UC San Diego
UC San Diego Previously Published Works

Title

Colorectal Cancer Risk Assessment and Precision Approaches to Screening: Brave New World or Worlds Apart?

Permalink

https://escholarship.org/uc/item/9f31h0fh

Journal

Gastroenterology, 164(5)

ISSN

0016-5085

Authors

Kastrinos, Fay

Kupfer, Sonia S

Gupta, Samir

Publication Date

2023-04-01

DOI

10.1053/j.gastro.2023.02.021

Copyright Information

Peer reviewed

Gastroenterology

Colorectal Cancer Risk Assessment and Precision Approaches to Screening: Brave New World or Worlds Apart?
--Manuscript Draft--

Manuscript Number:	GASTRO-D-23-00114
Full Title:	Colorectal Cancer Risk Assessment and Precision Approaches to Screening: Brave New World or Worlds Apart?
Article Type:	Invited 2023 13th Issue: GI Cancer Risk Assessment
Keywords:	Precision Colorectal Cancer Screening, Colorectal Cancer Risk Prediction Models, Polygenic Risk Scores, Colorectal Cancer Risk Assessment
Corresponding Author:	Fay Kastrinos, M.D., MPH Columbia University College of Physicians & Surgeons New York, NY UNITED STATES
Corresponding Author Secondary Information:	
Corresponding Author's Institution:	Columbia University College of Physicians & Surgeons
Corresponding Author's Secondary Institution:	
First Author:	Fay Kastrinos, M.D., MPH
First Author Secondary Information:	
Order of Authors:	Fay Kastrinos, M.D., MPH
	Sonia S. Kupfer, MD
	Samir Gupta, MD
Order of Authors Secondary Information:	
Abstract:	The premise for precision cancer screening is that an individual's risk, related to age, genetics, environment, and lifestyle factors, is associated with the level of benefit received from cancer screening.1 Under this framework, risk stratification for cancer screening can be used to identify, recommend, and tailor screening for those whose cancer risk is high enough that benefits outweigh potential harms. In the case of colorectal cancer (CRC), traditional population-based screening programs take a one size-fits-all approach by using age as the major criterion to initiate screening. However, systematic use of well-established risk factors associated with CRC, beyond age, could better identify those who might harbor advanced colorectal neoplasia, improve the diagnostic yield of current screening modalities, and optimize selection of individuals who might benefit most from preventive strategies.2 "Personalization" of population screening through risk stratification using prediction models has the potential to further reduce CRC morbidity and mortality, by targeting high-risk groups for more intensive screening, with the potential to more appropriately use non-invasive screening tests and less intense screening frequency in low-risk groups. In fact, the benefit of screening colonoscopy has been shown to be greatest among individuals with high-risk profiles determined by prediction models.3 In this review, we address current CRC screening strategies and highlight the potential benefits and challenges related to precision CRC screening. We evaluate evolving approaches to risk assessment in precision CRC screening and potential issues related to the implementation of systematic risk assessment in clinical practice. While precision cancer screening holds promise for further reducing CRC incidence and mortality, additional research is needed to optimize the benefits of these approaches in a comprehensive and equitable manner.
Order of Authors (with Contributor Roles):	Fay Kastrinos, M.D., MPH (Conceptualization: Lead; Writing – original draft: Lead; Writing – review & editing: Lead)
	Sonia S. Kupfer, MD (Conceptualization: Equal; Writing – review & editing: Supporting)

	Samir Gupta, MD (Conceptualization: Equal; Writing – review & editing: Equal)

Colorectal Cancer Risk Assessment and Precision Approaches to Screening:
Brave New World or Worlds Apart?

Fay Kastrinos[1,2], Sonia S. Kupfer[3], Samir Gupta[4]

[1]Herbert Irving Comprehensive Cancer Center, Columbia University Medical Center, New York, NY

[2]Division of Digestive and Liver Diseases, Columbia University Medical Center and the Vagelos College of Physicians and Surgeons, New York

[3]University of Chicago, Section of Gastroenterology, Hepatology and Nutrition, Chicago, IL

[4]Division of Gastroenterology, Department of Internal Medicine, University of California, San Diego, La Jolla, CA; VA San Diego Healthcare System, San Diego, CA

Correspondence:

Fay Kastrinos, MD, MPH
630 West 168th Street #318
New York, NY 10032
Phone: 617-771-1570
Email: fk18@columbia.edu

Word Count: 6,179

Introduction

The premise for precision cancer screening is that an individual's risk, related to age, genetics, environment, and lifestyle factors, is associated with the level of benefit received from cancer screening.[1] Under this framework, risk stratification for cancer screening can be used to identify, recommend, and tailor screening for those whose cancer risk is high enough that benefits outweigh potential harms. In the case of colorectal cancer (CRC), traditional population-based screening programs take a one size-fits-all approach by using age as the major criterion to initiate screening. However, systematic use of well-established risk factors associated with CRC, beyond age, could better identify those who might harbor advanced colorectal neoplasia, improve the diagnostic yield of current screening modalities, and optimize selection of individuals who might benefit most from preventive strategies.[2] "Personalization" of population screening through risk stratification using prediction models has the potential to further reduce CRC morbidity and mortality, by targeting high-risk groups for more intensive screening, with the potential to more appropriately use non-invasive screening tests and less intense screening frequency in low-risk groups. In fact, the benefit of screening colonoscopy has been shown to be greatest among individuals with high-risk profiles determined by prediction models.[3] In this review, we address current CRC screening strategies and highlight the potential benefits and challenges related to precision CRC screening. We evaluate evolving approaches to risk assessment in precision CRC screening and potential issues related to the implementation of systematic risk assessment in clinical practice. While precision cancer screening holds promise for further reducing CRC incidence and mortality, additional research is needed to optimize the benefits of these approaches in a comprehensive and equitable manner.

One-size-fits-all vs. Precision CRC Screening

CRC incidence and mortality can be reduced by screening.[4] However, CRC remains the second leading cause of cancer death and the third most commonly diagnosed cancer worldwide.[5] This, along with the increasing incidence in early-onset CRC in recent years, highlights challenges related to CRC screening and prevention. While a number of screening tests are available,[6] the effectiveness of any population-based screening program extends beyond the performance of those tests and also relates to successful delivery and organization of testing programs, patient participation, and risk stratification to improve personalized screening. Furthermore, tailoring CRC risk assessment can also address issues related to appropriate distribution and utilization of available resources, where the best test is chosen based on an individual's risk profile.

Most CRC screening programs in the US and globally recommend screening for adults over a certain age and do not consider additional individual CRC risk factors.[7-9] However, the screen-eligible "average risk" population 45 years and older actually represents a wide range of risk that can be estimated based on additional demographic, lifestyle, and genetic risk factors. For example, older age, male sex, obesity, and cigarette smoking[10-15] are all associated with colorectal adenomas and cancer and these factors may be used to provide risk-based CRC screening recommendations, versus the current, "one-size-fits all" reliant solely on age. A risk-based approach aims to define a group of individuals with a "high-risk" profile that is associated with a high prevalence of advanced colorectal neoplasia who could benefit most from referral directly to colonoscopy.[2,16] In contrast, those individuals with a predicted "low-risk" profile are selected for alternative non-invasive screening tests that are easily accessible and carry less risk and cost than colonoscopy (Figure 1). This is particularly relevant since CRC screening leads to a large clinical benefit for the minority but exposes many to potential burden and harms with low likelihood to benefit.

Structured screening programs are needed to optimal CRC screening participation rates. Currently, the most accepted screening testing across most programs globally are colonoscopy and fecal testing, notably fecal immunohistochemical testing (FIT).[17,18] While there is world-wide variation in implemented screening strategies, virtually all programs limit their risk assessment to age, with a few including a family history of CRC.[18]

Why Precision CRC Screening?

Improved risk assessment for CRC has the potential to address a number of shortcomings across the care continuum that relate to the patient, provider, and healthcare system (Table 1).[19] A one-size-fits-all approach to CRC screening is unlikely to increase screening uptake or desired outcomes owing to barriers stemming from behavioral, cultural, and socioeconomic causes[20], especially when combined with inefficiencies in delivery of screening technologies across various healthcare systems. However, improved risk-based CRC screening may offer benefits to patients and healthcare providers related to improved decision-making which may improve uptake of screening and influence the choice of screening test.[21,22] This may further lead to improved utilization of resources, many of which are finite and potentially limited by geographic location, healthcare systems and institutions.

Patient. A personalized risk assessment has the potential to better educate patients on their individual risk of colorectal neoplasia which may promote participation in CRC screening programs. In a systematic review of 11 randomized trials that evaluated the use of seven CRC risk assessment tools among 7,677 subjects in diverse practice settings, there was improved patient knowledge, understanding of the importance of screening and the perception of CRC risk among those who used the risk assessment tools.[19,23] Additionally, the intention to participate in CRC screening and screening uptake was increased in the intervention group compared with the control group (43% versus 5%).[24] Furthermore, patient participation is an key determinant in assessing a screening strategy's effectiveness, where individual preferences should be solicited with shared decision-making to select the most acceptable strategy, and support strategy adherence.

Provider. For healthcare professionals, enhanced risk assessment could help improve the identification of patients at greatest risk of harboring or developing advanced colorectal neoplasia, thereby improving test selection, and, for patients referred for colonoscopy, the diagnostic yield of colonoscopy. This aspect has the further important benefit of identifying patients who might benefit from other targeted prevention strategies such as lifestyle modification, including weight loss, dietary changes, or smoking cessation. Furthermore, risk stratification can potentially enable tailoring of the post- polypectomy surveillance interval to the individual patient.[19]

Healthcare system. The impact on healthcare systems is that appropriate risk-based screening can translate into improved efficiency and utilization of services. A reduction in overutilization or mismatched resources, along with an increased capacity for appropriate procedures with decreased waiting times, ultimately leads to higher health-care cost savings.[19] An example where this is relevant is the expansion of CRC screening to individuals between 45 to 49 years and the burden it poses on the healthcare system. Initiation of CRC screening at age 45 years has been estimated to add 21 million eligible individuals to the existing screening pool of 94 million, which represents a 22% increase. Increased uptake in the younger age group, who have low absolute numbers of CRC, potentially diverts already limited resources from higher risk populations who are more likely to harbor advanced neoplasia or CRC[25-27]; these individuals

include not only older, unscreened individuals, but also ethnic minorities and individuals of low SES, potentially deepening already present racial and socioeconomic disparities in screening.[28]

What approaches could be used for risk assessment in precision CRC screening?

Individual Risk Factors for CRC risk assessment. Most population-based cancer screening programs use age as the major criterion to initiate screening. There is additional use of family history and assessment of inherited risk to help guide recommendations that tailor preventive strategies, including the age of screening initiation, the type of screening test selected, and the appropriate interval for surveillance.

Age. The incidence of CRC is strongly related to chronologic age.[29] There has been an alarming increase in the incidence of CRC before age 50 over the last 20 years due to a birth cohort effect, where individuals born 1960 and later are experiencing an earlier rise in age specific incidence.[30] In the US, the rates of colon and rectal cancer in those between 40 to 49 years old have increased by 1.3% and 2.3% per year, respectively and the proportion of CRC in those less than 50 years has doubled since 1990.[30,31] Further, more recent data suggests that the birth cohort effect is increasing CRC incidence among individuals 50 to 59 year old.[32] As such, longstanding decreasing trends in incidence among individuals age 50 years and older, attributed to CRC screening and uptake of colonoscopy, as well as reduction in exposure to CRC lifestyle factors such as smoking, are at risk for flattening and reversing.[31,33]

Genetic Risk: Familial, Germline, and Polygenic Risk of CRC. Current recommendations modify screening initiation and surveillance intervals based on the presence of at least one first-degree relative (FDR) with CRC or a known inherited cancer syndrome, and intensive colonoscopy is the preferred screening approach. The presence of a family member with CRC or advanced neoplasia increases an individual's risk of CRC two-fold,[34,35] and the number of relatives, degree of relatedness and age of diagnosis are important factors to consider,[36] particularly in the evaluation for a genetic predisposition to cancer development, such as Lynch syndrome.[37]
Genomic medicine can inform cancer preventive care by assessing an individual's genetic information, i.e. by DNA sequencing or SNP genotyping, and thereafter personalize cancer screening and risk-reducing strategies. A successful example of CRC prevention has been the implementation of genetic risk assessment for the identification and management of the most common monogenic CRC cancer syndrome, Lynch syndrome (see "xxx" in this Special issue). In addition to the well-described monogenic CRC cancer syndromes, it is well-established by heritability analyses that CRC is highly polygenic. Data from genome-wide association studies (GWAS) for CRC risk prediction holds promise for risk stratification for primary and secondary prevention.[38,39] PRS is a quantifiable genetic risk score determined by the cumulative impact of genome-wide variants, aimed to improved risk prediction.

Lifestyle associated Risk: Numerous risk factors are linked to CRC and include smoking, obesity, increased consumption of red meat,[40] excessive alcohol consumption,[41] and physical inactivity.[42] Conversely, protective factors reduce CRC risk and involve regular aspirin use,[43,44] particular dietary patterns,[45,46] and increased physical activity.[42] The impact of each individual risk factor is modest with low relative risk estimates and none carry sufficient risk on their own to be incorporated into current screening recommendations. However, combining these risk factors and creating composite scores can better discern individuals at high and low risk of CRC development.

Sex: Men have a 1.3 fold higher risk of developing CRC[47,48] than women and comparison of age-specific rates reveal that women develop CRC 4-6 years older than men.[15] However, results from decision analyses do not report differences in optimal screening strategies between the sexes and the majority of screening programs worldwide do not include sex-specific recommendations.[48-51]

Race, ethnicity and social determinants of health. It is well-established that CRC incidence and mortality vary by race and ethnicity. Non-Hispanic Black (NHB) individuals have the highest incidence and mortality rates of CRC of any ethnic group in the US, with an incidence of CRC that is more than 20% higher than in White individuals and an even larger difference in mortality.[52,53] When disaggregated from American Indian populations, Alaska Native people have even higher incidence and mortality.[54] While these differences are most likely driven by social determinants of health such as access to care, including CRC screening, and other socioeconomic factors, a significant portion of the disparity remains after adjustment for these factors. Furthermore, NHB individuals are diagnosed at earlier ages and with later stages of disease. The increased risk of disease and cancer-related death in this patient population has led to changes in screening recommendations, specifically in lowering the age to initiate screening to 45 years for NHB individuals.[55]

CRC Prediction models to improve and systematically provide risk assessment

Development of effective CRC risk prediction models and suitable risk-adapted screening strategies are highly promising and deserve further attention in the era of precision medicine. A number of prediction models that provide risk scores and/or profiles have been developed in recent years and show modest discriminative ability to distinguish between individuals with and without CRC and its precursors (Table 2).[16,56-70] However, performance of these prediction models warrants scrutiny as there has been variability in the eligibility criteria used for development and external validation is often limited.

Clinical CRC Prediction Models

A systematic review and meta-analysis of 17 risk models in 22 studies found that five risk factors were consistently identified as predictive of advanced colorectal neoplasia and CRC.[56] These predictors included age, sex,[12] family history of CRC in FDRs,[71] body mass index, and history of smoking.[10] The risk scores' discrimination was associated with area under the receiver operating characteristic curve (ROC) ranging from 0.62 to 0.77 in the individual studies and 0.61 to 0.70 in the meta-analyses.[56]

The predictive power of risk models can be further refined with the inclusion of additional risk factors related to lifestyle, diet and exposure history. They include but are not limited to obesity, tobacco and alcohol use, red meat consumption, and sedentary lifestyle. While these factors provide minimal improvement in prediction, the ability to readily retrieve all of this information may be challenging. While age, sex, BMI, and smoking history may be easily obtained, other lifestyle and dietary-related factors are more difficult to ascertain and collection of lifestyle factors especially over one's lifetime may also be prone to recall bias.[72] Continued collection over time and selection of key factors, while leveraging the electronic medical record (EMR) or other technologies may streamline this evaluation.

The Asia-Pacific Colorectal Screening (APCS) score is a well-validated prediction model derived from asymptomatic individuals undergoing screening colonoscopy that combines demographic and clinical risk factors, associated with CRC and advanced neoplasia, including

family history.[73] In its original form, the score relied on age, sex, family history of CRC in a FDR, and smoking exposure, generating an AUC of 0.64 in a validation cohort. The model has been expanded to improve discrimination with the addition of BMI and dietary information, yielding an AUC as high as 0.74.[62,74]

The National Cancer Institute's Colorectal Cancer Risk Assessment Tool is a rigorously developed and extensively validated calculator that can be used in the clinical setting to provide 5-year and lifetime risk estimates.[75-78] The model estimates relative risks and attributable risk parameters from US population-based case-control data separately for proximal, distal, and rectal cancer and combines these estimates with baseline age-specific cancer hazard rates based on Surveillance, Epidemiology, and End Results (SEER) incidence rates and competing mortality risks; key risk factors include demographic data, diet, lifestyle, and medical histories, as well as any colonoscopy findings. In addition to estimating future CRC risk, it may also be used to estimate current risk for advanced neoplasia, making it potentially useful for tailoring and improving CRC screening efficiency among average-risk individuals.

A more recent prediction model was developed to generate low-risk, intermediate-risk and high-risk groups for advanced colorectal neoplasia and had high discrimination with AUC of 0.78 in the development and internal validation cohorts.[16] The model includes sociodemographic and physical features, medical and family history and lifestyle factors and results from first-time screening colonoscopy in average risk, asymptomatic individuals. The model's ability to generate risk categories based on risk cut-off values can facilitate patient–provider discussions of screening options, notably non-invasive testing in the low-risk subgroup, with colonoscopy preferred in the high-risk subgroup.

Multifactorial Prediction Models

Incorporating FIT results to Improve CRC Risk Assessment

Risk prediction models have also combined FIT results with demographic, clinical and lifestyle factors, given the promising discriminatory performance of fecal hemoglobin concentration at screening. A number of studies have combined clinical risk factors for advanced neoplasia with FIT and have reported similar increases in the accuracy of FIT-based screening[79-85] (Table 2); in one study discrimination improved from an AUC of 0.69 to 0.76 with the risk-based plus FIT approach.[83] In addition, incorporating clinical factors, such as age and sex, for a risk-stratified FIT screening approach and using risk cut-off values instead of a FIT cut-offs may potentially improve the selection of high-risk individuals to colonoscopy by identifying more advanced neoplasia and CRC. However, in the United States, no currently available FIT is marketed to report quantitative hemoglobin concentration, even though some available FITs are indeed quantitative FITs.

Incorporating Genetic Risk to Personalize CRC Risk Assessment.

Risk prediction based on polygenic risk scores (PRS) may be used to identify individuals at high risk of CRC to enable enhanced screening and other interventions, including lifestyle related recommendations and possibly chemoprevention.[86] Furthermore, the age of screening initiation, surveillance intervals, or the modality of screening could potentially be informed by PRS. As the identified genetic risk variants tend to show similar risks in advanced adenomas, it is likely that the PRS can be important for the prediction of both advanced adenoma and CRC.[87] As the number of CRC risk loci continue to increase, it is also expected that the predictive

power of the PRS will further improve as machine learning approaches are applied to very large genetic studies to refine genome-wide genetic risk scores.[88]

Predictive models that include both non-genetic and genetic risk factors could provide a more complete assessment of CRC risk (Table 3).[88-94] Of critical importance are large-scale GWAS collaborations, including one that combines data from three consortia including the Genetics and Epidemiology of Colorectal Cancer Consortium (GECCO), the Colorectal Cancer Transdisciplinary Study (CORECT), and the Colon Cancer Family Registry (CCFR).[38] With GWAS results from over 125,000 individuals, the study demonstrated how a PRS derived from 95 independent association signals could impact clinical guidelines for preventive screening. The results were able to guide the age to initiate screening for those in the highest 1% (and 10%) percentiles of polygenic risk compared with lowest percentiles where the age difference decreased by 18 years (and 10 years) for men, and 24 years (and 12 years) for women.[95]

Data from this collaborative initiative also evaluated CRC risk based on lifestyle and environmental factors, in addition to genetic variants, in order to identify an optimal age to begin screening.[88] This model of CRC risk was created based on family history, 19 lifestyle and environmental factors (E-score), and 63 CRC-associated SNPs to incorporate genetic risk (G-score). The model projected a 10-year absolute risk of CRC for given risk profiles with recommended ages to initiate screening, as compared to the current practice of screening average risk individuals based on age alone. E-score and G-score each determined risk of CRC with greater accuracy than family history and the model that combined all factors estimated CRC risk with an AUC value of 0.63 (95% confidence interval (CI), 0.62-0.64) for men and 0.62 (95% CI, 0.61-0.63) for women. Discrimination was lowest based only on family history (ranging from 0.53 to 0.54) with comparable improvement based on E-score or G-score (ranging from 0.59 to 0.60). When using a combined E-score and G-score, starting age of colonoscopy differed by 12 years for men and 14 years for women, for those with the highest vs lowest 10% of risk, respectively.

What is the potential impact of population-based implementation of precision CRC screening*?*

There is growing evidence that a risk-adaptive screening approach may improve the yield of screening tests with a relatively lower utilization of colonoscopy than traditional strategies, in addition to changing the age of screening initiation. In a prospective study using data from 2 large US cohorts, the Nurses' Health Study and Health Professionals Follow-up Study, the relative and absolute risk of CRC incidence and mortality associated with colonoscopy exposure according to individuals' risk profiles was assessed.[3] A CRC risk score from 0 to 8 was generated based on family history, height, body mass index, smoking, physical activity, alcohol, aspirin use, and diet. The absolute benefit of colonoscopy exposure was more than twice higher for individuals with the highest than lowest CRC risk profile. In addition, those with a high- and low-risk profile could potentially start CRC screening up to 6-7 years earlier and later, respectively, than the currently recommended age of 45 years.

The TARGET-C Study is currently the only large-scale, multicenter randomized controlled trial to report on the feasibility, participation, yield and cost related to colonoscopy, FIT and a risk-adapted approach for three rounds of CRC screening conducted in China.[96,97] The study used a modified version of the Asia-Pacific Colorectal Screening score for risk stratification in the risk-adaptive screening cohort; the score uses age, sex, family history of CRC among FDRs, smoking, and body mass index. A score of 4 or greater categorizes a patient as high risk, and less than 4 defines low-risk patients. High- and low-risk patients were

referred to either colonoscopy or FIT screening, respectively and patients with positive FIT were referred for a diagnostic colonoscopy. The primary outcome of the study was detection rate of advanced colorectal neoplasms, including CRC and advanced adenomas.

Among 19,373 subjects, higher participation rates were in patients undergoing first-time FIT (94.0%, 7326/7793) and risk-adapted screening (85.2%, 6557/7697) compared with those undergoing colonoscopy (42.3%, 1644/3883). In the risk-adapted screening group, high-risk subjects (18.9%) were referred for colonoscopy and low-risk (80.8%) were referred for FIT. The detection rate of advanced neoplasms during the intention-to-screen analysis was highest for the colonoscopy group (2.76%) and lowest for the FIT group (1.15%), with the risk-adaptive approach yielding 1.65%. There were no statistically significant differences noted in the corresponding odds ratios for the detection rate of advanced neoplasia between the subgroups of risk-adapted and FIT screening at baseline. However, with cumulative screening and participation in all three rounds, adenoma detection rates increased to 2.17 for FIT and 2.35 for the risk-adapted screening group, with a final screening yield comparable to that of the one-time colonoscopy subgroup. More prospective studies are needed to understand the potential effectiveness and yield of screening strategies that take into account risk stratification.

What are the major challenges related to the realization of precision CRC screening?

Targeted CRC screening through risk assessment was a concept introduced 30 years ago[98] and despite a growing number of studies providing reliable prediction through use of models, large-scale, implementation-based studies to integrate risk scores into clinical practice are currently lacking. A number of potential barriers and limitations need consideration prior to use of prediction models in real-world practice settings (Table 4).

Reliable and accurate models are needed, in addition to patient and provider acceptability. Cost-effectiveness analysis has shown that a discriminatory performance with AUC of at least 0.65 is required for risk-based screening to be more cost-effective than uniform screening[48,99] and values of 0.7-0.8 are considered to indicate modest/good discrimination.[2] Some of the existing prediction models have low discriminative accuracy with AUCs less than 0.65 and resulting misclassification can produce an incorrect risk profile and recommendations. In addition, appropriate risk-thresholds need to be defined in order to best identify who and how to consider screening and to avoid excluding a large group of individuals who are moderate (or low risk) that may harbor CRC. Model risk cut-offs and provider recommendations could be adapted to specific contexts and available resources. For example, a model with cutoffs selected for high sensitivity could help providers feel comfortable offering non-invasive options. In the case of tests with moderate sensitivity (such as non-invasive tests), model cut-offs optimized for sensitivity could help providers and patients consider colonoscopy over a non-invasive test. Furthermore, acceptability by healthcare providers may rely on how confident they feel in recommending reduced screening intensity or later age to initiate screening for those individuals identified with a low-risk profile. There is likely to be less hesitancy by healthcare providers to accept a prediction score that identifies high-risk patients and allows for screening that may have not been considered by an age only eligibility criterion. Conversely, if individuals with a low-risk profile do not accept an alternative screening strategy to colonoscopy (which may be the case most often in opportunistic CRC screening programs), the cost-benefit of risk-based screening will be mitigated; more devastating would be if these individuals chose not to undergo any CRC screening. In a cost-effective analysis, tailored screening with risk prediction tools was preferred over the usual care of uniform screening only when there was no misclassification of risk and no cost to apply the risk-prediction tool; imperfect risk prediction can

lead to potential harms through misclassification than a simpler, uniform population-wide approach.[100]

Moving from a risk score to clinically actionable recommendations. Use of prediction models for risk assessment can identify low and high-risk groups, but how that data is used to determine when to initiate screening, how often, and by what approach, on an individual basis, will generate a wide range of screening and surveillance possibilities that will require the development of smart algorithms to efficiently determine optimal screening strategies by risk.[48] Such algorithms extrapolate data from risk-based screening trials which are currently limited. We also assume that the biological progression from precancerous neoplasia to CRC is the same in individuals with high and low risk profiles, which will also be elucidated through clinical trials to inform optimal surveillance strategies. We postulate that algorithms might be most useful when interactive, and able to elicit information about the clinical decision-making scenario. For example, an algorithm might return a different test recommendation for a patient-provider scenario where default is to pursue colonoscopy screening, and there is a desire to know whether a non-invasive option with lower sensitivity for CRC could be a safe option vs. a clinical scenario where the default is to elect for a less sensitive, non-invasive test, and there is a desire to make sure that choosing the non-invasive option is safe with respect to CRC risk.

Data collection and capture of key risk factors. Collection of relevant data elements to predict risk may require standardization to ensure that a score can be generated from complete and correct data. In addition, determining the appropriate time to generate a prediction score and how often, will require active engagement by both patient and caregiver as many risk factors, particularly those related to lifestyle, do not remain fixed over time. Systematic risk assessment that is structured and applied often and consistently is of importance and implementation strategies may leverage the EMR. In addition, patient engagement and personalizing risk could enhance patients' understanding of risk information and even encourage patient-driven risk assessment with potential to alter modifiable risk factors.

Translation and integration of '-omic' data. The additional risk stratification provided by PRS, and other 'omic strategies (e.g., transcriptomics, proteomics, methylome, metabolomics and microbiome), may be outweighed by their cost, complexity of the interpretation of data and population risk-profiling, with the potential for reduced patient access and participation, particularly among underrepresented populations. While the value of additional biomarkers to improve the targeting of measures for cancer prevention and early detection may be significant, for PRS to be clinically useful, it must provide sufficient risk discrimination that is also meaningful in the context of absolute CRC risk and applicable in the context of respective screening for CRC prevention and early detection.[101] Future research will likely extend from clinical risk factors and genomics to integrative multi-omic strategies to optimize risk assessment and to identify and validate biomarkers that underpin precision approaches.

What is the future for precision CRC screening?

Do the "one-size-fits-all" and "personalized risk-based" approaches to CRC screening need to be mutually exclusive? We should not lose sight that proven prevention measures exist and new strategies are meant to help improve these measures so that they are more broadly accessible, clinically applicable and used, particularly by patients who are from underrepresented populations. First steps to address the potential challenges of risk-based CRC screening programs require well-designed studies to help inform what personalized risk assessment approaches are reliable and feasible to apply across diverse populations and communities, so that they can provide more efficient and equitable CRC screening programs

without compromising current prevention efforts or widening the gap for those who remain unscreened. The outlook for precision CRC screening requires a research agenda to better prepare for a more comprehensive approach to risk-based CRC screening.

Build and validate better models, for all: The majority of current models need further validation in large, diverse populations. There has been little investigation of whether or how race and ethnicity, and other social determinants of health should be included in risk models, likely owing to the dearth of data from large cohorts with sufficient numbers of individuals in underrepresented groups, notably NHB and Hispanic individuals. For example, data on PRS for CRC risk assessment in diverse populations is limited, so current models that incorporate genomic data may only be considered for White individuals. Genomic studies have been predominantly conducted in White individuals of European descent and CRC associated SNPs may not apply to individuals with other genetic ancestry. In addition, individuals with other ancestry might have other risk relevant SNPs that are not incorporated into recent risk prediction models. Even clinical prediction models with simple demographic and lifestyle factors need additional external validation and potential correction for simple variables that may impact performance, such as race. Furthermore, to optimize clinical utility there should be a balance between simplicity of the model and prediction accuracy so that the risk factors are easy to obtain and measure and the means to generate the risk scores are not only reliable, but user-friendly.

Engage providers and patients to assess "buy-in": Precision screening and its implementation can become complex across the multiple phases needed to assess CRC risk. If a validated and reliable prediction model is identified, will it be consistently used, by whom, and which patients are more likely to be impacted? For the provider, it has been well-established that provider behaviors are difficult to modify, even when there is evidence to suggest operator-dependence can improve CRC screening and outcomes. Will providers consistently complete and update multiple data points for a CRC prediction model, at least annually? Will providers interpret the results accurately and provide information reliably and consistently to all patients for shared decision-making? Will providers adhere to recommendations for less intensive/optimal screening strategies for low-risk individuals? For the patients, we may potentially decrease screening participation if recommendations are not perceived to be universal and are difficult to interpret. Furthermore, mistrust may be a potential issue for certain patient populations and the precision screening message may get lost or misconstrued, particularly when the "best" screening tests are not offered to many. Risk perception drives participation in cancer screening programs;[102-104] those who participate in cancer screening versus those who do not, usually differ in their risk and perception of cancer and its associated mortality, comorbidities, and socioeconomic status.

Incorporate CRC screening results to redefine (and refine) risk assessment: It is unclear whether CRC risk scores can be applied over time to adjust screening intensity or whether previous findings at screening or surveillance will prove to be more relevant. The preventive effect of colonoscopy may offset certain clinical and genetic risk factors and impact future screening and surveillance recommendations. In a population-based study, colonoscopy was found to drastically reduce the absolute risk of CRC at a predefined genetic risk.[105] Future risk assessment should incorporate at least results from colonoscopy since many years of screening can be saved with a negative evaluation which provides cost savings and optimizes allocation of available resources.

Assess feasibility, resources, cost and cost-effectiveness of precision CRC screening on a population scale: Successful implementation of precision CRC screening on a population

level across various screening programs and healthcare systems will require careful assessment of feasibility and practicality. Decision-making about CRC screening in opportunistic programs is already time-consuming and complex for providers and patients due to availability of several screening modalities; the addition of detailed risk assessment could make this process more complicated and thereby limit efficiency and efficacy. Addition of risk assessment in organized screening programs would also add complexity in that additional clinical information and/or biospecimens (i.e., blood or saliva) would need to be collected and input into models. Automated risk assessment using accurate and up-to-date data from the EMR and other reliable sources will need to be considered and could be facilitated by artificial intelligence and machine learning approaches. For payers, the economic value of risk stratification will need to be demonstrated prior to widespread adoption through modeling and real-world studies.

"The Future depends on what we do in the Present"

The armamentarium of CRC screening tests, particularly non-invasive options, will continue to grow. Biomarker discovery for potential blood-based CRC screening tests is gaining momentum and will undoubtedly outpace our efforts to identify and implement the optimal risk assessment strategy for precision prevention in the very near future. Results from the ECLIPSE (Evaluation of ctDNA LUNAR Assay In an Average Patient Screening Episode) study highlight the urgency to appropriately identify high-risk individuals most suitable for colonoscopy rather than the option for a more convenient blood-based test that has lower reported sensitivity and specificity (83% and 13% sensitivity for CRC and advanced adenomas, and 90% specificity). For individuals at higher than average risk for CRC, opting for "up-front" colonoscopy, the test most sensitive for CRC and advanced adenomas, will help to optimize the impact of CRC screening efforts. As more convenient options such as blood tests become available, there is a danger the high-risk patients most likely to benefit from exposure to the most sensitive test may systematically be offered a one-size all approach and miss opportunities for early detection and prevention. While at a population-level we can subscribe to "the best test is the one that gets done" for CRC screening, we have the opportunity to optimize the benefits of CRC screening for early detection and prevention if we select "the right test for the right patient" and increase the diagnostic yield and preventive potential through colonoscopy in high-risk individuals.

Selecting the "right test for the right patient" in the near term can have a narrow focus, with systematic assessment of simple risk factors known to be associated with CRC which are readily available in the EMR or can be easily provided by the patient. Educating patients about their individual risk profile allows them to appreciate why they may be at high risk, that colonoscopy is the optimal screening approach, and how they may benefit from other targeted prevention strategies such as lifestyle modification, including weight loss, dietary changes, or smoking cessation. Knowledge of one's high-risk profile may also improve adherence to CRC screening. Even if high-risk individuals are "over-identified" and proceed to screening colonoscopy without any detected colorectal neoplasia, they would not warrant further testing for 10 years[6] (as per current guidelines; 5 years if FDR with CRC), where the relative single-time sensitivity of colonoscopy versus an alternate non-invasive test becomes relevant. Furthermore, colonoscopy will outperform alternate tests (including less expensive FIT) on a per high-risk participant basis for the detection of advanced adenomas and sessile serrated lesions, which account for up to 30% of CRC cases.[106]

Another simple way to optimize CRC risk assessment in the present is to increase the identification of individuals with family history of CRC. It is estimated that less than 40% of individuals with family history of CRC have disclosed this information to their healthcare

providers[107]; this can be increased with more patient access to the EMR and completing family history information in FDRs, which providers inconsistently obtain and record.[86,108] The critical importance of family CRC history has been recently elucidated among new CRC cases diagnosed in individuals younger than 50 years. Amongst those diagnosed with early CRC, two registry studies report that approximately 25% of these patients have a family history of CRC which would make them eligible for earlier colonoscopy initiation with the potential for CRC prevention.[109,110] In addition, 83-98% of patients could have been screened earlier than their age at diagnosis, suggesting a missed opportunity for averted or down-staged cancers.[110] Providers have an opportunity to identify those at high risk through family cancer history assessment and can recommend to CRC patients screening guidelines for at-risk relatives that include younger age of colonoscopy initiation.

Given the many potential benefits of risk-based CRC screening discussed in this review, it is incumbent upon the gastroenterology community to conduct well-designed studies that demonstrate the effectiveness of precision approaches. In addition to showing benefits over current one-size-fits-all approaches, these studies must also address feasibility, resources, efficiency, acceptability, cost, and cost effectiveness of risk-based strategies in order to ensure these approaches are generalizable, adaptable, acceptable and equitable across communities, screening programs and healthcare systems. Current ongoing risk-based breast cancer screening studies (i.e., US WISDOM study; European My Personal Breast Cancer Screening, MyPeBS; Canadian PERSPECTIVE I & II; UK PROCAS) could provide examples and cautionary tales of precision cancer screening, understanding that there are unique considerations in CRC screening.

Precision CRC screening has the potential, in theory, to further reduce CRC incidence and mortality through targeted screening with the hope of increasing patient participation and providing the "right test for the right patient". Achieving precision CRC screening will require accurate and validated risk models, adaptation of model cutoffs depending on different clinical scenarios and settings, buy-in from all stakeholders as well as assessment of practicality, resources, cost and cost effectiveness. While we design studies and await data on comprehensive risk-based CRC screening approaches, we should continue our efforts to provide risk-based screening recommendations based on age and family history that are already part of screening guidelines, as this will prepare us for the brave new world of precision CRC screening in the future.

REFERENCES

1.   Roberts MC. Implementation Challenges for Risk-Stratified Screening in the Era of Precision Medicine. *JAMA Oncol.* 2018;4(11):1484-1485.
2.   Robertson DJ, Ladabaum U. Opportunities and Challenges in Moving From Current Guidelines to Personalized Colorectal Cancer Screening. *Gastroenterology.* 2019;156(4):904-917.
3.   Wang K, Ma W, Wu K, et al. Long-Term Colorectal Cancer Incidence and Mortality After Colonoscopy Screening According to Individuals' Risk Profiles. *J Natl Cancer Inst.* 2021;113(9):1177-1185.
4.   Levin TR, Corley DA, Jensen CD, et al. Effects of Organized Colorectal Cancer Screening on Cancer Incidence and Mortality in a Large Community-Based Population. *Gastroenterology.* 2018;155(5):1383-1391 e1385.
5.   Keum N, Giovannucci E. Global burden of colorectal cancer: emerging trends, risk factors and prevention strategies. *Nat Rev Gastroenterol Hepatol.* 2019;16(12):713-732.
6.   Ladabaum U, Dominitz JA, Kahi C, Schoen RE. Strategies for Colorectal Cancer Screening. *Gastroenterology.* 2020;158(2):418-432.
7.   Shaukat A, Kahi CJ, Burke CA, Rabeneck L, Sauer BG, Rex DK. ACG Clinical Guidelines: Colorectal Cancer Screening 2021. *Official journal of the American College of Gastroenterology | ACG.* 2021;116(3):458-479.
8.   Wolf AMD, Fontham ETH, Church TR, et al. Colorectal cancer screening for average-risk adults: 2018 guideline update from the American Cancer Society. *CA Cancer J Clin.* 2018;68(4):250-281.
9.   Force USPST, Davidson KW, Barry MJ, et al. Screening for Colorectal Cancer: US Preventive Services Task Force Recommendation Statement. *JAMA.* 2021;325(19):1965-1977.
10.   Hoffmeister M, Schmitz S, Karmrodt E, et al. Male sex and smoking have a larger impact on the prevalence of colorectal neoplasia than family history of colorectal cancer. *Clin Gastroenterol Hepatol.* 2010;8(10):870-876.
11.   Hidayat K, Zhou HJ, Shi BM. Influence of physical activity at a young age and lifetime physical activity on the risks of 3 obesity-related cancers: systematic review and meta-analysis of observational studies. *Nutr Rev.* 2020;78(1):1-18.
12.   Nguyen SP, Bent S, Chen YH, Terdiman JP. Gender as a risk factor for advanced neoplasia and colorectal cancer: a systematic review and meta-analysis. *Clin Gastroenterol Hepatol.* 2009;7(6):676-681 e671-673.
13.   Shaw S, Berry S, Thomson J, Murray GI, El-Omar E, Hold GL. Gut Mucosal Microbiome Signatures of Colorectal Cancer Differ According to BMI Status. *Front Med (Lausanne).* 2021;8:800566.
14.   Ye P, Xi Y, Huang Z, Xu P. Linking Obesity with Colorectal Cancer: Epidemiology and Mechanistic Insights. *Cancers (Basel).* 2020;12(6).
15.   Brenner H, Hoffmeister M, Arndt V, Haug U. Gender differences in colorectal cancer: implications for age at initiation of screening. *Br J Cancer.* 2007;96(5):828-831.

16.   Imperiale TF, Monahan PO, Stump TE, Ransohoff DF. Derivation and validation of a predictive model for advanced colorectal neoplasia in asymptomatic adults. *Gut.* 2021;70(6):1155-1161.

17.   Schreuders EH, Ruco A, Rabeneck L, et al. Colorectal cancer screening: a global overview of existing programmes. *Gut.* 2015;64(10):1637-1649.

18.   Shaukat A, Levin TR. Current and future colorectal cancer screening strategies. *Nat Rev Gastroenterol Hepatol.* 2022;19(8):521-531.

19.   Hull MA, Rees CJ, Sharp L, Koo S. A risk-stratified approach to colorectal cancer prevention and diagnosis. *Nat Rev Gastroenterol Hepatol.* 2020;17(12):773-780.

20.   Melson JE, Imperiale TF, Itzkowitz SH, et al. AGA White Paper: Roadmap for the Future of Colorectal Cancer Screening in the United States. *Clin Gastroenterol Hepatol.* 2020;18(12):2667-2678 e2662.

21.   Inadomi JM, Vijan S, Janz NK, et al. Adherence to colorectal cancer screening: a randomized clinical trial of competing strategies. *Arch Intern Med.* 2012;172(7):575-582.

22.   Gupta S, Halm EA, Rockey DC, et al. Comparative effectiveness of fecal immunochemical test outreach, colonoscopy outreach, and usual care for boosting colorectal cancer screening among the underserved: a randomized clinical trial. *JAMA Intern Med.* 2013;173(18):1725-1732.

23.   Walker JG, Licqurish S, Chiang PP, Pirotta M, Emery JD. Cancer risk assessment tools in primary care: a systematic review of randomized controlled trials. *Ann Fam Med.* 2015;13(5):480-489.

24.   Schroy PC, 3rd, Emmons KM, Peters E, et al. Aid-assisted decision making and colorectal cancer screening: a randomized controlled trial. *Am J Prev Med.* 2012;43(6):573-583.

25.   Ladabaum U, Mannalithara A, Meester RGS, Gupta S, Schoen RE. Cost-Effectiveness and National Effects of Initiating Colorectal Cancer Screening for Average-Risk Persons at Age 45 Years Instead of 50 Years. *Gastroenterology.* 2019;157(1):137-148.

26.   Liang PS, Allison J, Ladabaum U, et al. Potential Intended and Unintended Consequences of Recommending Initiation of Colorectal Cancer Screening at Age 45 Years. *Gastroenterology.* 2018;155(4):950-954.

27.   Imperiale TF, Kahi CJ, Rex DK. Lowering the Starting Age for Colorectal Cancer Screening to 45 Years: Who Will Come...and Should They? *Clin Gastroenterol Hepatol.* 2018;16(10):1541-1544.

28.   Muller C, Ihionkhan E, Stoffel EM, Kupfer SS. Disparities in Early-Onset Colorectal Cancer. *Cells.* 2021;10(5).

29.   Patel SG, May FP, Anderson JC, et al. Updates on Age to Start and Stop Colorectal Cancer Screening: Recommendations From the U.S. Multi-Society Task Force on Colorectal Cancer. *Gastroenterology.* 2022;162(1):285-299.

30.   Siegel RL, Fedewa SA, Anderson WF, et al. Colorectal Cancer Incidence Patterns in the United States, 1974-2013. *J Natl Cancer Inst.* 2017;109(8).

31.   Murphy CC, Sandler RS, Sanoff HK, Yang YC, Lund JL, Baron JA. Decrease in Incidence of Colorectal Cancer Among Individuals 50 Years or Older After Recommendations for Population-based Screening. *Clin Gastroenterol Hepatol.* 2017;15(6):903-909 e906.

32.   Zaki TA, Singal AG, May FP, Murphy CC. Increasing Incidence Rates of Colorectal Cancer at Ages 50-54 Years. *Gastroenterology.* 2022;162(3):964-965 e963.

33. Cho MY, Siegel DA, Demb J, Richardson LC, Gupta S. Increasing Colorectal Cancer Incidence Before and After Age 50: Implications for Screening Initiation and Promotion of "On-Time" Screening. *Dig Dis Sci.* 2022;67(8):4086-4091.

34. Fuchs CS, Giovannucci EL, Colditz GA, Hunter DJ, Speizer FE, Willett WC. A prospective study of family history and the risk of colorectal cancer. *N Engl J Med.* 1994;331(25):1669-1674.

35. Samadder NJ, Curtin K, Tuohy TM, et al. Increased risk of colorectal neoplasia among family members of patients with colorectal cancer: a population-based study in Utah. *Gastroenterology.* 2014;147(4):814-821 e815; quiz e815-816.

36. Ng SC, Lau JY, Chan FK, et al. Increased risk of advanced neoplasms among asymptomatic siblings of patients with colorectal cancer. *Gastroenterology.* 2013;144(3):544-550.

37. Giardiello FM, Allen JI, Axilbund JE, et al. Guidelines on genetic evaluation and management of Lynch syndrome: a consensus statement by the US Multi-Society Task Force on colorectal cancer. *Gastroenterology.* 2014;147(2):502-526.

38. 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(3):432-444.

39. Jenkins MA, Makalic E, Dowty JG, et al. Quantifying the utility of single nucleotide polymorphisms to guide colorectal cancer screening. *Future Oncol.* 2016;12(4):503-513.

40. Han MA, Zeraatkar D, Guyatt GH, et al. Reduction of Red and Processed Meat Intake and Cancer Mortality and Incidence: A Systematic Review and Meta-analysis of Cohort Studies. *Ann Intern Med.* 2019;171(10):711-720.

41. McNabb S, Harrison TA, Albanes D, et al. Meta-analysis of 16 studies of the association of alcohol with colorectal cancer. *Int J Cancer.* 2020;146(3):861-873.

42. Clinton SK, Giovannucci EL, Hursting SD. The World Cancer Research Fund/American Institute for Cancer Research Third Expert Report on Diet, Nutrition, Physical Activity, and Cancer: Impact and Future Directions. *J Nutr.* 2020;150(4):663-671.

43. Bosetti C, Santucci C, Gallus S, Martinetti M, La Vecchia C. Aspirin and the risk of colorectal and other digestive tract cancers: an updated meta-analysis through 2019. *Ann Oncol.* 2020;31(5):558-568.

44. Guo CG, Ma W, Drew DA, et al. Aspirin Use and Risk of Colorectal Cancer Among Older Adults. *JAMA Oncol.* 2021;7(3):428-435.

45. Schwingshackl L, Schwedhelm C, Hoffmann G, et al. Food groups and risk of colorectal cancer. *Int J Cancer.* 2018;142(9):1748-1758.

46. Wang P, Song M, Eliassen AH, Wang M, Giovannucci EL. Dietary patterns and risk of colorectal cancer: a comparative analysis. *Int J Epidemiol.* 2022.

47. Siegel RL, Miller KD, Goding Sauer A, et al. Colorectal cancer statistics, 2020. *CA Cancer J Clin.* 2020;70(3):145-164.

48. Lansdorp-Vogelaar I, Meester R, de Jonge L, Buron A, Haug U, Senore C. Risk-stratified strategies in population screening for colorectal cancer. *Int J Cancer.* 2022;150(3):397-405.

49. Lansdorp-Vogelaar I, van Ballegooijen M, Zauber AG, et al. Individualizing colonoscopy screening by sex and race. *Gastrointest Endosc.* 2009;70(1):96-108, 108 e101-124.

50. Meester RGS, Peterse EFP, Knudsen AB, et al. Optimizing colorectal cancer screening by race and sex: Microsimulation analysis II to inform the American Cancer Society colorectal cancer screening guideline. *Cancer.* 2018;124(14):2974-2985.

51. Meulen MPV, Kapidzic A, Leerdam MEV, et al. Do Men and Women Need to Be Screened Differently with Fecal Immunochemical Testing? A Cost-Effectiveness Analysis. *Cancer Epidemiol Biomarkers Prev.* 2017;26(8):1328-1336.

52. Augustus GJ, Ellis NA. Colorectal Cancer Disparity in African Americans: Risk Factors and Carcinogenic Mechanisms. *Am J Pathol.* 2018;188(2):291-303.

53. Siegel R, Desantis C, Jemal A. Colorectal cancer statistics, 2014. *CA Cancer J Clin.* 2014;64(2):104-117.

54. Siegel RL, Miller KD, Fedewa SA, et al. Colorectal cancer statistics, 2017. *CA Cancer J Clin.* 2017;67(3):177-193.

55. Carethers JM. Screening for colorectal cancer in African Americans: determinants and rationale for an earlier age to commence screening. *Dig Dis Sci.* 2015;60(3):711-721.

56. Peng L, Weigl K, Boakye D, Brenner H. Risk Scores for Predicting Advanced Colorectal Neoplasia in the Average-risk Population: A Systematic Review and Meta-analysis. *Am J Gastroenterol.* 2018;113(12):1788-1800.

57. Usher-Smith JA, Walter FM, Emery JD, Win AK, Griffin SJ. Risk Prediction Models for Colorectal Cancer: A Systematic Review. *Cancer Prev Res (Phila).* 2016;9(1):13-26.

58. Smith T, Muller DC, Moons KGM, et al. Comparison of prognostic models to predict the occurrence of colorectal cancer in asymptomatic individuals: a systematic literature review and external validation in the EPIC and UK Biobank prospective cohort studies. *Gut.* 2019;68(4):672-683.

59. Ma GK, Ladabaum U. Personalizing colorectal cancer screening: a systematic review of models to predict risk of colorectal neoplasia. *Clin Gastroenterol Hepatol.* 2014;12(10):1624-1634 e1621.

60. Kaminski MF, Polkowski M, Kraszewska E, Rupinski M, Butruk E, Regula J. A score to estimate the likelihood of detecting advanced colorectal neoplasia at colonoscopy. *Gut.* 2014;63(7):1112-1119.

61. Tao S, Hoffmeister M, Brenner H. Development and validation of a scoring system to identify individuals at high risk for advanced colorectal neoplasms who should undergo colonoscopy screening. *Clin Gastroenterol Hepatol.* 2014;12(3):478-485.

62. Kim DH, Cha JM, Shin HP, Joo KR, Lee JI, Park DI. Development and validation of a risk stratification-based screening model for predicting colorectal advanced neoplasia in Korea. *J Clin Gastroenterol.* 2015;49(1):41-49.

63. Sekiguchi M, Kakugawa Y, Matsumoto M, Matsuda T. A scoring model for predicting advanced colorectal neoplasia in a screened population of asymptomatic Japanese individuals. *J Gastroenterol.* 2018;53(10):1109-1119.

64. Hong SN, Son HJ, Choi SK, et al. A prediction model for advanced colorectal neoplasia in an asymptomatic screening population. *PLoS One.* 2017;12(8):e0181040.

65. Yang HJ, Choi S, Park SK, et al. Derivation and validation of a risk scoring model to predict advanced colorectal neoplasm in adults of all ages. *J Gastroenterol Hepatol.* 2017;32(7):1328-1335.

66. Sung JJY, Wong MCS, Lam TYT, et al. A modified colorectal screening score for prediction of advanced neoplasia: A prospective study of 5744 subjects. *J Gastroenterol Hepatol.* 2018;33(1):187-194.

67. Imperiale TF, Monahan PO, Stump TE, Glowinski EA, Ransohoff DF. Derivation and Validation of a Scoring System to Stratify Risk for Advanced Colorectal Neoplasia in Asymptomatic Adults: A Cross-sectional Study. *Ann Intern Med.* 2015;163(5):339-346.

68. Schroy PC, 3rd, Wong JB, O'Brien MJ, Chen CA, Griffith JL. A Risk Prediction Index for Advanced Colorectal Neoplasia at Screening Colonoscopy. *Am J Gastroenterol.* 2015;110(7):1062-1071.

69. Park YM, Kim HS, Park JJ, et al. A simple scoring model for advanced colorectal neoplasm in asymptomatic subjects aged 40-49 years. *BMC Gastroenterol.* 2017;17(1):7.

70. Chen G, Mao B, Pan Q, Liu Q, Xu X, Ning Y. Prediction rule for estimating advanced colorectal neoplasm risk in average-risk populations in southern Jiangsu Province. *Chin J Cancer Res.* 2014;26(1):4-11.

71. Taylor DP, Burt RW, Williams MS, Haug PJ, Cannon-Albright LA. Population-based family history-specific risks for colorectal cancer: a constellation approach. *Gastroenterology.* 2010;138(3):877-885.

72. Bortniker E, Anderson JC. Do recent epidemiologic observations impact who and how we should screen for CRC? *Dig Dis Sci.* 2015;60(3):781-794.

73. Yeoh KG, Ho KY, Chiu HM, et al. The Asia-Pacific Colorectal Screening score: a validated tool that stratifies risk for colorectal advanced neoplasia in asymptomatic Asian subjects. *Gut.* 2011;60(9):1236-1241.

74. Cai QC, Yu ED, Xiao Y, et al. Derivation and validation of a prediction rule for estimating advanced colorectal neoplasm risk in average-risk Chinese. *Am J Epidemiol.* 2012;175(6):584-593.

75. Freedman AN, Slattery ML, Ballard-Barbash R, et al. Colorectal cancer risk prediction tool for white men and women without known susceptibility. *J Clin Oncol.* 2009;27(5):686-693.

76. Park Y, Freedman AN, Gail MH, et al. Validation of a colorectal cancer risk prediction model among white patients age 50 years and older. *J Clin Oncol.* 2009;27(5):694-698.

77. Ladabaum U, Patel A, Mannalithara A, Sundaram V, Mitani A, Desai M. Predicting advanced neoplasia at colonoscopy in a diverse population with the National Cancer Institute colorectal cancer risk-assessment tool. *Cancer.* 2016;122(17):2663-2670.

78. Imperiale TF, Yu M, Monahan PO, et al. Risk of Advanced Neoplasia Using the National Cancer Institute's Colorectal Cancer Risk Assessment Tool. *J Natl Cancer Inst.* 2017;109(1).

79. Chiu HM, Ching JY, Wu KC, et al. A Risk-Scoring System Combined With a Fecal Immunochemical Test Is Effective in Screening High-Risk Subjects for Early Colonoscopy to Detect Advanced Colorectal Neoplasms. *Gastroenterology.* 2016;150(3):617-625 e613.

80. He XX, Yuan SY, Li WB, et al. Improvement of Asia-Pacific colorectal screening score and evaluation of its use combined with fecal immunochemical test. *BMC Gastroenterol.* 2019;19(1):226.

81. Park CH, Jung YS, Kim NH, Park JH, Park DI, Sohn CI. Usefulness of risk stratification models for colorectal cancer based on fecal hemoglobin concentration and clinical risk factors. *Gastrointest Endosc.* 2019;89(6):1204-1211 e1201.

82. Cooper JA, Parsons N, Stinton C, et al. Risk-adjusted colorectal cancer screening using the FIT and routine screening data: development of a risk prediction model. *Br J Cancer.* 2018;118(2):285-293.

83. Stegeman I, de Wijkerslooth TR, Stoop EM, et al. Combining risk factors with faecal immunochemical test outcome for selecting CRC screenees for colonoscopy. *Gut.* 2014;63(3):466-471.

84. Kortlever TL, van der Vlugt M, Dekker E, Bossuyt PMM. Individualized faecal immunochemical test cut-off based on age and sex in colorectal cancer screening. *Prev Med Rep.* 2021;23:101447.

85. Aniwan S, Rerknimitr R, Kongkam P, et al. A combination of clinical risk stratification and fecal immunochemical test results to prioritize colonoscopy screening in asymptomatic participants. *Gastrointest Endosc.* 2015;81(3):719-727.

86. Burnett-Hartman AN, Newcomb PA, Peters U. Challenges With Colorectal Cancer Family History Assessment-Motivation to Translate Polygenic Risk Scores Into Practice. *Gastroenterology.* 2020;158(2):433-435.

87. Burnett-Hartman AN, Passarelli MN, Adams SV, et al. Differences in epidemiologic risk factors for colorectal adenomas and serrated polyps by lesion severity and anatomical site. *Am J Epidemiol.* 2013;177(7):625-637.

88. 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(8):2152-2164 e2119.

89. Balavarca Y, Weigl K, Thomsen H, Brenner H. Performance of individual and joint risk stratification by an environmental risk score and a genetic risk score in a colorectal cancer screening setting. *Int J Cancer.* 2020;146(3):627-634.

90. Hsu L, Jeon J, Brenner H, et al. A model to determine colorectal cancer risk using common genetic susceptibility loci. *Gastroenterology.* 2015;148(7):1330-1339 e1314.

91. Smith T, Gunter MJ, Tzoulaki I, Muller DC. The added value of genetic information in colorectal cancer risk prediction models: development and evaluation in the UK Biobank prospective cohort study. *Br J Cancer.* 2018;119(8):1036-1039.

92. Weigl K, Thomsen H, Balavarca Y, Hellwege JN, Shrubsole MJ, Brenner H. Genetic Risk Score Is Associated With Prevalence of Advanced Neoplasms in a Colorectal Cancer Screening Population. *Gastroenterology.* 2018;155(1):88-98 e10.

93. Ibanez-Sanz G, Diez-Villanueva A, Alonso MH, et al. Risk Model for Colorectal Cancer in Spanish Population Using Environmental and Genetic Factors: Results from the MCC-Spain study. *Sci Rep.* 2017;7:43263.

94. Sassano M, Mariani M, Quaranta G, Pastorino R, Boccia S. Polygenic risk prediction models for colorectal cancer: a systematic review. *BMC Cancer.* 2022;22(1):65.

95. Huyghe JR, Bien SA, Harrison TA, et al. Discovery of common and rare genetic risk variants for colorectal cancer. *Nat Genet.* 2019;51(1):76-87.

96. Chen H, Lu M, Liu C, et al. Comparative Evaluation of Participation and Diagnostic Yield of Colonoscopy vs Fecal Immunochemical Test vs Risk-Adapted Screening in Colorectal

Cancer Screening: Interim Analysis of a Multicenter Randomized Controlled Trial (TARGET-C). *Am J Gastroenterol.* 2020;115(8):1264-1274.

97. Chen H, Shi J, Lu M, et al. Comparison of Colonoscopy, Fecal Immunochemical Test, and Risk-Adapted Approach in a Colorectal Cancer Screening Trial (TARGET-C). *Clin Gastroenterol Hepatol.* 2022.

98. Lieberman DA. Targeted colon cancer screening: a concept whose time has almost come. *Am J Gastroenterol.* 1992;87(9):1085-1093.

99. Naber SK, Kundu S, Kuntz KM, et al. Cost-Effectiveness of Risk-Stratified Colorectal Cancer Screening Based on Polygenic Risk: Current Status and Future Potential. *JNCI Cancer Spectr.* 2020;4(1):pkz086.

100. 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(2):318-328.

101. Sud A, Turnbull C, Houlston R. Will polygenic risk scores for cancer ever be clinically useful? *NPJ Precis Oncol.* 2021;5(1):40.

102. Atkinson TM, Salz T, Touza KK, Li Y, Hay JL. Does colorectal cancer risk perception predict screening behavior? A systematic review and meta-analysis. *J Behav Med.* 2015;38(6):837-850.

103. Ward SH, Lin K, Meyer B, et al. Increasing colorectal cancer screening among African Americans, linking risk perception to interventions targeting patients, communities and clinicians. *J Natl Med Assoc.* 2008;100(6):748-758.

104. Koo JH, Arasaratnam MM, Liu K, et al. Knowledge, perception and practices of colorectal cancer screening in an ethnically diverse population. *Cancer Epidemiol.* 2010;34(5):604-610.

105. Carr PR, Weigl K, Edelmann D, et al. Estimation of Absolute Risk of Colorectal Cancer Based on Healthy Lifestyle, Genetic Risk, and Colonoscopy Status in a Population-Based Study. *Gastroenterology.* 2020;159(1):129-138 e129.

106. Leggett B, Whitehall V. Role of the serrated pathway in colorectal cancer pathogenesis. *Gastroenterology.* 2010;138(6):2088-2100.

107. Fletcher RH, Lobb R, Bauer MR, et al. Screening patients with a family history of colorectal cancer. *J Gen Intern Med.* 2007;22(4):508-513.

108. Murff HJ, Greevy RA, Syngal S. The comprehensiveness of family cancer history assessments in primary care. *Community Genet.* 2007;10(3):174-180.

109. Gupta S, Bharti B, Ahnen DJ, et al. Potential impact of family history-based screening guidelines on the detection of early-onset colorectal cancer. *Cancer.* 2020;126(13):3013-3020.

110. Stanich PP, Pelstring KR, Hampel H, Pearlman R. A High Percentage of Early-age Onset Colorectal Cancer Is Potentially Preventable. *Gastroenterology.* 2021;160(5):1850-1852.

Figure 1. Current and Proposed Precision CRC Screening Paradigms

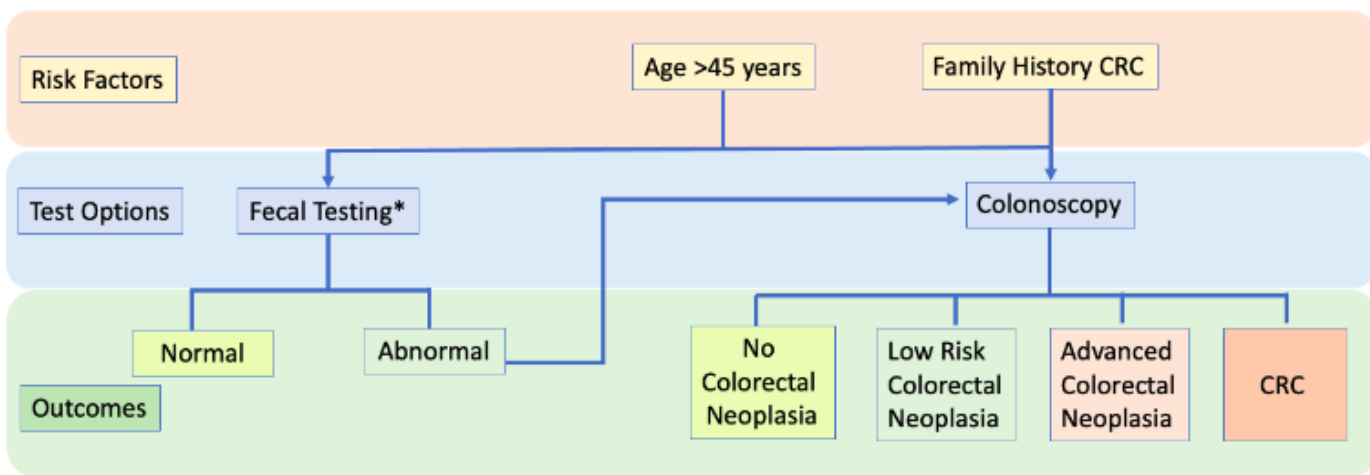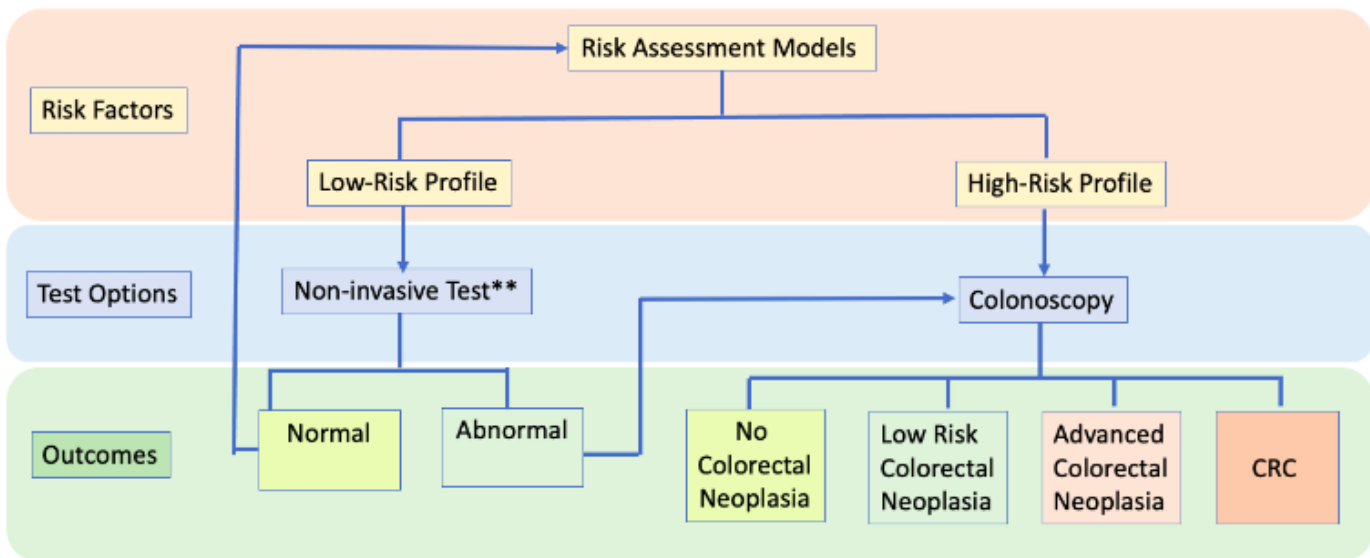Figure 1A. Current CRC Screening Paradigm

Figure 1B. Risk Assessment for Precision CRC Screening Paradigm

*Fecal testing: Fecal immunohistochemical testing (FIT) or multi-target stool DNA testing;
**Fecal testing or other future non-invasive testing options

Table 1. Potential Benefits of Risk Assessment for Precision CRC Screening for Patient, Provider and Healthcare System

Patient	Provider	Healthcare system
▪ Improved decision-making and test selection	▪ Improved decision-making and testing selection	▪ Optimize utilization/Decrease overutilization
▪ Personalized care	▪ Improve diagnostic yield of tests based on high-risk profile	▪ Direct invasive, costly testing to those with high-risk profile
▪ Mitigate unnecessary testing and associated harms	▪ Mitigate unnecessary testing and associated harms	▪ Cost-effective approach based on risk-profile
▪ Opportunity for lifestyle modification	▪ Counsel on lifestyle modification	▪ Decrease time to testing
▪ Recognize familial risk	▪ Improve patient adherence	▪ Improve patient adherence
	▪ Recognize familial risk	

Table 2

Table 2. Select Risk Prediction Models for Advanced Colorectal Neoplasia

CRC Risk Model/First Author	Country/ Region	Subject number**	Risk Factors	AUC (95% CI), Development	AUC (95% CI), Validation: Internal versus External*
Clinical Models					
Imperiale[16], 2021	US	3.025	Age, sex, smoking, alcohol, NSAID, aspirin, metabolic syndrome, red meat, physical activity, education, marital status	0.77	Internal; 0.78
Sekiguchi[63], 2018	Japan	5,218	Age, sex, FH, BMI, smoking	0.70 (0.67-0.73)	Internal; 0.70 (0.67-0.73)
Hong[64], 2017	Korea	24,725	Age, sex, smoking, alcohol, aspirin	0.72 (0.69-0.74)	Internal; 0.71 (0.69-0.74)
Park[69], 2017	Korea	2,781	Age, sex, HPylori serology, low HDL, high triglycerides	0.74 (0.72-0.76)	Internal; 0.72 (0.70-0.75)
Sung[66], 2018	Hong Kong	3,829	Age, sex, FH, BMI, smoking	0.65 (0.61-0.69)	Internal; 0.65 (0.61-0.69)
Yang[65], 2017	Korea	49,130	Age, sex, FH, BMI, smoking, serum fasting glucose, LDL, CEA	0.73 (0.71-0.75)	Internal; 0.68 (0.67-0.69)
Imperiale[67], 2015	US	2,993	Age, sex, FH, smoking, waist circumference	0.72	Internal; 0.77
Kim[62], 2015	Korea	3,561	Age, sex, FH, BMI, smoking	0.68 (0.61-0.76)	External*; 0.63 (0.59-0.67)

Study	Country	N	Variables	AUC (95% CI)	Validation; AUC (95% CI)
Schroy[68], 2015	US	3,543	Age, sex, race/ethnicity, FH, smoking, alcohol, height	0.69 (0.66-0.72)	External*; 0.68 (0.66-0.70)
Chen[70], 2014	China	905	Age, sex, cardiovascular disease, bowel movement frequency, egg intake	0.75 (0.69-0.82)	Internal; 0.75 (0.70-0.82)
Kaminski[60], 2014	Poland	17,979	Age, sex, FH, BMI, smoking	0.62 (0.60-0.64)	External*; 0.61 (0.59-0.64)
Tao[61], 2014	Germany	7,891	Age, sex, FH, smoking, alcohol, NSAIDs, aspirin, physical activity, prior colonoscopy, history of polyps	0.67 (0.65-0.69)	External*; 0.65 (0.63-0.68)
Cai[74], 2012	China	5,229	Age, sex, smoking, diabetes, consumption of vegetables/specific foods	0.74 (0.72-0.77)	External*; 0.70 (0.61-0.79)
Yeoh[73], 2011	Asia-Pacific	860	Age, sex, FH, smoking	0.66 (0.58-0.74)	External*; 0.63 (0.60-0.66)
Freedman[75], 2009	US	Case/Control# Colon cancer: 1599/1974; Rectal cancer: 664/859	Age, sex, FH, smoking, BMI, NSAID, aspirin, physical activity, HRT, vegetable intake, prior colonoscopy, prior polyp	Relative and Absolute Risk estimates	External[76]; Women: 0.61 (0.59-0.62); Men: 0.61 (0.60-0.62)
Clinical + FIT Models					
Kortlever[84], 2019	Netherlands	1,112	Age, sex, FIT	0.71 (0.65-0.79)	n/a
Park[81], 2019	Korea	3,733	Age, smoking, diabetes, FIT (square root)	0.75 (0.73-0.78)	n/a

He[80], 2019	China	955	Age, BMI, FH, diabetes, smoking, alcohol, FIT	0.69 (0.65-0.73)	External; 0.74 (0.70-0.78)
Cooper[82], 2018	UK	1,810	Age, sex, previous screening history, FIT	0.69 (0.66-0.71)	n/a
Chiu[79], 2016	Asia-Pacific	5,657	Age, sex, FH, smoking, FIT	Sensitivity 70.6% (AN), 95.1% (CRC)	External; Sensitivity 66.9% (AN), 96.7% (CRC)
Stegeman[83], 2014	Netherlands	1,112	Age, FH, calcium intake, FIT	0.76	n/a

*Pooled AUC from External Validation[56], **Development cohort, # SEER=Surveillance, Epidemiology, and End Results; FH=family history, BMI= body mass index, FIT=fecal immunohistochemical testing, LDL=low density lipoprotein, HDL=high density lipoprotein, CEA= carcinoembryonic antigen; AN=advanced neoplasia, n/a=not available.

Table 3

Table 3. Select Studies of CRC Risk Models that Integrate Genetic Risk

Model/First Author	Country	Case/ Controls, n	SNPs, n	Risk Factors	AUC (95% CI) without SNPs	AUC (95% CI) with SNPs
Balavarca[89], 2019	Germany	291 CRC, 236 non-advanced adenomas/ 487 controls	39	Age, sex, FH, smoking, alcohol, red meat, NSAIDs, history of colonoscopy or polyps	0.58 (0.55-0.62)	0.62 (0.58-0.65)
Jeon[88], 2018	Europe	4,875/5291	63	Age, sex, FH, height, BMI, smoking, alcohol, diabetes, NSAID, Aspirin, HRT, physical activity, dietary factors, education	Men: 0.60 (0.59-0.61); Women: 0.60 (0.59-0.61)	Men: 0.63 (0.62-0.64); Women: 0.62 (0.61-0.63)
Smith[91], 2018	UK	1294/286,877 (Wells model)	41	Age, FH, BMI, smoking, alcohol, diabetes, multivitamin, NSAID, red meat, HRT, physical activity, education	0.68 (0.67-0.69)	0.69 (0.65-0.68)
Weigl[92], 2018	Germany	294 (advanced neoplasia), 249 (non-advanced adenomas)/ 500 controls	48	Age, sex, BMI, history of colonoscopy, physical activity	0.615	0.665
Ibanez-Sanz[93], 2017	Spain	1,336/2,744	21	FH. BMI, alcohol, red meat, vegetables, NSAID, Aspirin, physical activity	0.61 (0.59-0.64)	0.63 (0.60-0.66)

| Hsu, 2015[90] | Europe/US | 12,113 | 27 | Age, sex, FH, history of colonoscopy | Women: 0.52 (0.50-0.55); Men: 0.51 (0.48-0.53) | Women: 0.56 (0.51-0.61); Men: 0.59 (0.54-0.64) |

SNP= single nucleotide polymorphism, AUC= area under the receiver operator curve, FH=family history, BMI=body mass index, NSAID=nonsteroidal anti-inflammatory drug; HRT=hormone replacement therapy

Table 4

Table 4. Potential challenges and opportunities related to predictive CRC risk models and implementation of precision CRC screening programs

CRC Prediction Models

- Need for reliable and accurate models to mitigate misclassification

- Use of complex versus simple models and consideration for risk thresholds

- Development and validation of models inclusive of racially and ethnically diverse populations worldwide

- Translation of risk profile into clinically actionable recommendations

- Integration of genomic and other "omic" data over time

- Integration of exposure to colonoscopy and impact of results into risk profile

- Patient and provider understanding and acceptability of risk profiling and directed decision-making

Implementation of precision CRC screening programs

- Feasibility and sustainability of integrating predictive CRC risk assessment

- Integration of risk factors and models into EMR

- Data collection and data integrity

- Cost and availability of resources for universal implementation of precision CRC screening programs

- Availability and delivery of colonoscopy for individuals with high risk profile and those with low risk and positive initial screening test

- Provider "buy in" and engagement by primary care physicians

- Stakeholder engagement at national, regional and community levels