HHS Public Access

Author manuscript

Eur J Cancer Prev. Author manuscript; available in PMC 2023 July 01.

Published in final edited form as:

Eur J Cancer Prev. 2022 July 01; 31(4): 318–325. doi:10.1097/CEJ.0000000000000715.

New Scoring Systems for Predicting Advanced Proximal Neoplasia in Asymptomatic Adults With or Without Knowing Distal Colorectal Findings: A Prospective, Cross-sectional Study

Thomas F. Imperiale, MD[1,2,3], **Patrick O. Monahan, PhD**[4], **Timothy E. Stump, MA**[4], **David F. Ransohoff, MD**[5]

[1]Division of Gastroenterology and Hepatology, Department of Medicine, Indiana University School of Medicine, Indianapolis, IN

[2]The Center for Innovation, Health Services Research and Development, Roudebush VA Medical Center, Indianapolis, IN

[3]Regenstrief Institute, Indianapolis, IN

[4]Department of Biostatistics, Indiana University School of Medicine, North Carolina.

[5]Department of Medicine, University of North Carolina at Chapel Hill, North Carolina.

Abstract

Background: Models estimating risk for advanced proximal colorectal neoplasia (APN) may be used to select a colorectal cancer (CRC) screening test, either prior to knowing distal colorectal findings or afterwards. Current models have only fair discrimination and nearly all require knowing distal findings.

Objective: Derive and test risk prediction models for APN with and without distal findings.

Setting: Selected endoscopy centers within central Indiana, U.S.A.

Participants: Average-risk persons undergoing first-time screening colonoscopy

Interventions: Demographics, personal and family medical history, lifestyle factors, and physical measures were linked to the most advanced finding in proximal and distal colorectal segments. For both models, logistic regression identified factors independently associated with APN on a derivation set. Based on equation coefficients, points were assigned to each factor, and

Corresponding author: Thomas F. Imperiale, MD, Indiana University Medical Center, Regenstrief Institute, Inc., 1101 West 10th Street, Indianapolis, IN 46202, TEL: 317-274-9046, FAX: 317-274-9304, timperia@iu.edu.

Authors' contribution: Acquisition of funding: Dr. Imperiale; Conception and design: Drs. Imperiale, Ransohoff; Study conduct: Dr. Imperiale; Analysis: Dr. Monahan, Mr. Stump; Drafting of the article: Dr. Imperiale, Dr. Monahan, Mr. Stump; Editing / critical revision of the article: Drs. Ransohoff and Monahan, Mr. Stump;

Competing Interest Statement: None of these authors has any competing financial or intellectual interests with the content of this study.

None of the authors has a competing interest with the content of this manuscript

Data Sharing Statement: Data sharing would be considered after reviewing a proposed study protocol.

Patient and Public Involvement Statement

Patients or the public WERE NOT involved in the design, or conduct, or reporting, or dissemination plans of our research

risk for APN examined for each score. Scores with comparable risks were collapsed into risk categories. Both models and their scoring systems were tested on the validation set.

Main outcome: APN, defined as any adenoma or sessile serrated lesion ≥1 cm, one with villous histology or high-grade dysplasia, or CRC proximal to the descending colon.

Results: Among 3,025 subjects in the derivation set (mean age 57.3 ± 6.5 years; 52% women), APN prevalence was 4.5%; 2,859 (94.5%) had complete data on risk factors. Independently associated with APN were age, sex, cigarette smoking, cohabitation status, metabolic syndrome, NSAID use, and physical activity. This model (without distal findings) was well-calibrated (P=0.62) and had good discrimination (c-statistic=0.73). In low-, intermediate-, and high-risk groups that comprised 21%, 58%, and 21% of the sample, respectively, APN risks were 1.47% (95% CI, 0.67–2.77%) 3.09% (CI, 2.31–4.04%), and 11.6% (CI, 9.10–14.4%), respectively (P<0.0001), with no proximal CRCs in the low-risk group and 2 in the intermediate-risk group. When tested in the validation set of 1455, the model retained good metrics (calibration P=0.85; c-statistic=0.83), with APN risks in low- (22%), intermediate- (56%), and high-risk (22%) subgroups of 0.62% (CI, 0.08– 2.23%) 2.20% (CI, 1.31–3.46%), and 13.0% (CI, 9.50–17.2%), respectively (P<0.0001). There were no proximal CRCs in the low-risk group, and two in the intermediate-risk group. The model with distal findings performed comparably, with validation set metrics of 0.18 for calibration, 0.76 for discrimination, and APN risk (% sample) in low-, intermediate-, and high-risk groups of 1.1% (69%), 8.3% (22%), and 22.3% (9%).

Conclusion: These models stratify large proportions of average-risk persons into clinically-meaningful risk groups, and could improve screening efficiency, particularly for non-colonoscopy-based programs.

Keywords

colorectal cancer screening; cancer prevention; colonoscopy; risk stratification; risk prediction

INTRODUCTION

Colorectal cancer (CRC) is the third most common visceral cancer both worldwide and in the U.S., and screening for CRC reduces its incidence and mortality(1). While screening has been implemented in many countries, the optimal strategy remains uncertain. Colonoscopy is the predominant screening test in the U.S., Germany, and Poland, while fecal blood testing predominates in Canada, the U.K, the Netherlands, and Australia, among other countries, in which colonoscopy resources may be limited.(2) Further, the current SARS-CoV-2 pandemic could require conservation of colonoscopy resources in countries where it is the predominant screening test. The U.S. Preventive Services Task Force supports CRC screening with any of several tests and strategies. While guidelines from other countries are more restrictive (3–6), all include both fecal blood testing and sigmoidoscopy. Among the guidelines, the most comprehensive are those from the European Union, a 450-page guideline published in book format by the European Commission that includes 10 chapters and over 250 recommendations, each of which is graded according to the strength of the recommendation and supporting evidence.(7)

For health care systems that perform population-based average-risk screening with sigmoidoscopy and modalities other than colonoscopy, screening efficiency could be improved by knowing the risk for advanced proximal colorectal neoplasia (i.e., APN, the combination of CRC and advanced, precancerous polyps in the proximal colon). While several risk prediction models for APN have been published(8–15), model performance varies, with most models having only fair discrimination, limited external validation, or both limitations. Further, nearly all models require knowing distal findings to estimate the risk for APN, limiting clinical utility to screening programs in which sigmoidoscopy is a primary modality. A model that does not require distal findings would have greater clinical application, as it could identify persons who require initial colonoscopy (because of high risk for APN) and who, because of low risk for APN, could be screened initially with sigmoidoscopy with or without FIT. For screening programs in which sigmoidoscopy is a primary modality, a prediction model that includes distal findings could be used to determine who – because of high risk of APN – requires examination of the proximal colon with colonoscopy.

Given the need for more discriminating models and, in particular, ones that do not require distal findings, we conducted this study with the objective of deriving and validating risk prediction models for APN among average-risk adults.

METHODS

This study was conducted at the Indiana University Medical Center in Indianapolis, Indiana, and was approved by the Institutional Review Board at Indiana University in Indianapolis (IRB study # 0404–59). Study subjects, who provided written informed consent, were not involved in the design, conduct, or reporting of this research. Study methods for subject recruitment, study procedures, and data management have been described previously (16, 17) and are herein described.

Study recruitment.

From December 2004 to September of 2011, we recruited persons aged 50–80 years who were scheduled to undergo their first screening colonoscopy. We initially targeted recruitment to two large corporations that provided screening colonoscopy to employees, retirees, and their eligible dependents, with procedures arranged by Indianapolis Gastroenterology Research Foundation, the research affiliate of Indianapolis, Gastroenterology and Hepatology. Because of nearly saturated uptake when recruitment began, we extended recruitment to Indianapolis Gastroenterology and Hepatology, a large, single-specialty practice in Indianapolis, Wishard Memorial Hospital, the Richard L. Roudebush Veterans Affairs Medical Center, and Margaret Mary Community Hospital, affiliates of Indiana University Medical Center. At all sites and throughout the study, we excluded persons with previous colorectal neoplasia, inflammatory bowel disease, and a reported history of polyps that required follow-up colonoscopy.

Study procedures.

Prior to screening colonoscopy, participants were mailed and completed a 12-page, 50-item self-administered survey that asked about candidate risk factors including family and personal medical history, sociodemographic features, medication use, and lifestyle factors that included diet, cigarette smoking, ethanol use, and leisure and dedicated physical activity. We included a 72-inch tape measure and asked participants to measure and record their height, weight, waist circumference, and hip circumference. Trained research assistants provided a follow-up call to confirm eligibility and to clarify both survey items and study procedures for participants. All returned surveys were reviewed for completeness by study personnel, who contacted participants for clarification or completion of survey items. At each participating site, colonoscopy was performed in standard fashion according to practice standards at the particular site. Colonoscopy quality metrics such as extent of examination, withdrawal time, and adenoma detection rate for individual endoscopists were not available because of inconsistent reporting in the case of cecal intubation or because the metric was established following study implementation. Previous data from a large segment of the participating endoscopists suggest high rates of complete examinations to the cecum.(18) Survey variables were linked to the most advanced finding on colonoscopy and that finding's location within the colorectum classified as follows: no neoplasia, non-advanced neoplasia, and advanced neoplasia. APN was the primary outcome and included adenomatous polyps or sessile serrated polyps 1 cm or larger, adenomatous polyps with villous histology and/or high-grade dysplasia, and adenocarcinoma in the splenic flexure and all segments proximal to it.

Data management and analysis.

Data were managed by the Department of Biostatistics, Indiana University School of Medicine. After review, completion, and coding, all data were scanned into a deidentified database with unique identifier numbers. Study sample size was based on both estimated prevalence of APN from a previous study of 3025 average-risk persons who had screening colonoscopy(10) and ensuring an adequate number of persons with APN for derivation and validation sets to avoid deriving an overfitted model. In analysis, a stratified random sample comprising two-thirds of the original sample was obtained using PROC SURVEYSELECT in SAS, version 9.3 (SAS Institute). Strata were created using the following variables: advanced neoplasia, sex, family history of cancer, and body mass index (BMI). Participants in this data set were used as the derivation set, and the other one third of participants were used as a validation set. The data set was divided in this way to ensure a random but equal distribution of the stratification variables in both derivation and validation sets.

The goal of the analysis was to identify the best performing models – one with and one without distal colorectal findings. The group of candidate variables was defined from responses to the survey. Potential independent variables included the following measures: gender, age (years), waist circumference (women: (1) ≥ 34.6 < 43.3 inches and (2) ≥ 43.3 inches; men: (1) ≥ 37.4 < 47.2 inches and (2) ≥ 47.2 inches), family history of CRC (≥1 first degree relatives with colon cancer), smoking (> 0 to < 30 pack-years and ≥ 30 pack years), education (college degree or higher), marital status (married or living with a significant other), any alcohol use over the previous 20 years (women: ≥ 6 drinks/week; men: ≥ 11

drinks/week), regular physical activity over past 10 years similar to brisk walking, jogging, bicycling, etc. (more than once a week for ≥ 2 years), hours spent sitting on average each day (≥ 10 hours), vigorous exercise (e.g., racquet sports, basketball, running, weight lifting, backpacking, swimming) over the past year (> 0 hours/week), moderate exercise (e.g., vacuuming, raking leaves, mowing the lawn, gardening, walking) over the past year (number of hours per week), insulin dependence, metabolic syndrome (evidence of three or more of the following: hypertension, high cholesterol, diabetes, and large waist size (≥ 40 inches for men, ≥ 35 inches for women), sigmoidoscopy or report of polyps in past 10 years, NSAID and aspirin use (daily use for 1 year or more), vegetable consumption (tomatoes, raw or cooked vegetables, carrots, corn, green leafy vegetables or cabbage - number of servings per week), red meat consumption (beef, liver, frankfurter/sausage, or ham - number of servings per week), estrogen or other female hormone use (men coded as no hormone use) and distal neoplasia findings (non-advanced and advanced).

The modeling process was performed two separate times, one excluding distal findings and one including it as a candidate variable, resulting in separate, independent model development for each scenario. For both processes, best subsets multiple logistic regression(19) was used to generate all possible models having 1 variable, 2 variables, 3 variables and so on up to the single model including all candidate variables. Best subset models were ranked by the following model metrics: lowest Mallow's C,(20) lowest Akaike information criterion (AIC) and the highest frequency with which each variable appeared in the top models. The final model was chosen based on triangulation of model metrics from the best subsets procedure, results from the backward elimination procedure, and judgment as to the feasibility of accurately measuring the model's variables in clinical practice. Model calibration and discrimination were measured with the Hosmer-Lemeshow goodness-of-fit (GOF) test and c-statistic, respectively. The final model was then run using the validation set, with reporting of the same model statistics.

For both models separately, we derived a risk scoring system using an approach described by Sullivan and colleagues.(21) Risk variables were organized into meaningful categories in which a reference value for each category was defined as 1 for indicator variables and as the mid-point for continuous variables. The log-odds coefficients were re-scaled into a point system in which 1 point was equivalent to the increase in risk for APN associated with a 5-year increase in age. Points were then rounded to the nearest integer. The base category for each risk variable was assigned 0 points. Consistent with previous work, we collapsed the resulting total point score into a smaller number of risk categories (low, intermediate, high) with numerically similar risk estimates. The chi-square test for trend was used to test for a trend in the risk for (or prevalence of) APN among the risk categories. In the validation set, model calibration and discrimination were assessed (without and with distal findings), and the chi-square test for trend was performed to validate the scoring system's risk categories using the same score cutoffs from the derivation set. SAS, version 9.3 was used for all analyses.

Role of the Funding Source ——The funding source had no role in the design, conduct, or analysis of the study or the decision to submit the manuscript for publication.

RESULTS

Between December 2004 and September of 2011, we recruited and enrolled 4,500 persons aged 50 to 80 years who were scheduled for their first screening colonoscopy. Demographic and clinical variables of the derivation (n=3,025) and validation (n=1,475) subgroups were comparable, including the proportion of participants with complete data who were included in the analyses (Table 1). For the model that did not use distal findings, there were four additional persons with complete data for the validation subset (Table 1). The study cohort overall was 94% white.

Final derivation models.

Variables used in the two models are shown in Table 2, which includes the criteria and definition for each variable, the prevalence of each variable's categories, and multivariable P-values, odds ratios (ORs) and 95% confidence intervals (CI). The model without distal findings included seven of the same factors as the model with distal findings, the exceptions being distal findings and regular aspirin use (Table 2). Age, male gender, smoking, metabolic syndrome and distal findings were associated with increased risk for APN (odds ratios ranging from 1.06 to 3.01) while cohabitation status, NSAID use, aspirin use and moderate physical activity were associated with decreased risk (ORs ranging from 0.43 to 0.99). Similar ORs were obtained for the model without distal findings. Both models demonstrated good discrimination and calibration in the derivation set (c-statistic = 0.76 [CI, 0.71–0.80] and P=0.18 for the model with distal findings; and c-statistic = 0.73 [CI, 0.69–0.78] and P = 0.62 for the model without distal findings).

Points assigned to the different values for each variable in the two models are shown in Table 3. For the model with distal findings, the oldest age category and advanced distal endoscopic findings had the most points (4), while frequent, regular NSAID use and 5 or more hours per week of moderate physical activity were most protective, at −3 and −2 points, respectively. While scores could range potentially from −7 to 14, actual scores ranged from −6 to 13 points. Similar point values were obtained for the model without distal findings, which had an actual score range equal to the possible score range of −7 to 10. For both models, we computed the risk for APN for each score and collapsed scores with numerically similar risks into risk categories of low, intermediate, and high risk for APN. Three risk categories were identified for both models, although with a different distribution of study participants in each risk category.

Model without distal findings.

Respective risks for APN in the derivation set for low-risk, intermediate-risk, and high-risk groups were 1.47% (CI, 0.67–2.77%), 3.03% (CI, 2.26–3.97%), and 11.6% (CI, 9.1–14.4%) (P-value for trend < 0.001), with respective group proportions of 21%, 58%, and 21% (bottom portion of Table 4). Nine low-risk participants had APN, none of whom had CRC. Of 1,651 intermediate-risk participants, two had CRC.

In the validation set of 1,455 participants, model metrics were comparable to or better than those of the derivation set: calibration P-value = 0.85, c-statistic = 0.83 (CI, 0.77–0.88).

Risks for APN were similar to those of the derivation set: 0.62% (CI, 0.08–2.23%) in the low-risk group, 2.20% (CI, 1.31–3.46%) in the intermediate-risk group, and 13.0% (CI, 9.5–17.2%) in the high-risk group (P-value for trend < 0.001) with respective group proportions of 22%, 56%, and 22%, which again was nearly identical to the derivation set (bottom of Table 4). Of 322 low-risk participants, none had CRC, while just 2 of 818 intermediate-risk participants had CRC.

Model with distal findings.

Respective risks for APN in the derivation set for the low-risk, intermediate-risk, and high-risk groups were 2.05% (CI, 1.47–2.78%), 5.67% (CI, 3.98–7.80%), and 18.1% (CI, 13.9–23.0%) (P-value for trend < 0.001), with respective group proportions of 68%, 22%, and 10% (Table 4). Forty low-risk participants had APN, one of whom had CRC and with no distal polyp. Eight of the 40 APN lesions would have been detected with sigmoidoscopy if colonoscopy were performed for any distal polyp.

In the validation set of 1,451 participants, model metrics were comparable to those of the derivation set: calibration P-value = 0.77, c-statistic = 0.84 (CI, 0.79–0.89). Table 4 shows risks for APN were similar to those of the derivation set: 1.10% (CI, 0.55–1.97%) in the low-risk group, 6.5% (CI, 4.06–9.74%) in the intermediate-risk group, and 22.3% (CI, 15.5–30.4%) in the high-risk group (P-value for trend < 0.001) with respective group proportions of 69%, 22%, and 9%, which is nearly identical to those in the derivation set. Eleven low-risk subjects had APN, none of whom had CRC. Two of the 11 APN lesions would have been detected with sigmoidoscopy if colonoscopy were performed for any distal polyp.

DISCUSSION

While several models are available for prediction of APN (8–15), they have important limitations that may reduce their real-world practical clinical application. Limitations include substantial variation in demographic features of the study populations, the variables associated with APN, how each variable is used to estimate APN risk, the number of risk categories, and in model performance, as measured by calibration, discrimination, and risk gradient across categories. In general, model discrimination is only fair, ranging from 0.55 to 0.74. Independent validation of the models has been limited or not done at all. Furthermore, nearly all previous models include distal findings as a risk factor, and thus cannot provide information about risk in persons who have not had sigmoidoscopy, limiting application of risk estimation for screening programs in which sigmoidoscopy is not utilized.

In this cohort of average-risk individuals who had first-time screening colonoscopy, we identified several factors associated with APN, which had a prevalence of 4.5% and 4.2% in derivation and validation sets, respectively. We used these factors to derive and validate two risk prediction models for APN: one without and one with distal findings. The models are an improvement over previous models, as they show greater discrimination than nearly all previous models, and identify sizeable subgroups at low-risk and high-risk, with a clinically-significant difference among the 3 risk levels in both models. These qualities facilitate their use in tailoring screening based on risk group: persons with low risk for APN could be initially screened with sigmoidoscopy, FIT, or both tests, while those at high risk – either

initially or following sigmoidoscopy – colonoscopy would be recommended because of high risk for APN.

We conducted the current study with the hypothesis that examining a greater number of candidate risk factors might provide greater discrimination than that of previous models and created models with and without distal findings. The model without distal findings may find more widespread use, as it is not limited to screening programs that are sigmoidoscopy-based. Further, we sought to improve model metrics of discrimination, risk gradient and the proportions of persons at low- and high-risk among those models that require distal findings. Previous studies have established the association between each candidate variable in these models and CRC, advanced adenomas, or both findings.(22) It is therefore not surprising that age, gender, smoking and metabolic syndrome had the greatest effect on APN risk or that physical activity, NSAID, and aspirin use had protective effects.

In a previous study of a separate cohort,(10) we identified age, gender, and distal findings as independent factors and used these to derive and validate a model that identified low-, intermediate-, and high-risk subgroups, in which respective APN risks were 0.4%, 1.92%, and 3.79% in 47%, 40% and 13% of the validation group, respectively. This model has been independently tested by two groups of investigators. Levitsky and colleagues tested it in a racially heterogenous sample of average-risk patients undergoing screening colonoscopy, and found - in low-, intermediate-, and high-risk groups - APN risks of 1.0% to 2.8% to 3.7% among 1,481 Whites, 1.0 to 2.2% to 4.2% among 1,329 Blacks, and 0.6% to 1.9% to 3.7% among 689 Hispanics, respectively, with c-statistics of 0.62–0.68. The investigators concluded that the model had limited ability to discriminate low from intermediate risk.(23) Ruco and colleagues reached a similar conclusion after testing the model in 5,139 asymptomatic 50-to-74-year-old Canadians in which the prevalence of APN was 3.2% overall and was 2.1%, 2.9% and 6.5% in the low-, intermediate-, and high-risk groups, respectively (c-statistic=0.62), findings indicating limited discrimination between low- and intermediate-risk groups, but good discrimination between low- and high-risk groups.(13)

Besides our previous model and its two validation studies, there are several other risk prediction models.(8, 9, 11–15) The studies from which the models originate are summarized in supplementary Table 1 (showing selected study features) and supplementary Table 2 (showing study results and model performance metrics). The studies vary by country, study design, and how the distal segment is defined, but nearly all are based on findings in average-risk persons undergoing screening colonoscopy. Sample sizes range from 2,210 to 7,589 and APN prevalence ranges from 1.8% to 3.4%. All except one of the models includes distal findings, a factor consistently associated with APN risk. From both clinical and population perspectives, however, the need for distal findings restricts application of these models because of the need to know the number and histology of distal polyps. In the only model without distal findings, Wong and colleagues applied a previously validated model for colorectal neoplasia anywhere in the colorectum to identify whether and how it might be useful for estimating APN risk.(14) The risk score, which ranges from 0 to 6, assigns one point each for age category, sex, smoking, family history of CRC, BMI, and diabetes. Dichotomizing the score into a low-risk group (scores of 0, 1, and 2) and high-risk group (scores of ≥ 3) resulted in APN risks of 1.1–2.3% and 3.4–9.1%, respectively. The

proposed strategy of initial sigmoidoscopy for scores of 0–2 and colonoscopy for scores of ≥ 3 detected only 32% of APN. The limited performance of these previous models and their requirement for distal findings prompted us to conduct the current study.

How these two new models are used will depend partly on the extent to which a screening program uses sigmoidoscopy, as either or both models may be useful alone or in sequence. While FIT was not part of the current study, we consider its use here for illustrative purpose because of its widespread use throughout the world. For countries or health care systems in which non-invasive testing, sigmoidoscopy, and colonoscopy are equally available, one suggestion (Figure) is to use the model without distal findings to tailor how initial screening is performed: persons at high risk (21–22% of the population) would be referred for colonoscopy, as their estimated risk for APN is 12–13%. For those at low-risk (also 21–22% of the population), sigmoidoscopy alone or following a negative FIT might be sufficient screening. For the remaining intermediate-risk group of 56–58%, sigmoidoscopy with or without FIT could be used initially. If FIT is positive, then a diagnostic colonoscopy is indicated. If FIT is negative, then sigmoidoscopy could be considered and if performed, a revised risk estimate for APN obtained based on the model that includes distal findings (Figure). In the current SARS-CoV-2 pandemic, the proposed strategy may help conserve colonoscopy and related equipment, as well as health care personnel resources.

This study has limitations that require comment. While discrimination of both models is better than nearly all previous models, it could be even higher (0.85 or more). The low-risk subgroups of both models include persons with APN, ranging from 1.1%−2.2%, one of whom had a proximal CRC with no distal findings. While this person was in the intermediate risk category of the model without distal findings or may have been FIT positive, neither model is perfectly discriminating, meaning that some APN will be missed. Second, model validation was limited to a split sample of a single cohort. Independent validation of both models is required. Finding comparable or better performance of either or both models in an independent cohort would provide reassurance about their potential utility in screening programs. Third, while there are several models that estimate risk for APN, there are no published data on their impact on screening uptake, adherence, efficiency, or cost-effectiveness. Fourth, distal findings were based not on actual sigmoidoscopy, but on colonoscopic findings in the distal colon, which included all segments distal to the splenic flexure. In sigmoidoscopy-based screening programs, examination is considered complete when the junction between the sigmoid and descending colons is reached, although often the junction is not readily discernible and descending colon may be visualized. Nonetheless, it is possible that our findings may not generalize to screening programs in which the descending colon is frequently not examined.

In conclusion, we have derived and validated two models that estimate the risk of APN with potentially practical clinical application. In the current era of personalized medicine, with shared decision making for CRC screening recommended in guidelines, and most recently, the world-wide need to conserve colonoscopy resources and the personal protective equipment it requires, these models may be useful for risk stratification, particularly in screening programs for which sigmoidoscopy and/or non-invasive testing are the predominant screening tests.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

Grant support: This work was supported by the National Cancer Institute ((R01-CA104459); the Walther Cancer Institute, Indianapolis, IN; The Indiana University Melvin and Bren Simon Cancer center; and a project development team within the Indiana Clinical and Translational Sciences Institute (grant UL1TR001108) from the National Center for Research Resources, National Institutes of Health), Indianapolis, IN.

REFERENCES

1. Siegel RL, Miller KD, Goding Sauer A, Fedewa SA, Butterly LF, Anderson JC, et al. Colorectal cancer statistics, 2020. CA Cancer J Clin. 2020.
2. IARC Working Group on the Evaluation of Cancer-Preventive Interventions. IARC Handbooks of Cancer Prevention. Colorectal cancer screening. Lyon (FR): International Agency for Research on Cancer; 2019.
3. Lin JS, Piper MA, Perdue LA, Rutter CM, Webber EM, O'Connor E, et al. Screening for Colorectal Cancer: Updated Evidence Report and Systematic Review for the US Preventive Services Task Force. JAMA. 2016;315(23):2576–94. [PubMed: 27305422]
4. Benard F, Barkun AN, Martel M, von Renteln D. Systematic review of colorectal cancer screening guidelines for average-risk adults: Summarizing the current global recommendations. World J Gastroenterol. 2018;24(1):124–38. [PubMed: 29358889]
5. Leddin DJ, Enns R, Hilsden R, Plourde V, Rabeneck L, Sadowski DC, et al. Canadian Association of Gastroenterology position statement on screening individuals at average risk for developing colorectal cancer: 2010. Can J Gastroenterol. 2010;24(12):705–14. [PubMed: 21165377]
6. Sung JJ, Lau JY, Young GP, Sano Y, Chiu HM, Byeon JS, et al. Asia Pacific consensus recommendations for colorectal cancer screening. Gut. 2008;57(8):1166–76. [PubMed: 18628378]
7. European guidelines for quality assurance in colorectal cancer screening and diagnosis. First ed. Luxembourg: Publication Office of the European Union; 2010.
8. Huang JL, Chen P, Yuan X, Wu Y, Wang HH, Wong MC. An algorithm to predict advanced proximal colorectal neoplasia in Chinese asymptomatic population. Scientific reports. 2017;7:46493. [PubMed: 28418028]
9. Ibáñez MB, Muñoz-Navas MA, Duque JM, Angós R, Macías E, Súbtil JC, et al. Diagnostic value of distal colonic polyps for prediction of advanced proximal neoplasia in an average-risk population undergoing screening colonoscopy. Gastrointestinal endoscopy. 2004;59(6):634–41. [PubMed: 15114305]
10. Imperiale TF, Wagner DR, Lin CY, Larkin GN, Rogge JD, Ransohoff DF. Using risk for advanced proximal colonic neoplasia to tailor endoscopic screening for colorectal cancer. Ann Intern Med. 2003;139(12):959–65. [PubMed: 14678915]
11. Park HW, Han S, Lee JS, Chang HS, Lee D, Choe JW, et al. Risk stratification for advanced proximal colon neoplasm and individualized endoscopic screening for colorectal cancer by a risk-scoring model. Gastrointest Endosc. 2012;76(4):818–28. [PubMed: 22884098]
12. Rabeneck L, Paszat LF, Hilsden RJ, McGregor SE, Hsieh E, Tinmouth JM, et al. Advanced proximal neoplasia of the colon in average-risk adults. Gastrointestinal endoscopy. 2014;80(4):660–7. [PubMed: 24679656]
13. Ruco A, Stock D, Hilsden RJ, McGregor SE, Paszat LF, Saskin R, et al. Evaluation of a risk index for advanced proximal neoplasia of the colon. Gastrointestinal endoscopy. 2015;81(6):1427–32. [PubMed: 25771065]
14. Wong MC, Ching JY, Chan VC, Lam TY, Luk AK, Wong SH, et al. Identification of subjects at risk of proximal advanced neoplasia for colorectal cancer screening. European Journal of Cancer. 2015;51(1):37–44. [PubMed: 25459390]

15. Wong MC, Lam TY, Tsoi KK, Hirai HW, Chan VC, Ching JY, et al. A validated tool to predict colorectal neoplasia and inform screening choice for asymptomatic subjects. Gut. 2014;63(7):1130–6. [PubMed: 24045331]

16. 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):339–46. [PubMed: 26259154]

17. Imperiale TF, Yu M, Monahan PO, Stump TE, Tabbey R, Glowinski E, et al. Risk of Advanced Neoplasia Using the National Cancer Institute's Colorectal Cancer Risk Assessment Tool. J Natl Cancer Inst. 2017;109(1).

18. Morelli MS, Miller JS, Imperiale TF. Colonoscopy performance in a large private practice: a comparison to quality benchmarks. J Clin Gastroenterol. 2010;44(2):152–3. [PubMed: 19770678]

19. Hosmer DW, Jovanovic B, Lemeshow S. Best subsets logistic regression. Biometrics. 1989:1265–70.

20. Mallows CL. Some comments on C p. Technometrics. 1973;15(4):661–75.

21. Sullivan LM, Massaro JM, D'Agostino RB Sr. Presentation of multivariate data for clinical use: The Framingham Study risk score functions. Statistics in medicine. 2004;23(10):1631–60. [PubMed: 15122742]

22. 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):1788–800. [PubMed: 30315282]

23. Levitzky BE, Brown CC, Heeren TC, Schroy PC 3rd. Performance of a risk index for advanced proximal colorectal neoplasia among a racially/ethnically diverse patient population (risk index for advanced proximal neoplasia). Am J Gastroenterol. 2011;106(6):1099–106. [PubMed: 21326221]

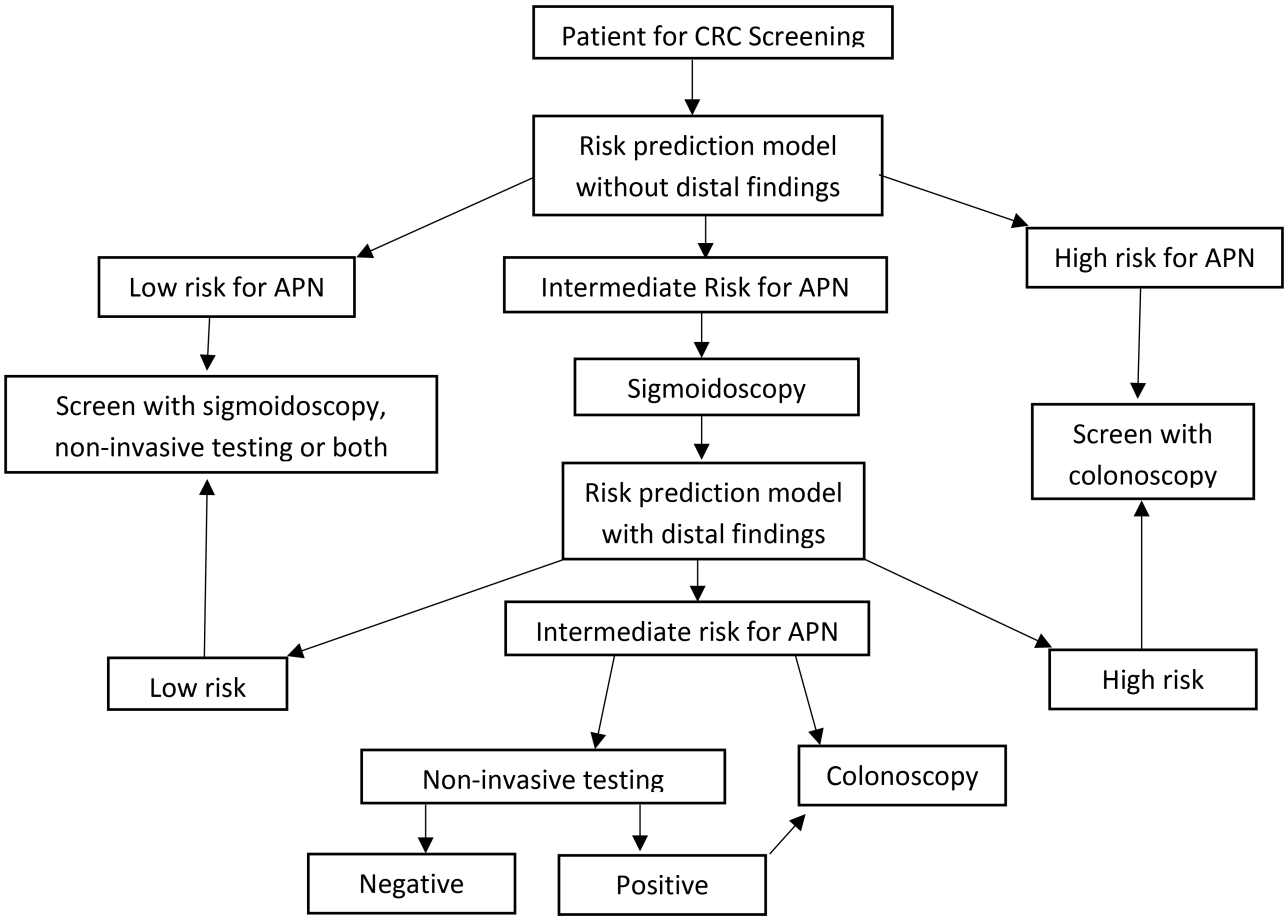

Figure.
Suggest strategy for application of the risk prediction models for APN

Table 1.

Descriptive Data

Variable	Derivation set	Validation set
N	3,025	1,475
Age (mean ± SD) years	57.3 ± 6.5	57.2 ± 7.0
Women (%)	51.6	51.5
Caucasian (%)	94	94
FDR with CRC (%)	9.6	9.2
Advanced neoplasia (%)	9.4	8.5
Advanced proximal neoplasia (%)	4.5	4.2
N (%) complete data	2,859 (94.5)	1,451 (98.3) or 1,455 (98.6) *

* The sample size was 1451 for the model with distal findings and 1455 for the model without distal findings.

Table 2.

Description, Prevalence and Odds Ratios of Model Variables Based on Derivation Set (N=2,859)

			With Distal Findings and Aspirin Use*		Without Distal Findings and Aspirin Use**	
Variable	**Description**	**Prevalence**	**P-value**	**Odds ratio (95% CI)**	**P-value**	**Odds ratio (95% CI)**
Age	Years	46% - <55 25 % - >=55 <60 17% - >=60 < 65 7% - >=65 < 70 5% - >=70	<0.0001	1.06 (1.04–1.09)	<0.0001	1.07 (1.04–1.09)
Gender	Men / Women	49% men	0.02	1.60 (1.07–2.38)	0.009	1.69 (1.14–2.49)
Cohabitation status	Married / living w/ significant other	84%	0.15	0.71 (0.45–1.12)	0.03	0.61 (0.39–0.95)
Smoking	>0 to <30 pack-years >30 pack-years	25% 15%	0.16 0.01	1.43 (0.92–2.24) 1.82 (1.14–2.89)	0.07 0.001	1.51 (0.97–2.34) 2.09 (1.33–3.30)
NSAID use	Daily and ≥ 1 year	10%	0.05	0.43 (0.19–1.00)	0.02	0.38 (0.16–0.87)
Aspirin use	Daily and ≥ 1 year	27%	0.12	0.72 (0.47–1.09)	NA	NA
Moderate activity (over last year)	hours / week (x # months)	44%: 0–1.6 42%: 1.7–4.9 13%: ≥ 5	0.03	0.99 (0.98–0.99)	0.015	0.99 (0.98–0.99)
Metabolic syndrome	≥ 3 criteria	17%	0.004	1.85 (1.23–2.80)	0.007	1.75 (1.17–2.63)
Distal non-advanced neoplasia	Tubular adenoma (TA) <10mm	11.3%	0.016	1.83 (1.12–2.99)	NA	NA
Distal advanced neoplasia	TA ≥ 10 mm, villous or HGD	6.3%	<0.0001	3.01 (1.81–5.00)	NA	NA

*C statistic = 0.76 (CI, 0.71–0.80), goodness of fit test P-value = 0.18

**Excludes aspirin use and distal non-advanced and advanced findings (denoted by NA); C statistic = 0.73 (CI, 0.69–0.78), goodness of fit test P-value = 0.62

HGD – high-grade dysplasia

Table 3.

Points and Ranges for Each Variable.

	With Distal Findings and Aspirin Use*	Without Distal Findings and Aspirin Use**
Variable	**Points**	**Points**
Age (5-year intervals)	0 to 4	0 to 4
Gender	Women 0; Men 2	Women 0; Men 2
Cohabitation status	0, −1	0, −2
Smoking	0 to 2	0 to 2
Metabolic syndrome	0, 2	0, 2
NSAID use	0, −3	0, −3
Aspirin use	0, −1	------
Moderate activity (during the last 12 months)	0 to −2	0 to −2
Distal, non-advanced neoplasia	2	------
Distal advanced neoplasia	4	------

* Potential range of score: from −7 to 14; Actual range: −6 to 13

** Potential range of score: from −7 to 10; Actual range: −7 to 10

Table 4.

Risk of Advanced Proximal Neoplasia by Risk Group

Witd distal findings and aspirin use							
		Derivation set (N=2859)			Validation set (N=1451)		
Risk Group	**Score**	**% Cohort**	**# CRC/AA**	**Risk AN (%) (CI)**	**% Cohort**	**#CRC/AA**	**Risk AN (%) (CI)**
Low	≤ 1	68	1/39	2.05 (1.47–2.78)	69	0/11	1.1 (0.55–1.97)
Intermediate	2–4	22	4/32	5.83 (4.12–7.99)	22	6/21	8.33 (5.56–11.9)
High	> 5	10	2/51	18.1 (13.9–23.0)	9	3/29	22.3 (15.5–30.4)

Without distal findings or aspirin use							
		Derivation set (N= 2859)			Validation set (N=1455)		
Risk Group	**Score**	**% Cohort**	**#CRC/AA**	**Risk AN (%) (CI)**	**% Cohort**	**#CRC/AA**	**Risk AN (%) (CI)**
Low	≤ 1	21	0/9	1.47 (0.67–2.77)	22	0/2	0.62 (0.08–2.23)
Intermediate	2–4	58	2/49	3.09 (2.31–4.04)	56	2/16	2.20 (1.31–3.46)
High	> 5	21	5/64	11.6 (9.1–14.4)	22	7/34	13.0 (9.50–17.2)

AA – Advanced adenoma; AN – advanced neoplasia (the combination of CRC and AA); CRC – colorectal cancer; CI – 95% confidence interval