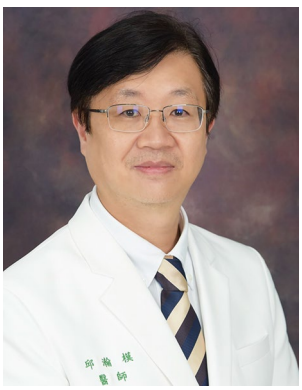
Digestive Diseases and Sciences (2025) 70:1616–1624
https://doi.org/10.1007/s10620-024-08696-z

REVIEW

# Adopting Non-invasive Approaches into Precision Colorectal Cancer Screening

**Han-Mo Chiu**[1] · **Takahisa Matsuda**[2]

Received: 5 September 2024 / Accepted: 14 October 2024 / Published online: 8 November 2024

## Abstract

Effective screening is essential to reducing CRC incidence and mortality by detecting the disease at early stages and identifying non-invasive precursors. While colonoscopy remains the most sensitive modality to visualize and remove neoplastic lesions thereby reducing CRC and the related death, its high cost and invasive nature limit its widespread use. The fecal immunochemical test (FIT), which offers a non-invasive alternative with higher public acceptance and comparable cost-effectiveness to colonoscopy, has become the preferred screening method in many regions. Newer non-invasive tests, such as multitarget stool DNA or RNA tests, have shown improved sensitivity for CRC and advanced adenomas, although their high costs and lower specificity present challenges for large-scale implementation. Blood-based circulating cell-free DNA test also offer promise but still require optimization to be cost-effective. The heterogeneity of the screening population further complicates the effectiveness of CRC screening programs. Variations in non-communicable disease risk factors, such as metabolic syndrome, lifestyle habits, and comorbidities, can significantly influence CRC risk and screening outcomes. Moreover, diverse screening behaviors, including inconsistent adherence to recommended screening intervals and the interchangeable use of different screening modalities, add complexity to achieving uniform effectiveness across populations. This variability underscores the need for personalized screening strategies that consider individual risk profiles and screening behaviors, as well as the application of cutting-edge technologies such as big data analytics, artificial intelligence, and digital twin approaches to evaluate its effectiveness. This article reviews the current CRC screening strategies, the advantages of

✉ Han-Mo Chiu
hanmochiu@ntu.edu.tw

[1] Department of Internal Medicine, National Taiwan University Hospital, No. 7, Chung-Shan South Road, Taipei, Taiwan

[2] Division of Gastroenterology and Hepatology, Toho University Omori Medical Center, Tokyo, Japan

non-invasive methods, and the potential of fecal hemoglobin concentration, to tailor screening intervals and improve risk stratification. It also discusses the emerging role of real-world data and advanced technologies in enhancing CRC screening accuracy and effectiveness, particularly in complex real-world scenarios where traditional methods may fall short. Before novel non-invasive approaches, such as ctDNA tests or polygenic risk scores, are validated and proven cost-effective, exploring the clinical utility of FIT and its quantitative measurement in both screening and surveillance by integrating real-world clinical big data seems a feasible direction for achieving sustained development in population screening.

**Keywords** Colorectal cancer · Screening · Fecal immunochemical test · Colonoscopy

**Abbreviations**

| | |
|---|---|
| CRC | Colorectal cancer |
| FIT | Fecal immunochemical test |
| FOBT | Fecal occult blood test |
| f-Hb | Fecal hemoglobin |
| MT-sDNA | Multitarget stool DNA |
| MT-sRNA | Multitarget stool RNA |
| cf-DNA | Cell-free DNA |
| RWD | Real-world data |
| MetS | Metabolic syndrome |

## Advantages of Two-Step Screening Approach Using Non-invasive Tests and Its New Developments

While colonoscopy enables direct visualization of the colonic mucosa and epithelial lesions and allows for the removal of neoplastic lesions, a two-step screening approach using non-invasive tests, such as FIT, significantly reduces the demand for colonoscopy—the most costly and invasive component of colorectal cancer screening. The positive cutoff for FIT is typically determined based on the available colonoscopy capacity within individual programs, and the positivity rate of FIT in most screening programs is reported to be around 5–10%. This rate is also influenced by the prevalence of CRC and advanced adenomas in the screening population.

Novel non-invasive tests, such as the multitarget stool DNA (mt-sDNA) test and the multitarget stool RNA (mt-sRNA) test, which combine FIT with various DNA or RNA biomarkers, have significantly improved sensitivity for both cancer and advanced adenoma. The reported sensitivity of mt-sDNA and mt-sRNA for CRC is 93.9% and 94%, respectively, and 43.4% and 46% for advanced adenoma. The reported specificity of these tests is 90.6% for advanced neoplasms (advanced adenoma and CRC combined) and 86.9% for any neoplasm [1, 2]. The blood-based circulating tumor DNA (ctDNA) test, which uses circulating cell-free DNA (cf-DNA) as a biomarker, demonstrated an overall sensitivity of 83.1% for CRC and 13.2% for advanced adenoma, with a specificity of 89.6% for advanced neoplasms in the screening population [3]. The improved sensitivity for early CRC and advanced adenoma is a breakthrough in these new technologies, offering hope for increased screening uptake and better detection of clinically relevant neoplasms. This advancement could significantly enhance the effectiveness of reducing CRC incidence and mortality. However, while non-invasive screening tests may lead to higher participation rates, the high cost of these new technologies presents a major barrier to their widespread adoption, particularly in large-scale, government-funded screening programs. Another concern is the potential impact on clinical capacity due to their lower specificity (compared to FIT), which could increase the demand for colonoscopies, thereby placing additional strain on endoscopy resources and leading to a higher number of colonoscopies without neoplastic findings. A recent modeling study suggests that, to be cost-effective, an effective blood-based CRC screening test should have a sensitivity greater than 90% for CRC and 80% for advanced adenoma, with a specificity of 90%, and cost less than USD 120-140. [4]

## FIT Is Not Just a Test to Determine Positivity: The Potential Application of Quantitative Measurement of FIT

With higher sensitivity for advanced adenomas and early-stage CRC (i.e., Stage 1), along with greater public acceptance, FIT has replaced guaiac FOBT as the most popular primary screening modality. It has the potential to reduce CRC mortality to levels approaching the effectiveness of colonoscopy. However, interval CRCs can still occur after a negative FIT result, and a recent cohort study demonstrated that FIT is less effective in preventing proximal colon cancer compared to distal CRC [5]. While its sensitivity for advanced adenomas is better than that of the guaiac test, it remains insufficient if the ultimate goal of screening is to reduce CRC incidence. Before implementing the aforementioned novel non-invasive molecular tests, which reportedly outperform FIT in detecting early-stage CRC and advanced adenomas, into population screening, it is worthwhile to explore the extended application of FIT to optimize its screening effectiveness.

Quantitative measurement of FIT, the fecal hemoglobin concentration (f-Hb), was initially designed and used only to determine positivity requiring colonoscopy. However, later studies have demonstrated that it can also be utilized for risk stratification and future risk prediction. In an early study from Taiwan in a community-based CRC screening program, it was demonstrated that f-Hb, even under the positive cutoff, was positively associated with the future risk of advanced neoplasm (AN) in a dose-respondent manner [6]. In this study with a median follow-up of 4.39 years for 45,992 participants, the incidence of advanced neoplasia increased from 1.74 per 1000 person-years for those with a baseline f-Hb of 1–19 ng/mL to 7.08 per 1000 person-years for those with a baseline concentration of 80–99 ng/mL. The adjusted hazard ratios (aHRs) rose from 1.43 (95% CI 1.08–1.88) for a baseline f-Hb of 20–39 ng/mL to 3.41 (2.02–5.75) for a baseline concentration of 80–99 ng/mL (trend test $p < 0.0001$), relative to 1–19 ng/mL. A later Dutch study also examined the relationship between baseline f-Hb below the FIT cut-off value and the subsequent risk of AN in a Dutch population-based screening cohort of 7663 individuals. Over a median follow-up of 4.7 years, those with baseline f-Hb of 8–10 µg/g had a significantly higher cumulative incidence of AN (33%) compared to those with 0 µg/g (5%). aHR for AN increased with higher baseline f-Hb levels, and participants with two consecutive f-Hb concentrations of 8 µg/g had a 14-fold increased risk of AN [7]. These two studies paved the way for applying quantitative measurement of FIT in CRC screening and the later serial works in *Taiwan CRC Screening Program* revealed that f-Hb could be applied in many aspects in the population screening program.

## Tailor Inter-screening Interval of FIT Screening

Yen and colleagues explored the potential of using f-Hb -guided screening intervals to CRC screening, aiming to reduce the number of FIT and colonoscopies required while maintaining the effectiveness of universal biennial screening. This retrospective cohort analysis of over 3 million participants in a FIT-based Taiwan CRC screening program demonstrated a clear gradient relationship between f-Hb levels and colorectal neoplasia and CRC mortality. Different risk categories and screening intervals based on f-Hb levels were developed, showing that a personalized f-Hb-guided approach could reduce the use of FITs and colonoscopies by 49% and 28%, respectively, without losing efficacy. The findings suggest that f-Hb-guided screening intervals offer a viable precision strategy for optimizing CRC screening resources [8].

## Risk Stratification After Colonoscopy

A study involving 29,969 subjects who underwent colonoscopy after a positive FIT in the national screening program during 2004 to 2009, a total of 162 PCCRC developed (incidence of 1.14 per 1000 person-years) and the risk of PCCRC was significantly higher in subjects who had their colonoscopy performed in units with lower adenoma detection rate (i.e., < 15%) and higher f-Hb (≥ 100 µg Hb/g) whatever they had colonoscopy with or without adenoma [9]. We can use this approach to risk-stratify and manage individuals who have undergone colonoscopy based on their f-Hb levels to reduce the risk of PCCRC.

## Setting Priority for Colonoscopy Referral After Positive FIT

Another study examined the impact of noncompliance with colonoscopy after a positive FIT on colorectal cancer (CRC) mortality among 59,389 Taiwanese individuals. Noncompliers had a 1.64-fold increased risk of CRC death compared to those who underwent colonoscopy. The risk increased with higher f-Hb levels with1.31-fold for f-Hb 20–49 µg/g, 2.21-fold for 50–99 µg/g, and 2.53-fold for f-Hb of 100 µg/g or higher. These findings offer new insights into the relationship between f-Hb levels and CRC mortality among individuals who do not comply with colonoscopy after a positive FIT. These findings offer new insights into the relationship between f-Hb levels and CRC mortality among individuals who do not comply with colonoscopy after a positive FIT. We can develop tailored strategies based on f-Hb to enhance colonoscopy compliance, particularly for those with higher f-Hb levels, who are at greater risk of significant colorectal neoplasms to reduce future risk of CRC [10].

## FIT as a Surveillance Test

FIT is not only a primary screening test but could be also used as an interval test before the surveillance colonoscopy to speed up the detection of overlooked or newly developed advanced neoplasm to reduce the risk of PCCRC. In an Australian study, Lane and colleagues investigated whether FIT between scheduled surveillance colonoscopies could lead to earlier detection of neoplasia in high-risk population with a family history or previous neoplasia. They enrolled 1736 subjects who underwent at least two colonoscopies, with FITs offered annually in the intervals between them. Among the 61% of asymptomatic subjects who received at least one FIT, the test detected 86% of cancers and 63%

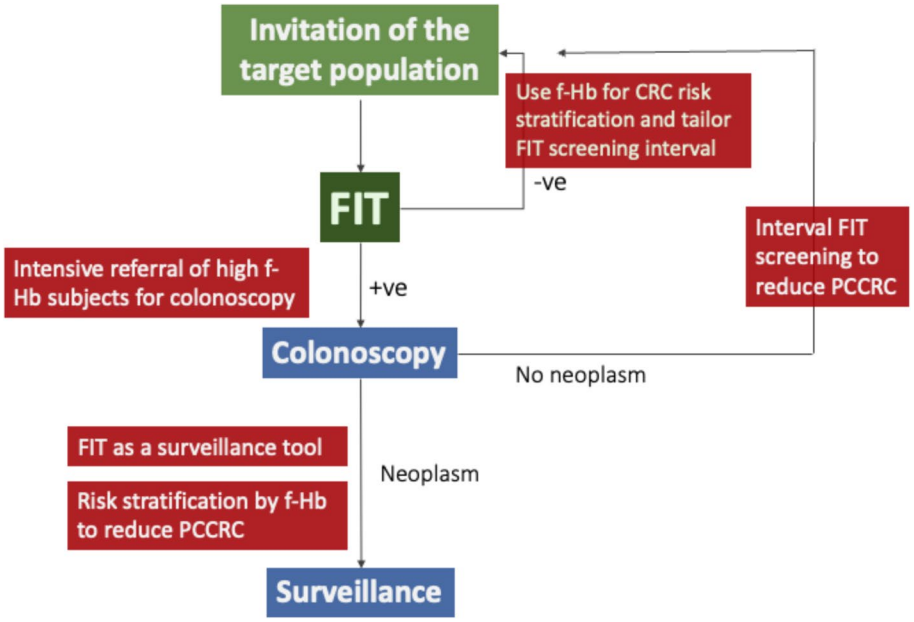



**Fig. 1** Potential application of f-Hb in the screening and surveillance workflow in the FIT-based colorectal cancer screening program

of advanced adenomas, allowing for earlier diagnosis by a median of 24–25 months. Patients with repeated negative FIT results had a significantly lower risk of cancer and advanced adenoma compared to those who were not tested. The results suggest that interval FITs can effectively detect missed or rapidly progressing lesions, reducing the risk of advanced-stage neoplasia [11]. A subsequent study by Peng et al. included 9179 subjects who had a negative diagnostic colonoscopy after a positive FIT in Taiwan CRC Screening Program between 2004 and 2009, with 6195 receiving subsequent FIT during the study period. The CRC incidence was 1.34 per 1000 person-years in those who received subsequent FIT compared to 2.69 in those who did not, with an adjusted HR (aHR) of 0.47 (95% CI 0.31–0.71). Lower adenoma detection rates were linked to higher CRC risk, but this association became non-significant after adjusting for subsequent FIT, showing that significant neoplasm being overlooked at a negative poor-quality colonoscopy could be detected by interval FIT during the surveillance interval before they become symptomatic at later stages. It was also demonstrated that higher baseline f-Hb were associated with an increased risk of CRC, which allows for the prioritization of individuals who should be invited for interval FIT testing. In this study, the positivity rate was 11.3%, which was higher than that in primary screening. However, the positive predictive value of 8.68%, which translates to a 'number needed to FIT' of 102 and an affordable 'number needed to scope' of 12 to detect one CRC, justifies this approach [12]. Another recent study from Netherlands also demonstrated that using FIT after polypectomy as a surveillance test is a safe and cost-effective alternative to reduce the burden of colonoscopy [13]. The potential applications of f-Hb in CRC screening and surveillance workflow are illustrated in Fig. 1.

## Adoption of Other Risk Factors and Polygenic Risk Score in CRC Screening

Although the risk of colorectal cancer (CRC) increases after the age of 50 (and now 45, due to the rising incidence of young-onset CRC), the risk may vary among individuals based on different risk factors and comorbidities. Those with more CRC risk factors theoretically benefit more from screening compared to those without. However, the presence of comorbidities may increase the risk of other causes of death, potentially reducing the effectiveness of screening. By considering these factors along with age and gender—the traditional risk factors for CRC—the efficiency and effectiveness of screening could be enhanced. Additionally, genomic information may also be helpful in this regard.

The results from the Metabolic Syndrome and Cancer Project (Me-Can) cohort study, which involved 578,700 men and women in Europe, explored the relationship between metabolic syndrome (MetS) and colorectal cancer (CRC) risk. Over a mean follow-up of 12 years, 2834 men and 1861 women were diagnosed with CRC. A higher MetS score was associated with an increased risk of CRC in both men (RR = 1.25) and women (RR = 1.14). Metabolic derangement is considered as one of the significant risk factors contributing to young-onset CRC. Among individual MetS factors, BMI, blood pressure, and triglycerides were significantly associated with increased CRC risk in men, while BMI was the significant factor in women [14]. Another study

by Chang et al. investigated the impact of gender, smoking, and MetS on the risk of colorectal neoplasms and the demand for colonoscopy based on different primary screening methods. The study involved 10,884 average-risk individuals in Taiwan who underwent both colonoscopy and FIT. The results showed that male smokers aged 40–49 years had a higher prevalence of advanced neoplasms and a higher positive predictive value for stool tests compared to non-smokers. Notably, men in this age group with both MetS and smoking had a higher prevalence of advanced neoplasms than average-risk women aged 50–59 years. The study highlighted that the risk of colorectal neoplasm, particularly advanced neoplasm, is influenced not only by age and gender but also by lifestyle habits and metabolic risk factors. The number needed to scope was smaller, even at a younger age, when these risk factors were present in men if compared with women [15]. A recent population-based cohort study from Korea examined the association between obesity, MetS, and the risk of CRC diagnosed before the age of 50. In this study involving 9,774,081 individuals who underwent health checkups between 2009 and 2010 and followed up until 2019, it was revealed that MetS was linked to a 20% increased risk of early-onset CRC, similar to its association with later-onset CRC (aHR = 1.19). The risk of early-onset CRC increased with the number of MetS components, particularly for distal colon and rectal cancers, and higher body mass index and waist circumference were significantly associated with increased risk [16]. The risk of having advanced neoplasms in the screening population, as well as the risk of developing metachronous or incident advanced neoplasms after colonoscopic polypectomy, differs between individuals with and without MetS. Our previous study examined the impact of MetS on the detection of advanced neoplasms during surveillance colonoscopy in 4483 subjects aged 50 and older. The findings revealed that advanced neoplasms were significantly more likely to be detected during follow-up in subjects with MetS, particularly among those initially classified as normal or low-risk at baseline colonoscopy, by 107% and 134%, respectively. This underscores the importance of considering factors beyond colonoscopic findings. [17] Current surveillance intervals recommended by major guidelines are based solely on endoscopic findings and the approximate risk of metachronous advanced adenoma, grouping together subjects with various comorbidities that may influence the risk of colorectal neoplasms. A tailored surveillance interval based on a more comprehensive risk profile could not only reduce the risk of CRC but also optimize the use of healthcare resources. (Fig. 2).

Some studies demonstrated the existence of gene-environment interactions that may increase the risk of CRC or early-onset CRC when exposed to environmental and lifestyle factors such as smoking, red meat, alcohol, aspirin use or antibiotics use in early life [18–21]. A polygenic risk score (PRS) is an estimate of an individual's genetic liability to a trait or disease, calculated according to their genotype profile and relevant genome-wide association study (GWAS)

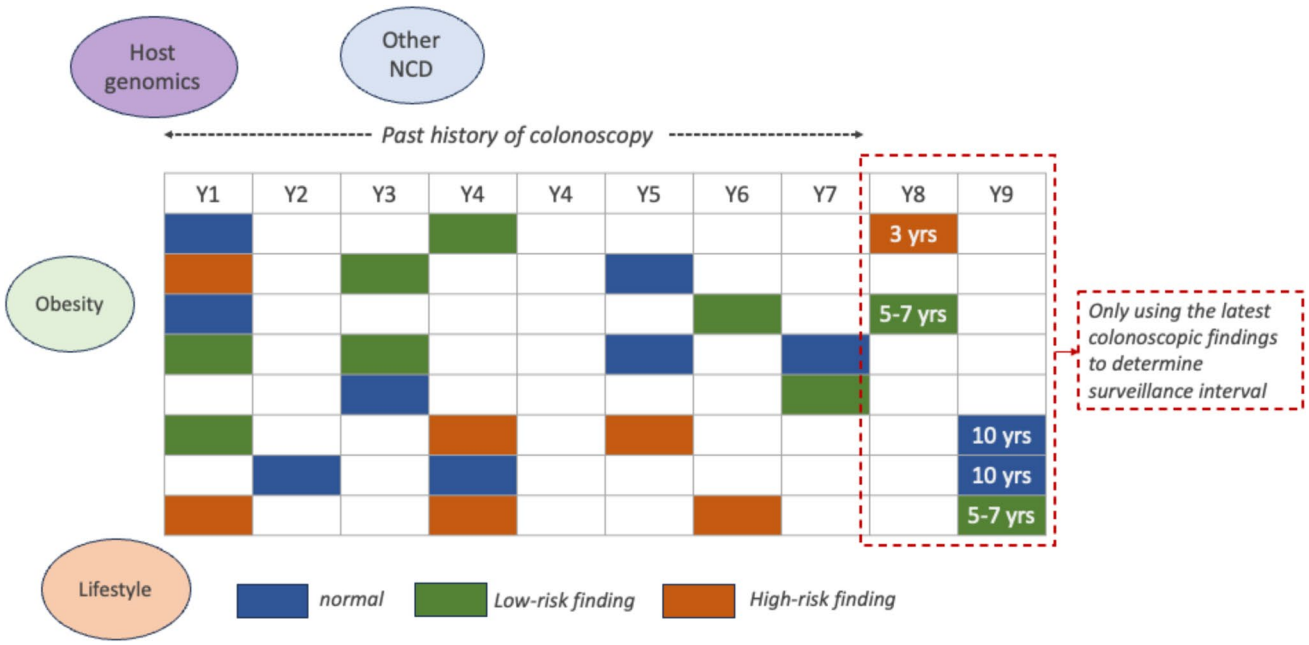



**Fig. 2** Factors that may influence the risk of incident or metachronous colorectal neoplasms. Traditional surveillance interval recommendations are based solely on the most recent colonoscopic findings. However, other factors, such as a patient's previous colonoscopy history, non-communicable diseases, lifestyle factors, or host genomics, may also influence risk

data [22]. Some studies have applied PRS in CRC screening to explore whether this approach could enable more effective, tailored screening or surveillance strategies for individuals at varying levels of CRC risk, balancing effectiveness with efficiency. A study compared different PRS models using GWAS data from over 55,000 CRC cases and 65,000 controls of European ancestry. One model, employing the LDpred Bayesian approach and incorporating nearly 1.2 million genetic variants, identified 30% of individuals without a family history of CRC as having a risk similar to those with a family history. This suggests that many individuals currently considered at average risk could benefit from earlier screening [23]. Jeon et al. developed models to predict CRC risk by incorporating lifestyle, environmental factors, genetic variants, and family history, with the goal of determining optimal ages to begin screening. Using data from nearly 20,000 participants in two large consortia, they created models based on 19 lifestyle/environmental factors (E-score), 63 genetic variants (G-score), and family history. The combined model showed higher accuracy in predicting CRC risk (AUC = 0.63 for men and 0.62 for women) compared to models using only family history (AUC = 0.53–0.54). The study demonstrated that the recommended starting age for CRC screening could vary by 12–14 years depending on an individual's combined risk score, compared to the standard age of 50 for those without a family history [24]. Fu and colleagues investigated the individual and combined effects of BMI and PRS on the risk of colorectal neoplasms in 4784 participants undergoing screening colonoscopy. They found that overweight and obesity increased the risk of any colorectal neoplasm, with obesity particularly linked to a higher risk of advanced colorectal neoplasm. A dose–response relationship for PRS, especially for advanced neoplasms, was observed, with no interaction between BMI and PRS, indicating a multiplicative effect. Obese individuals with a high PRS had significantly elevated risks of both any and advanced colorectal neoplasms. The impact of obesity was comparable to having a PRS 38 percentiles higher, underscoring the importance of maintaining a normal weight to reduce genetic risk [25]. Guo et al. investigated whether PRS could be used alongside adenoma characteristics to create personalized and risk-adapted CRC surveillance intervals. In a case–control study involving 4696 CRC cases and 3709 controls, participants were classified by genetic risk based on PRS tertiles. The results revealed significant variations in CRC risk according to PRS, even among individuals who had adenomas detected and removed during colonoscopy. For instance, the 10-year absolute CRC risk for 50-year-olds without polyps was 0.2%, but those with low-risk adenomas and a high PRS reached similar risk levels within 3 to 5 years. The study suggests that incorporating PRS could enhance personalized surveillance intervals, although further research is needed to determine its clinical applicability [26].

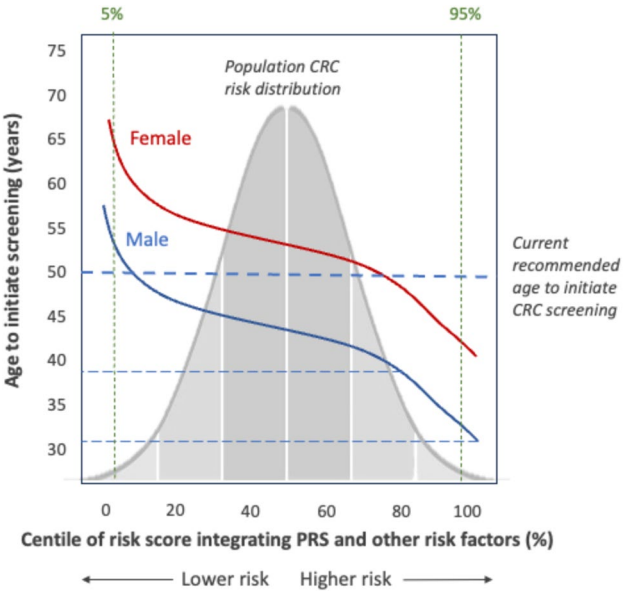



**Fig. 3** Conceptual framework of the risk-based precision screening approach integrating conventional risk factors and polygenic risk score. The age to initiate screening varies based on an individual's risk of CRC, which could be determined using polygenic risk score and conventional clinical risk factors

Despite the potential benefits of PRS-based approaches for CRC screening, modeling studies have shown that the current uniform screening method is more cost-effective than personalized screening based on PRS and family history. However, the cost-effectiveness of personalized screening largely depends on the expense of determining risk, which is primarily driven by the cost of genetic testing [27, 28]. The conceptual framework of the risk-based precision screening approach integrating conventional risk factors and PRS is illustrated in Fig. 3.

## Future Perspectives: Addressing the Complexity of Real-World CRC Screening Scenario

The comparison of different screening strategies and the related evidence are primarily based on the results of randomized trials, cohort studies, or modeling studies. When comparing these strategies, study designs often include only "pure" populations or exclude "contaminated" populations, limiting their applicability to real-world general populations. For instance, in a biennial FIT screening program, not everyone is strictly compliant to the fixed 2-year interval (e.g., 2–4–2 or 2–3–6 or any other combinations of the intervals) (Fig. 4A), and some individuals may even switch between government-subsidized FIT screening and colonoscopy

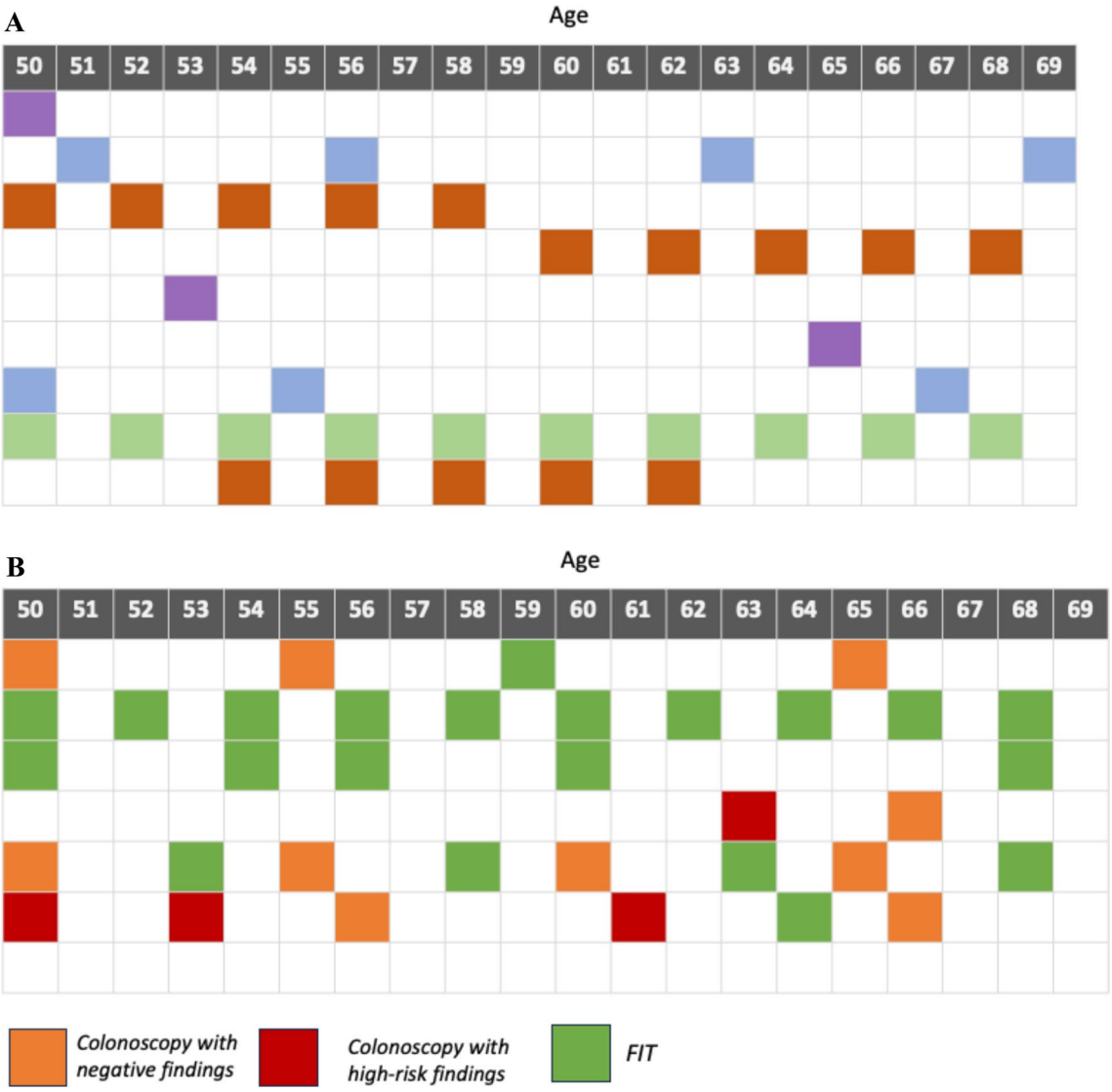



**Fig. 4** Complexity of Screening Behavior in Real-World Colorectal Cancer Screening. **A** Irregularity of inter-screening intervals. Different colors denote different individuals. **B** Using different screening modalities interchangeably. Different colors denote different screening modalities

screenings subsidized by commercial companies (Fig. 4B). As a result, the clinical evidence mentioned above may not fully apply to real-world populations. With the emergence of other novel non-invasive tests, such as MT-sDNA, MT-sRNA, and blood cf-DNA, this complexity is expected to increase. Moreover, environmental exposure, lifestyle factors, comorbidities and medication may change over time and all affect the risk of CRC or the risk of advanced neoplasm after colonoscopy.

With new healthcare policies, scientific discoveries, and innovative healthcare technologies, the variety and volume of available health data have significantly increased. There are also new types of data that can be used to obtain valuable insights and improve CRC screening. These include disease registries, patient-reported outcome data, patient-generated health data (e.g., health data collected by wearable devices), genomic data, and social determinants of health (e.g., poverty, education, race, exposure to polluted air and water, access to healthy and nutritious foods, and opportunities for physical activity). Although real-world data (RWD) is valuable for evaluating the safety and efficacy of medical products in real clinical settings, real-world evidence has traditionally been used by the FDA primarily for post-market safety monitoring. However, there is a growing trend toward the acceptance of RWD for regulatory decision-making, with the FDA increasingly considering its use as a substitute for clinical trials in certain situations. Clinical trials can be particularly challenging for rare diseases, vulnerable patients (e.g., pediatric patients or hereditary cancer patients), or outcomes that require prolonged observation

periods (observation of a cancer to occur or related death to happen). In such cases, using real-world evidence in place of traditional clinical trials applying the cutting-edge artificial intelligence and digital twin technology may accelerate the generation of new clinical evidence [29, 30].

## Key Messages

- While colonoscopy is effective, it is also invasive and costly. The fecal immunochemical test (FIT) is currently the most popular non-invasive screening method for colorectal cancer (CRC) due to its proven effectiveness and cost-efficiency.
- Novel non-invasive methods, such as multitarget stool DNA tests, stool RNA tests, and blood-based liquid biopsies using circulating cell-free DNA, show potential in improving CRC detection. However, their high costs and lower specificity present challenges.
- Quantitative measurements of FIT, such as fecal hemoglobin concentration, can help personalize screening intervals and enhance risk stratification, improving the targeting of high-risk individuals. They can also be used in various aspects of CRC screening, including referrals for diagnostic colonoscopy, surveillance, and the prevention of post-colonoscopy CRC.
- The effectiveness of CRC screening is influenced by diverse risk factors, including metabolic syndrome, lifestyle habits, genomic background, and varying adherence to screening protocols, underscoring the need for tailored screening approaches.
- Leveraging real-world data and advanced technologies, such as AI and digital twins, can refine CRC screening strategies and improve outcomes, particularly in complex real-world settings.

**Author's contribution** H.C: Conception and draft of the manuscript T.M: Conception and critical review of the manuscript.

**Data availability** No datasets were generated or analyzed during the current study.

## Declarations

**Competing interests** Han-Mo Chiu: Han-Mo Chiu: Speaker honorarium—Olympus, Fujifilm, Boston Scientific, Research funding—Boston Scientific, Volition Rx, aether AI. Takahisa Matsuda: None.

## References


1. Imperiale TF, Porter K, Zella J et al. Next-Generation Multitarget Stool DNA Test for Colorectal Cancer Screening. *N Engl J Med.* 2024;390:984–993.
2. Barnell EK, Wurtzler EM, La Rocca J et al. Multitarget Stool RNA Test for Colorectal Cancer Screening. *JAMA* 2023;330:1760–1768.
3. Chung DC, Gray DM 2nd, Singh H et al. A Cell-free DNA Blood-Based Test for Colorectal Cancer Screening. *N Engl J Med.* 2024;390:973–983.
4. Ladabaum U, Mannalithara A, Weng Y et al. Comparative Effectiveness and Cost-Effectiveness of Colorectal Cancer Screening With Blood-Based Biomarkers (Liquid Biopsy) vs Fecal Tests or Colonoscopy. *Gastroenterology*. 2024;167:378–391.
5. Chiu HM, Jen GH, Wang YW et al. Long-term effectiveness of faecal immunochemical test screening for proximal and distal colorectal cancers. *Gut* 2021;70:2321–2329.
6. Chen LS, Yen AM, Chiu SY, Liao CS, Chen HH. Baseline faecal occult blood concentration as a predictor of incident colorectal neoplasia: longitudinal follow-up of a Taiwanese population-based colorectal cancer screening cohort. *Lancet Oncol.* 2011;12:551–558.
7. Grobbee EJ, Schreuders EH, Hansen BE et al. Association Between Concentrations of Hemoglobin Determined by Fecal Immunochemical Tests and Long-term Development of Advanced Colorectal Neoplasia. *Gastroenterology* 2017;153:e1252.
8. Yen AM, Hsu CY, Lin TY et al. Precision Colorectal Cancer Fecal Immunological Test Screening With Fecal-Hemoglobin-Concentration-Guided Interscreening Intervals. *JAMA Oncol*. 2024;10:765–772.
9. Chiu SY, Chuang SL, Chen SL et al. Faecal haemoglobin concentration influences risk prediction of interval cancers resulting from inadequate colonoscopy quality: analysis of the Taiwanese Nationwide Colorectal Cancer Screening Program. *Gut* 2017;66:293–300.
10. Lee YC, Li-Sheng Chen S, Ming-Fang Yen A et al. Association Between Colorectal Cancer Mortality and Gradient Fecal Hemoglobin Concentration in Colonoscopy Noncompliers. *J Natl Cancer Inst*. 2017;109.
11. Lane JM, Chow E, Young GP et al. Interval fecal immunochemical testing in a colonoscopic surveillance program speeds detection of colorectal neoplasia. *Gastroenterology* 2010;139:1918–1926.
12. Peng SM, Hsu WF, Wang YW et al. Faecal immunochemical test after negative colonoscopy may reduce the risk of incident colorectal cancer in a population-based screening programme. *Gut* 2021;70:1318–1324.
13. Carvalho B, de Klaver W, van Wifferen F et al. Stool-based testing for post-polypectomy colorectal cancer surveillance safely reduces colonoscopies: The MOCCAS study. *Gastroenterology*. 2024.
14. Stocks T, Lukanova A, Bjorge T et al. Metabolic factors and the risk of colorectal cancer in 580,000 men and women in the metabolic syndrome and cancer project (Me-Can). *Cancer*. 2011;117:2398–2407.
15. Chang LC, Wu MS, Tu CH, Lee YC, Shun CT, Chiu HM. Metabolic syndrome and smoking may justify earlier colorectal cancer screening in men. *Gastrointest Endosc*. 2014;79:961–969.
16. Jin EH, Han K, Lee DH et al. Association Between Metabolic Syndrome and the Risk of Colorectal Cancer Diagnosed Before Age 50 Years According to Tumor Location. *Gastroenterology*. 2022;163:637–648 e632.
17. Chiu HM, Lee YC, Tu CH et al. Effects of metabolic syndrome and findings from baseline colonoscopies on occurrence of colorectal neoplasms. *Clin Gastroenterol Hepatol.* 2015;13:e1138.
18. Stern MC, Sanchez Mendez J, Kim AE et al. Genome-Wide Gene-Environment Interaction Analyses to Understand the Relationship between Red Meat and Processed Meat Intake and Colorectal Cancer Risk. *Cancer Epidemiol Biomarkers Prev.* 2024;33:400–410.
19. Davies JR, Mell T, Fuller H et al. Polymorphisms in Cyclooxygenase, Lipoxygenase, and TP53 Genes Predict Colorectal Polyp Risk Reduction by Aspirin in the seAFOod Polyp Prevention Trial. *Cancer Prev Res (Phila)*. 2023;16:621–629

20. Hou R, Liu Y, Feng Y et al. Association of single nucleotide polymorphisms of ERCC1 and XPF with colorectal cancer risk and interaction with tobacco use. *Gene*. 2014;548:1–5
21. Jiang F, Boakye D, Sun J et al. Association between antibiotic use during early life and early-onset colorectal cancer risk overall and according to polygenic risk and FUT2 genotypes. *Int J Cancer*. 2023;153:1602–1611.
22. Choi SW, Mak TS, O'Reilly PF. Tutorial: a guide to performing polygenic risk score analyses. *Nat Protoc*. 2020;15:2759–2772
23. Thomas M, Sakoda LC, Hoffmeister M et al. Genome-wide Modeling of Polygenic Risk Score in Colorectal Cancer Risk. *Am J Hum Genet.* 2020;107:432–444.
24. Jeon J, Du M, Schoen RE et al. Determining Risk of Colorectal Cancer and Starting Age of Screening Based on Lifestyle. *Environmental, and Genetic Factors Gastroenterology.* 2018;154:e2119.
25. Fu R, Chen X, Niedermaier T, Seum T, Hoffmeister M, Brenner H. Excess Weight, Polygenic Risk Score, and Findings of Colorectal Neoplasms at Screening Colonoscopy. *Am J Gastroenterol*. 2024.
26. Guo F, Edelmann D, Cardoso R et al. Polygenic Risk Score for Defining Personalized Surveillance Intervals After Adenoma Detection and Removal at Colonoscopy. *Clin Gastroenterol Hepatol.* 2023;21:e211.
27. Cenin DR, Naber SK, de Weerdt AC et al. Cost-Effectiveness of Personalized Screening for Colorectal Cancer Based on Polygenic Risk and Family History Cancer. *Epidemiol Biomarkers Prev.* 2020;29:10–21.
28. Ladabaum U, Mannalithara A, Mitani A, Desai M. Clinical and Economic Impact of Tailoring Screening to Predicted Colorectal Cancer Risk: A Decision Analytic Modeling Study Cancer. *Epidemiol Biomarkers Prev.* 2020;29:318–328.
29. Katsoulakis E, Wang Q, Wu H et al. Digital twins for health: a scoping review. *NPJ Digit Med.* 2024;7:77.
30. Lin TY, Chiu SY, Liao LC, Chen SL, Chiu HM, Chen TH. Assessing overdiagnosis of fecal immunological test screening for colorectal cancer with a digital twin approach. *NPJ Digit Med.* 2023;6:24.