and outcomes.

Figure 4. Clinical outcomes with existing and emerging CRC screening technologies.*



*Not all assays available in all countries

Adapted from Ladabaum, U. et al. Projected Impact and Cost-Effectiveness of Novel Molecular Blood-Based or Stool-Based Screening Tests for Colorectal Cancer. 2024. Annals of Internal Medicine, Volume 177, Number 12

FIT cut-point selection

Performance (sensitivity/specificity) can vary with the FIT cut-point selected. Each laboratory should establish the cut-off value for the FIT assay used and population tested.

Data show rates of colonoscopy referral and CRC detection can vary by the cut-point selected and are specific to individual FIT assays. While quantitative FIT values are not standardized, good performance has been demonstrated across a range of cut-points and FIT assays in differing testing populations.[14,39,40,46-48]

While no assay will always achieve 100 percent accuracy, multiple FIT assays have demonstrated the ability to identify a significant percentage of CRC. One study using the Sentinel FOB Gold assay found a low incidence of CRC following a negative FIT test and >80 percent detection of CRC across all cut-points investigated, supporting use of the assay in risk assessment.[47] The authors concluded that those with a negative result from a screening FIT should be tested again at the currently recommended interval of 2 years.[47]

> *"We observed a low cumulative incidence of interval CRCs because of a high FIT sensitivity for CRC."*[47]

Generally, a lower cut-point can improve sensitivity (detection) but often with a trade-off on specificity. With a quantitative FIT assay, the cut-off can be adjusted to optimize referrals in the target population.[49,50]

FIT testing sensitivity may show some variation with stage and tumor location, with lower sensitivity reported for stage 1 cancers and in the distal colon, even when assessed across a range of cut points.[51-53] Alternative tests also demonstrate lower performance for stage 1 detection vs. late-stage cancers.[51,52]

Early-stage CRC detection

Importantly, data show that FIT screening can detect many early and late-stage cancers.[47,54] One study (using Sentinel FOB Gold) found the majority of CRC detected was Stage I/II (66.5%) vs. 33.5% for Stage III/IV.[54] Use of the recommended second round of screening resulted in additional detection, including 67.7 percent with Stage I/II (Table 4). Detection was superior using lower values, again highlighting the importance of screening programs and selection of an appropriate cut-point for the testing population with the FIT assay used.

Table 4.[54]

FIT assay (FOB Gold)	Percent w/ Stage II/II	Percent w/ Stage III/IV
First FIT screen	66.5%	33.5%
Second FIT screen	67.7%	32.3%

Conclusion

Screening programs recommend FIT testing and increase CRC detection leading to improved outcomes. Data show testing with FIT may reduce colonoscopy burden and help prioritize those at higher risk. The ability to fully automate FIT testing on the widely available **Atellica Solution and Atellica Solution with Atellica Integrated Automation** supports the large number of tests mandated by screening programs and cancer reduction initiatives. Direct load and testing from the primary Sentinel FOB Gold sample collection tube without the need for cap removal minimizes operator exposure and enhances workflow and the delivery of timely results.

For more information on integrating automated FIT testing in your chemistry workflow, please contact your local Siemens Healthineers representative.

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