Hvidovre Hospital

FACULTY OF HEALTH AND MEDICAL SCIENCES
UNIVERSITY OF COPENHAGEN

REGION

Improving fecal immunochemical test-based colorectal cancer screening by addition of blood-based biomarkers

Mees Mansvelders, PhD student
Gastro Unit, Copenhagen University Hospital, Hvidovre, Denmark
13th October, 2023

Hvidovre Hospital

FACULTY OF HEALTH AND MEDICAL SCIENCES
UNIVERSITY OF COPENHAGEN

REGION

Improving fecal immunochemical test-based colorectal cancer screening by addition of blood-based biomarkers

Mees Mansvelders, PhD student
Gastro Unit, Copenhagen University Hospital, Hvidovre, Denmark
13th October, 2023

Mathias Mertz Pedersen

Danish colorectal cancer FIT screening program

Danish colorectal cancer FIT screening program

All citizens aged 50-74
receive FIT kit by mail

Danish colorectal cancer FIT screening program

All citizens aged 50-74 receive FIT kit by mail

FIT < 100 mg Hb/ml

FIT ≥ 100 mg Hb/ml

Danish colorectal cancer FIT screening program

Return to screening program

All citizens aged 50-74 receive FIT kit by mail

FIT < 100 mg Hb/ml → No colonoscopy

FIT ≥ 100 mg Hb/ml

Danish colorectal cancer FIT screening program

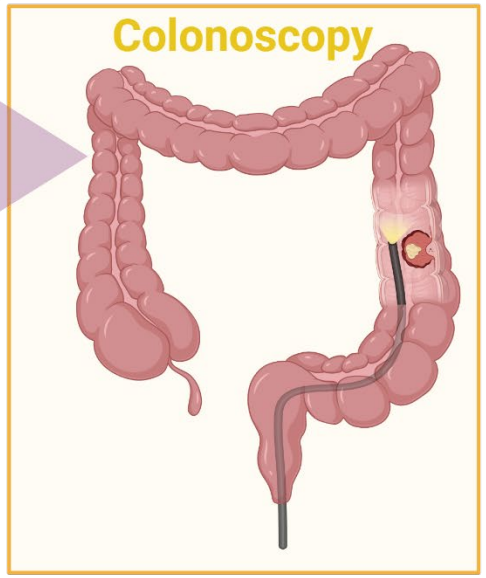
Return to screening program

All citizens aged 50-74 receive FIT kit by mail

FIT < 100 mg Hb/ml

No colonoscopy

FIT ≥ 100 mg Hb/ml



Danish colorectal cancer FIT screening program

Return to screening program

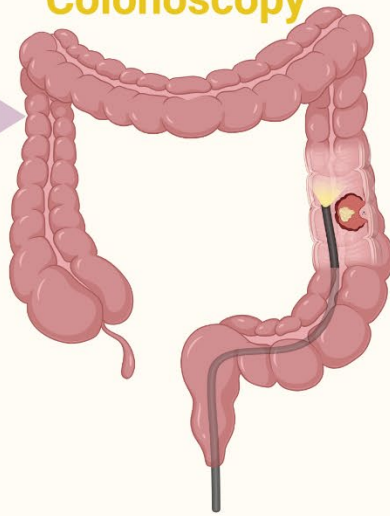
All citizens aged 50-74 receive FIT kit by mail

FIT < 100 mg Hb/ml

No colonoscopy

FIT ≥ 100 mg Hb/ml

Colonoscopy



Danish colorectal cancer FIT screening program

Return to screening program

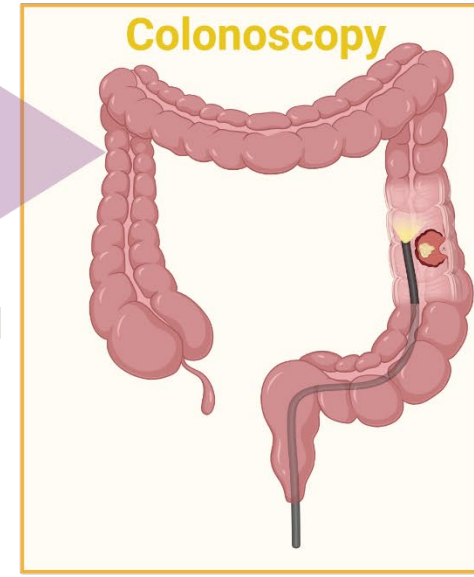
All citizens aged 50-74 receive FIT kit by mail

FIT < 100 mg Hb/ml

No colonoscopy

FIT ≥ 100 mg Hb/ml

Increased burden on colonoscopy capacity and longer waiting times



Danish colorectal cancer FIT screening program

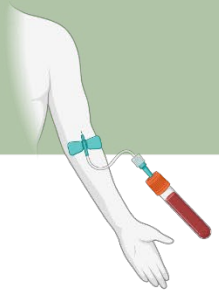
Return to screening program

All citizens aged 50-74 receive FIT kit by mail

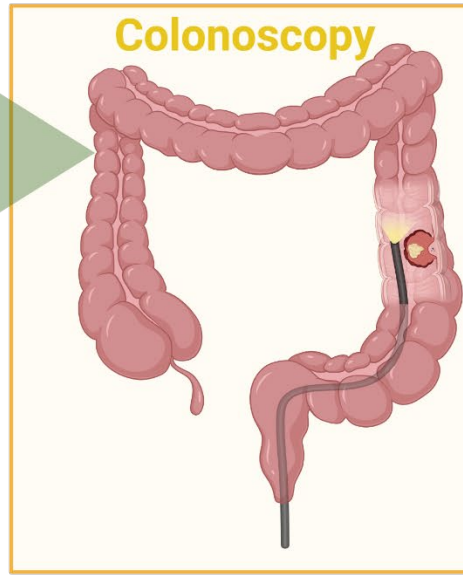
FIT < 100 mg Hb/ml

No colonoscopy

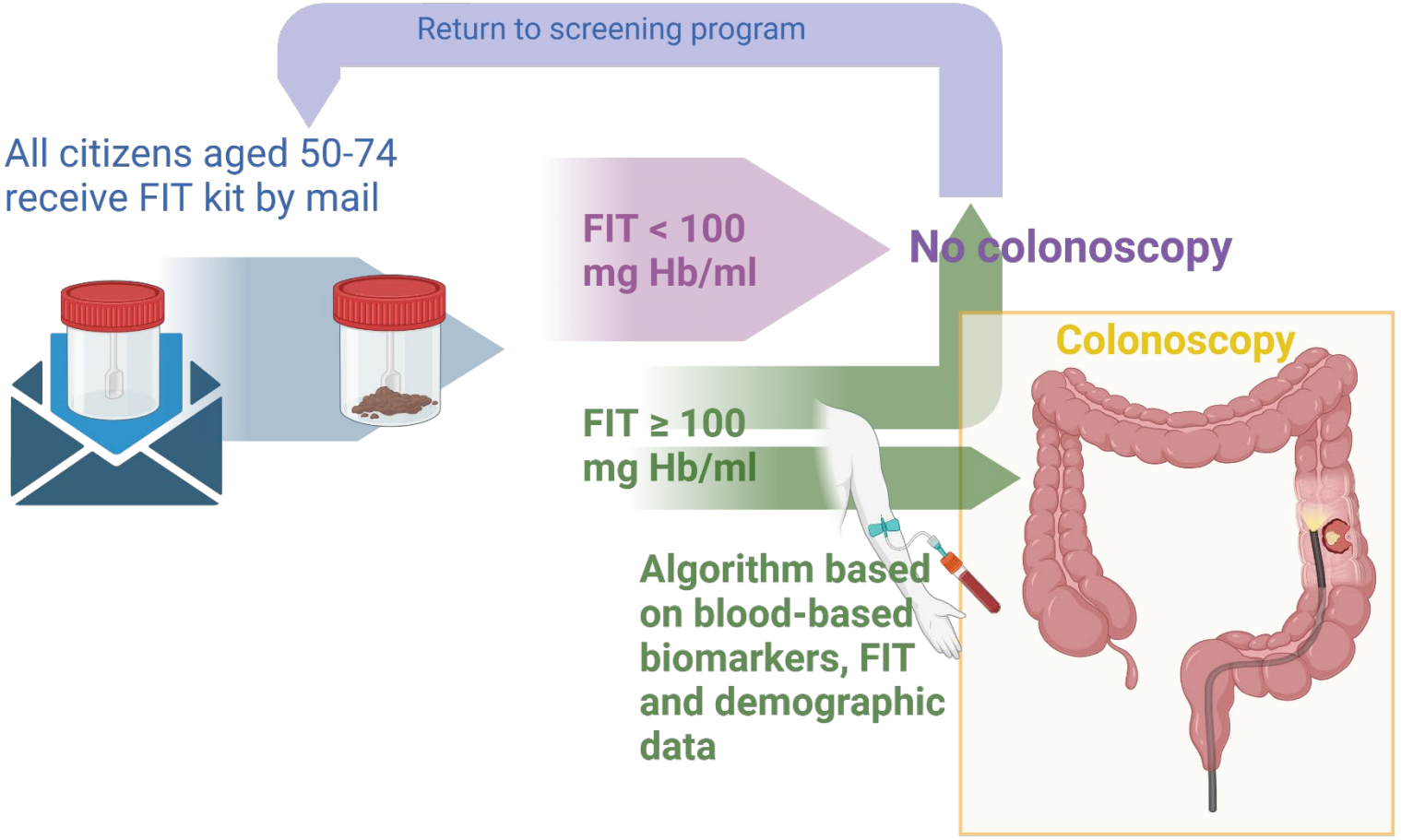
FIT ≥ 100 mg Hb/ml



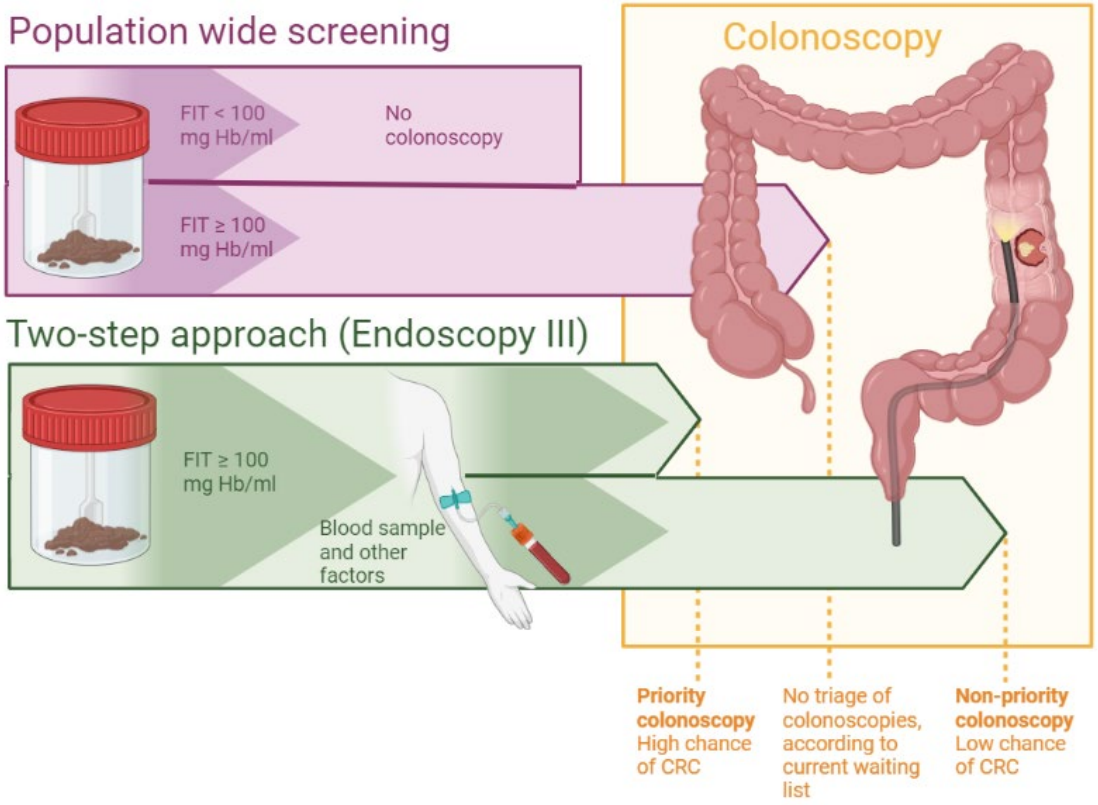
Colonoscopy



Danish colorectal cancer FIT screening program

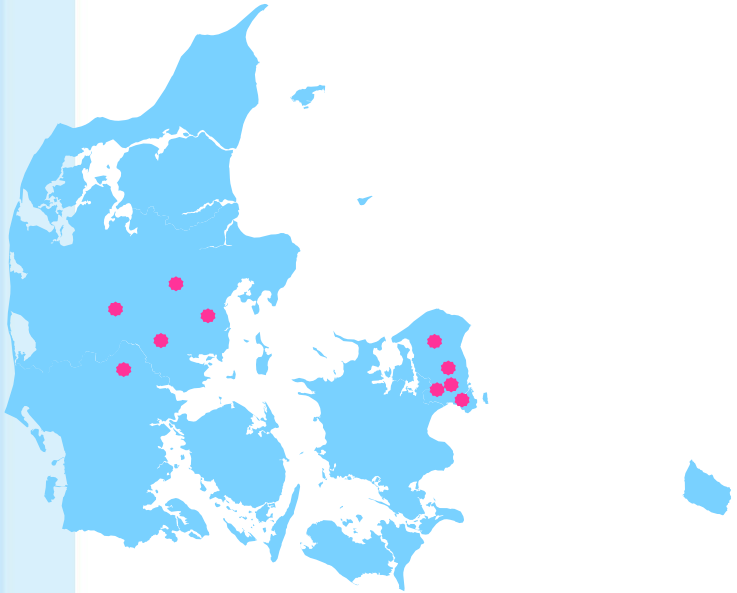


Endoscopy III cohort



Endoscopy III cohort

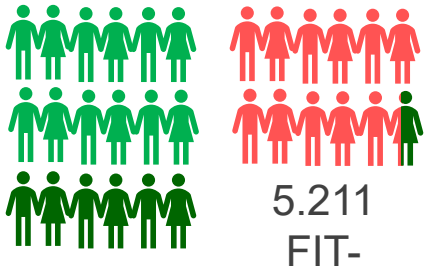
Endoscopy III cohort



Endoscopy III cohort

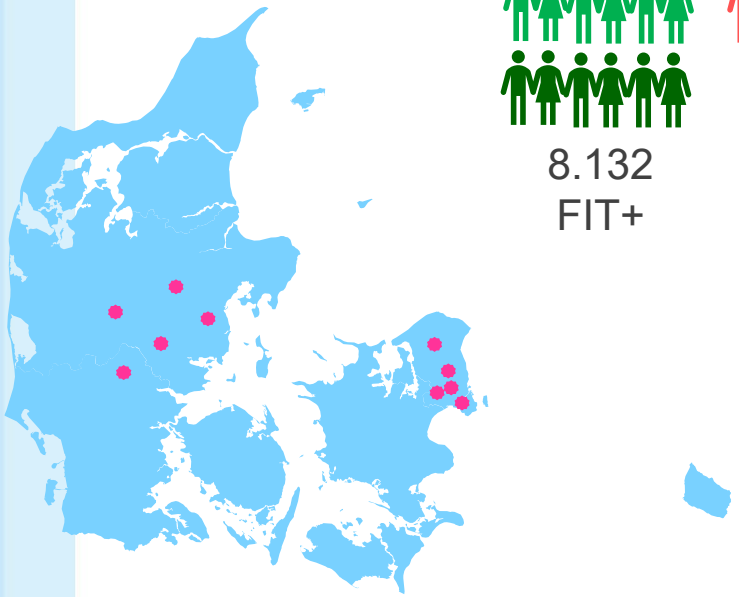
Endoscopy III
N = 48.657
2014-2021

Part 1



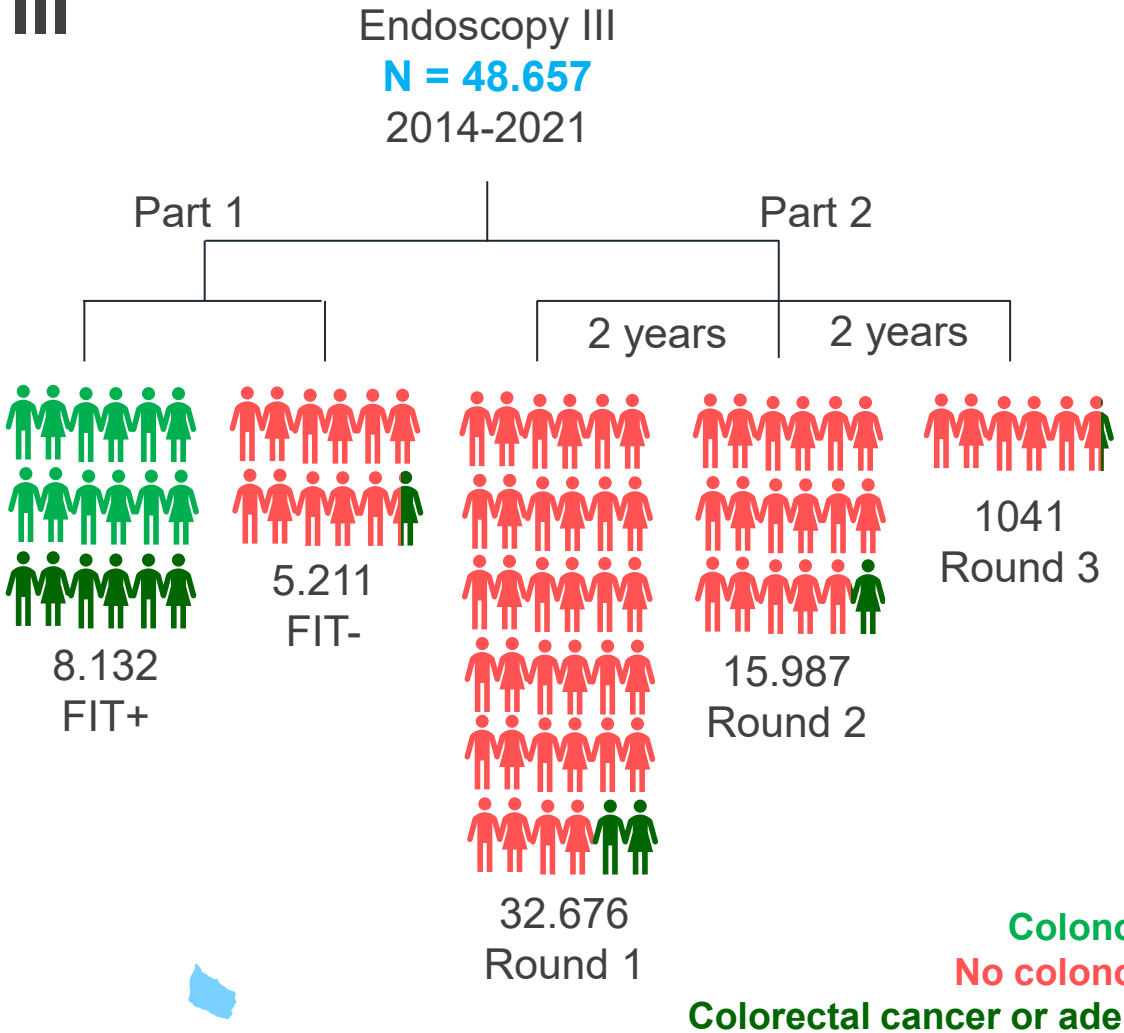
8.132
FIT+

5.211
FIT-

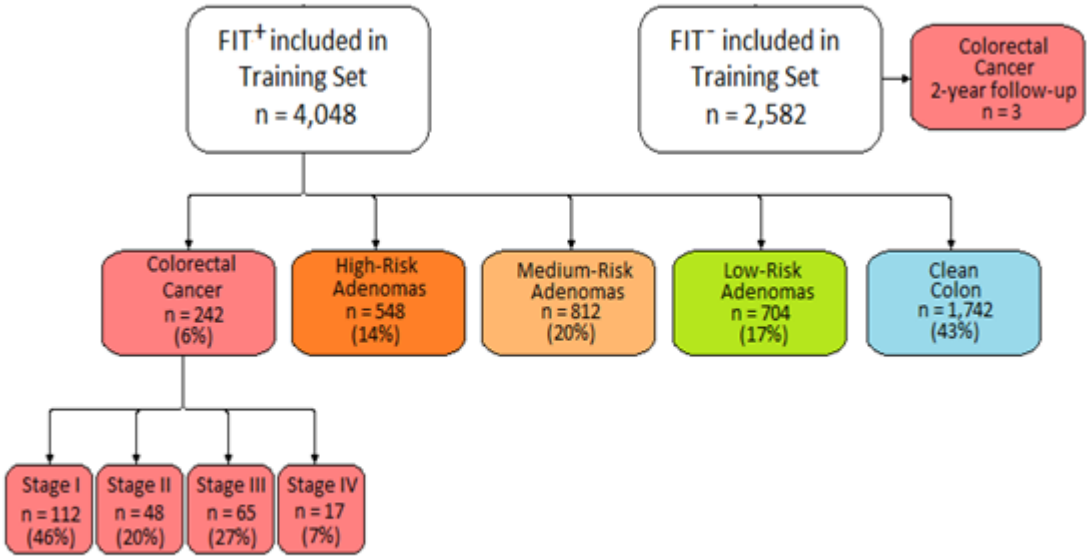


Colonoscopy
No colonoscopy
Colorectal cancer or adenomas

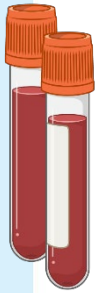
Endoscopy III cohort



Endoscopy III cohort



Blood-based biomarkers



Ferritin, CEA, TIMP-1, hsCRP, Galectin-3, HE-4, CyFra-21, B2M, and Pepsinogen-2

British Journal of Cancer www.nature.com/bjc

ARTICLE

Clinical Studies

Early detection of colorectal neoplasia: application of a blood-based serological protein test on subjects undergoing population-based screening

Jakob Kleif[1,2,3✉], Lars Nannestad Jørgensen[3,4], Jakob W. Hendel[5], Mogens R. Madsen[6], Jesper Vilandt[2], Søren Brandsborg[7], Lars Maagaard Andersen[8], Ali Khalid[9], Peter Ingeholm[10], Linnea Ferm[1], Gerard J. Davis[11], Susan H. Gawel[11], Frans Martens[12], Berit Andersen[8,13], Morten Rasmussen[4], Ib Jarle Christensen[1] and Hans Jørgen Nielsen[1,3,14]

© The Author(s), under exclusive licence to Springer Nature Limited 2022

BACKGROUND: Blood-based biomarkers used for colorectal cancer screening need to be developed and validated in appropriate screening populations. We aimed to develop a cancer-associated protein biomarker test for the detection of colorectal cancer in a screening population.

METHODS: Participants from the Danish Colorectal Cancer Screening Program were recruited. Blood samples were collected prior to colonoscopy. The cohort was divided into training and validation sets. We present the results of model development using the training set. Age, sex, and the serological proteins CEA, hsCRP, TIMP-1, Pepsinogen-2, HE4, CyFra21-1, Galectin-3, ferritin and B2M were used to develop a signature test to discriminate between participants with colorectal cancer versus all other findings at colonoscopy.

RESULTS: The training set included 4048 FIT-positive participants of whom 242 had a colorectal cancer. The final model for discriminating colorectal cancer versus all other findings at colonoscopy had an AUC of 0.70 (95% CI: 0.66–0.74) and included age, sex, CEA, hsCRP, HE4 and ferritin.

CONCLUSION: The performance of the biomarker signature in this FIT-positive screening population did not reflect the positive performance of biomarker signatures seen in symptomatic populations. Additional biomarkers are needed if the serological biomarkers are to be used as a frontline screening test.

British Journal of Cancer (2022) 126:1387–1393; https://doi.org/10.1038/s41416-022-01712-x

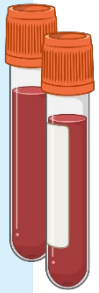
BACKGROUND

Colorectal cancer (CRC) is the third leading cause of cancer and accounts for approximately one-tenth of cancer cases and cancer-related deaths globally [1]. While the incidence and mortality from CRC are increasing in low- and middle-income countries, a decreasing trend is observed in several high-income countries [2]. Overall, the risk of being diagnosed with CRC is associated with increasing age [3], but emerging results have shown, however, that the risk of young-onset CRC is increasing in some high-income countries [4–6]. In addition, the disease is a leading cause of cancer-related mortality among adults younger than 50 years of age in the USA [7].

Survival from CRC is highly dependent on the stage at diagnosis; screening leads to more early-stage diagnoses, thereby improving survival from CRC [8, 9]. Identification and removal of adenomas generally prevents long-term mortality from colorectal cancer [10]. Furthermore, evidence suggests that organised screening programmes reduce the incidence of colorectal cancer [11].

The number of subjects undergoing CRC screening will most likely increase in coming years as a consequence of both increased demand in low- and middle-income countries [12] and an extended age interval for screening recommendations in high-income countries, for instance 45-85 years of age in USA [13]. Direct colonoscopy is the "gold" standard for early detection of CRC, but high costs and limited capacity makes direct colonoscopy unrealistic and infeasible for general population-based screening [14, 15]. Most nationwide colorectal screening programmes use the faecal immunochemical test (FIT) with compliance rates above the minimum acceptable rate of 45% but below the desirable rate of 65% [16–18].

Blood-based biomarkers



Ferritin, CEA, TIMP-1, hsCRP, Galectin-3, HE-4, CyFra-21, B2M, and Pepsinogen-2

as predictors for **CRC** and **CRC combined with advanced adenomas**

British Journal of Cancer www.nature.com/bjc

ARTICLE

Clinical Studies

Early detection of colorectal neoplasia: application of a blood-based serological protein test on subjects undergoing population-based screening

Jakob Kleif[1,2,3✉], Lars Nannestad Jørgensen[3,4], Jakob W. Hendel[5], Mogens R. Madsen[6], Jesper Vilandt[2], Søren Brandsborg[7], Lars Maagaard Andersen[8], Ali Khalid[9], Peter Ingeholm[10], Linnea Ferm[1], Gerard J. Davis[11], Susan H. Gawel[11], Frans Martens[12], Berit Andersen[8,13], Morten Rasmussen[4], Ib Jarle Christensen[1] and Hans Jørgen Nielsen[1,3,14]

© The Author(s), under exclusive licence to Springer Nature Limited 2022

BACKGROUND: Blood-based biomarkers used for colorectal cancer screening need to be developed and validated in appropriate screening populations. We aimed to develop a cancer-associated protein biomarker test for the detection of colorectal cancer in a screening population.
METHODS: Participants from the Danish Colorectal Cancer Screening Program were recruited. Blood samples were collected prior to colonoscopy. The cohort was divided into training and validation sets. We present the results of model development using the training set. Age, sex, and the serological proteins CEA, hsCRP, TIMP-1, Pepsinogen-2, HE4, CyFra21-1, Galectin-3, ferritin and B2M were used to develop a signature test to discriminate between participants with colorectal cancer versus all other findings at colonoscopy.
RESULTS: The training set included 4048 FIT-positive participants of whom 242 had a colorectal cancer. The final model for discriminating colorectal cancer versus all other findings at colonoscopy had an AUC of 0.70 (95% CI: 0.66–0.74) and included age, sex, CEA, hsCRP, HE4 and ferritin.
CONCLUSION: The performance of the biomarker signature in this FIT-positive screening population did not reflect the positive performance of biomarker signatures seen in symptomatic populations. Additional biomarkers are needed if the serological biomarkers are to be used as a frontline screening test.

British Journal of Cancer (2022) 126:1387–1393; https://doi.org/10.1038/s41416-022-01712-x

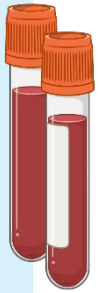
BACKGROUND

Colorectal cancer (CRC) is the third leading cause of cancer and accounts for approximately one-tenth of cancer cases and cancer-related deaths globally [1]. While the incidence and mortality from CRC are increasing in low- and middle-income countries, a decreasing trend is observed in several high-income countries [2]. Overall, the risk of being diagnosed with CRC is associated with increasing age [3], but emerging results have shown, however, that the risk of young-onset CRC is increasing in some high-income countries [4–6]. In addition, the disease is a leading cause of cancer-related mortality among adults younger than 50 years of age in the USA [7].

Survival from CRC is highly dependent on the stage at diagnosis; screening leads to more early-stage diagnoses, thereby improving survival from CRC [8, 9]. Identification and removal of adenomas generally prevents long-term mortality from colorectal cancer [10]. Furthermore, evidence suggests that organised screening programmes reduce the incidence of colorectal cancer [11].

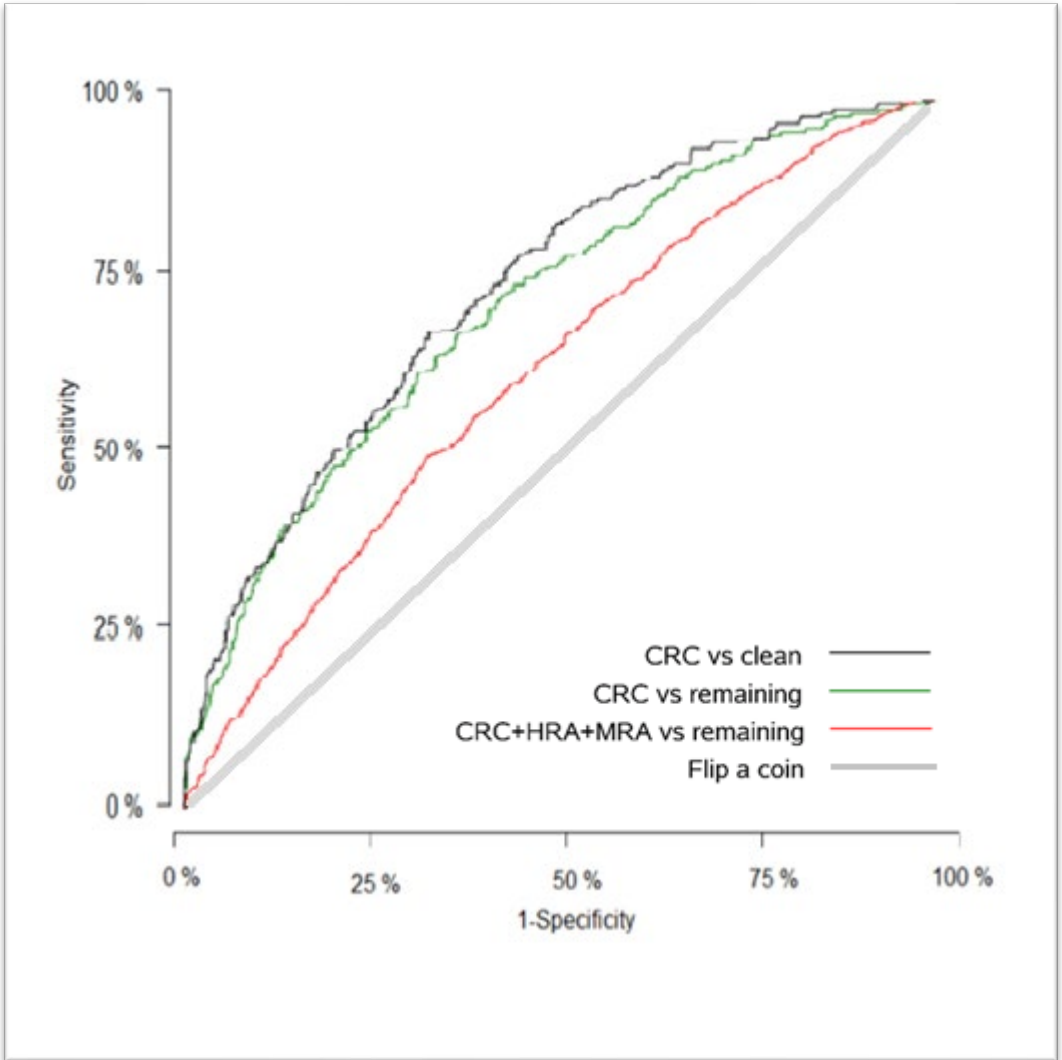
The number of subjects undergoing CRC screening will most likely increase in coming years as a consequence of both increased demand in low- and middle-income countries [12] and an extended age interval for screening recommendations in high-income countries, for instance 45-85 years of age in USA [13]. Direct colonoscopy is the "gold" standard for early detection of CRC, but high costs and limited capacity makes direct colonoscopy unrealistic and infeasible for general population-based screening [14, 15]. Most nationwide colorectal screening programmes use the faecal immunochemical test (FIT) with compliance rates above the minimum acceptable rate of 45% but below the desirable rate of 65% [16–18].

Blood-based biomarkers

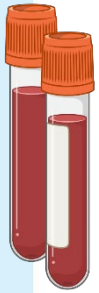


Ferritin, CEA, TIMP-1, hsCRP, Galectin-3, HE-4, CyFra-21, B2M, and Pepsinogen-2

as predictors for **CRC** and **CRC combined with advanced adenomas**



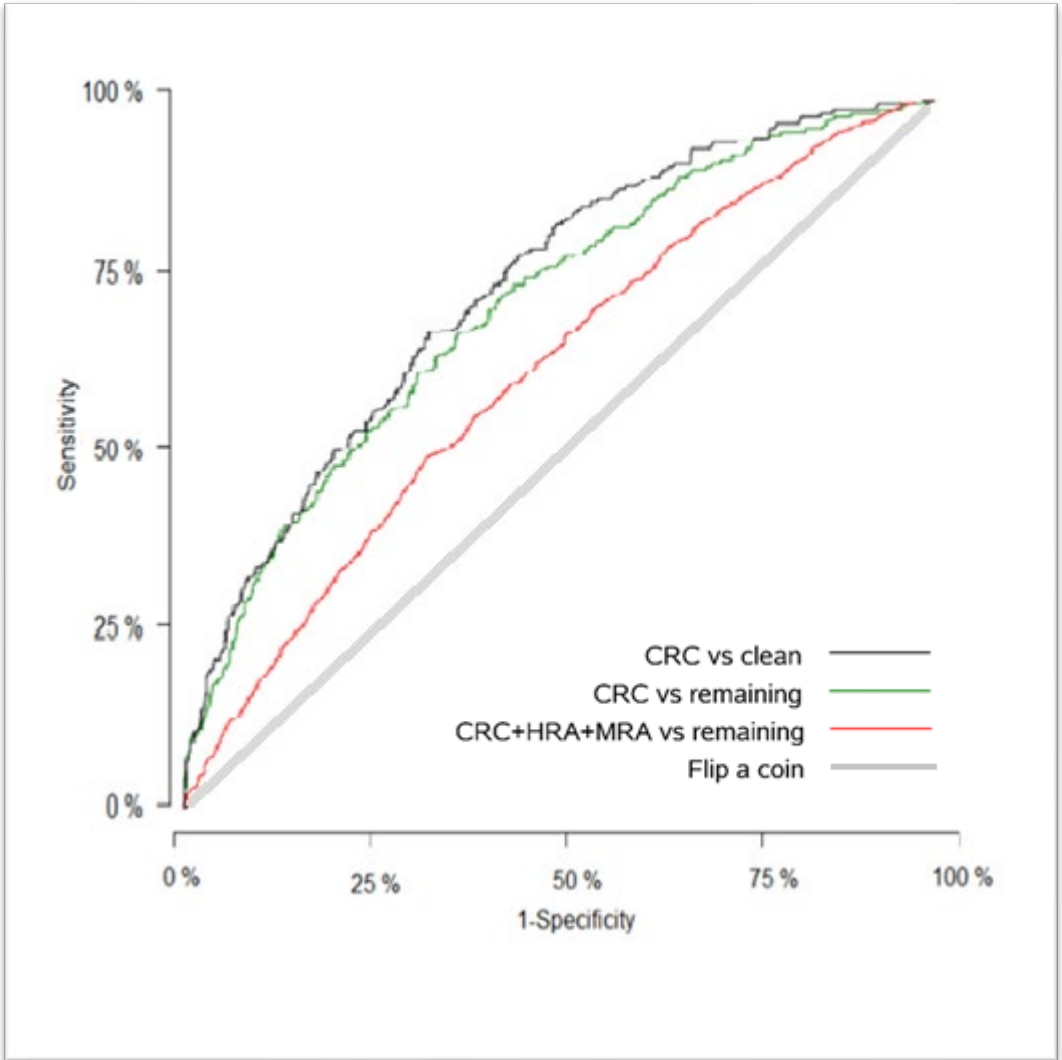
Blood-based biomarkers



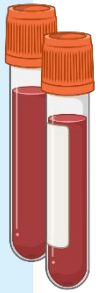
Ferritin, CEA, TIMP-1, hsCRP, Galectin-3, HE-4, CyFra-21, B2M, and Pepsinogen-2

as predictors for **CRC** and **CRC combined with advanced adenomas**

AUC = 0.70 (95% CI 0.66-0.74)
AUC = 0.61 (95% CI 0.59-0.63)

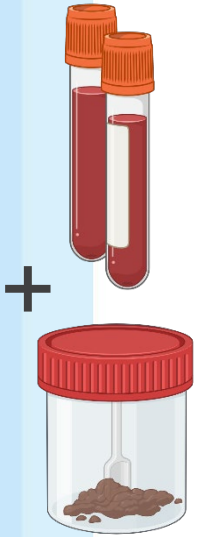


Blood-based biomarkers



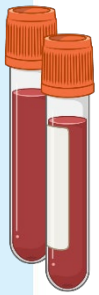
Ferritin, CEA, TIMP-1, hsCRP, Galectin-3, HE-4, CyFra-21, B2M, and Pepsinogen-2

Blood-based biomarkers combined with FIT



Ferritin, CEA, TIMP-1, hsCRP, Galectin-3, HE-4, CyFra-21, B2M, Pepsinogen-2 and FIT

Blood-based biomarkers combined with FIT



Ferritin, CEA, TIMP-1, hsCRP, Galectin-3, HE-4, CyFra-21, B2M, Pepsinogen-2 and FIT

+

Combined in two algorithms

Original Study

Check for updates

Optimizing Screening for Colorectal Cancer: An Algorithm Combining Fecal Immunochemical Test, Blood-Based Cancer-Associated Proteins and Demographics to Reduce Colonoscopy Burden

Mathias M. Petersen,[1,2] Jakob Kleif,[1,2,3] Lars N. Jørgensen,[2,4] Jakob W. Hendel,[5] Jakob B. Seidelin,[5] Mogens R. Madsen,[6] Jesper Vilandt,[3] Søren Brandsborg,[7] Jørn S. Rasmussen,[7] Lars M. Andersen,[8] Ali Khalid,[10] Linnea Ferm,[1] Susan H. Gawel,[11] Frans Martens,[12] Berit Andersen,[8,9] Morten Rasmussen,[2] Gerard J. Davis,[11] Ib J. Christensen,[1] Christina Therkildsen[1]

Abstract

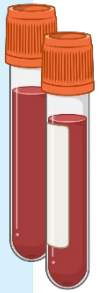
This study aimed to investigate if a 2-step algorithm using fecal immunochemical test, blood-based biomarkers and demographics of a subject could enhance screening for colorectal cancer. Our results indicate that the algorithm could reduce the number of colonoscopies by up to 11% without compromising colorectal cancer detection.

Background: Fecal Immunochemical Test (FIT) is widely used in population-based screening for colorectal cancer (CRC). This had led to major challenges regarding colonoscopy capacity. Methods to maintain high sensitivity without compromising the colonoscopy capacity are needed. This study investigates an algorithm that combines FIT result, blood-based biomarkers associated with CRC, and individual demographics, to triage subjects sent for colonoscopy among a FIT positive (FIT^+) screening population and thereby reduce the colonoscopy burden. **Materials and methods:** From the Danish National Colorectal Cancer Screening Program, 4048 FIT^+ (≥100 ng/mL Hemoglobin) subjects were included and analyzed for a panel of 9 cancer-associated biomarkers using the ARCHITECT *i*2000. Two algorithms were developed: 1) a predefined algorithm based on clinically available biomarkers: FIT, age, CEA, hsCRP and Ferritin; and 2) an exploratory algorithm adding additional biomarkers: TIMP-1, Pepsinogen-2, HE4, CyFra21-1, Galectin-3, B2M and sex to the predefined algorithm. The diagnostic performances for discriminating subjects with or without CRC in the 2 models were benchmarked against the FIT alone using logistic regression modeling. **Results:** The discrimination of CRC showed an area under the curve (AUC) of 73.7 (70.5-76.9) for the predefined model, 75.3 (72.1-78.4) for the exploratory model, and 68.9 (65.5-72.2) for FIT alone. Both models performed significantly better ($P < .001$) than the FIT model. The models were benchmarked vs. FIT at cutoffs of 100, 200, 300, 400, and 500 ng/mL Hemoglobin using corresponding numbers of true positives and false positives. All performance metrics were improved at all cutoffs. **Conclusion:** A screening algorithm including a combination of FIT result, blood-based biomarkers and demographics

1533-0028/$ - see front matter © 2023 The Authors. Published by Elsevier Inc. This is an open access article under the CC BY license (http://creativecommons.org/licenses/by/4.0/)
https://doi.org/10.1016/j.clcc.2023.02.001

Clinical Colorectal Cancer June 2023

Blood-based biomarkers combined with FIT



Ferritin, CEA, TIMP-1, hsCRP, Galectin-3, HE-4, CyFra-21, B2M, Pepsinogen-2 and FIT

+

Combined in two algorithms

Predefined

Clinically available biomarkers

Original Study

Check for updates

Optimizing Screening for Colorectal Cancer: An Algorithm Combining Fecal Immunochemical Test, Blood-Based Cancer-Associated Proteins and Demographics to Reduce Colonoscopy Burden

Mathias M. Petersen,[1,2] Jakob Kleif,[1,2,3] Lars N. Jørgensen,[2,4] Jakob W. Hendel,[5] Jakob B. Seidelin,[5] Mogens R. Madsen,[6] Jesper Vilandt,[3] Søren Brandsborg,[7] Jørn S. Rasmussen,[7] Lars M. Andersen,[8] Ali Khalid,[10] Linnea Ferm,[1] Susan H. Gawel,[11] Frans Martens,[12] Berit Andersen,[8,9] Morten Rasmussen,[2] Gerard J. Davis,[11] Ib J. Christensen,[1] Christina Therkildsen[1]

Abstract

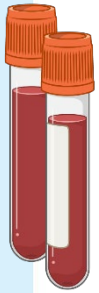
This study aimed to investigate if a 2-step algorithm using fecal immunochemical test, blood-based biomarkers and demographics of a subject could enhance screening for colorectal cancer. Our results indicate that the algorithm could reduce the number of colonoscopies by up to 11% without compromising colorectal cancer detection.

Background: Fecal Immunochemical Test (FIT) is widely used in population-based screening for colorectal cancer (CRC). This had led to major challenges regarding colonoscopy capacity. Methods to maintain high sensitivity without compromising the colonoscopy capacity are needed. This study investigates an algorithm that combines FIT result, blood-based biomarkers associated with CRC, and individual demographics, to triage subjects sent for colonoscopy among a FIT positive (FIT^+) screening population and thereby reduce the colonoscopy burden. **Materials and methods:** From the Danish National Colorectal Cancer Screening Program, 4048 FIT^+ ($\geq$100 ng/mL Hemoglobin) subjects were included and analyzed for a panel of 9 cancer-associated biomarkers using the ARCHITECT *i*2000. Two algorithms were developed: 1) a predefined algorithm based on clinically available biomarkers: FIT, age, CEA, hsCRP and Ferritin; and 2) an exploratory algorithm adding additional biomarkers: TIMP-1, Pepsinogen-2, HE4, CyFra21-1, Galectin-3, B2M and sex to the predefined algorithm. The diagnostic performances for discriminating subjects with or without CRC in the 2 models were benchmarked against the FIT alone using logistic regression modeling. **Results:** The discrimination of CRC showed an area under the curve (AUC) of 73.7 (70.5-76.9) for the predefined model, 75.3 (72.1-78.4) for the exploratory model, and 68.9 (65.5-72.2) for FIT alone. Both models performed significantly better ($P < .001$) than the FIT model. The models were benchmarked vs. FIT at cutoffs of 100, 200, 300, 400, and 500 ng/mL Hemoglobin using corresponding numbers of true positives and false positives. All performance metrics were improved at all cutoffs. **Conclusion:** A screening algorithm including a combination of FIT result, blood-based biomarkers and demographics

1533-0028/$ - see front matter © 2023 The Authors. Published by Elsevier Inc. This is an open access article under the CC BY license (http://creativecommons.org/licenses/by/4.0/)
https://doi.org/10.1016/j.clcc.2023.02.001

Clinical Colorectal Cancer June 2023

Blood-based biomarkers combined with FIT



Ferritin, CEA, TIMP-1, hsCRP, Galectin-3, HE-4, CyFra-21, B2M, Pepsinogen-2 and FIT

+

Combined in two algorithms

Predefined

Clinically available biomarkers

Exploratory

Statistically selected biomarkers

Original Study

Check for updates

Optimizing Screening for Colorectal Cancer: An Algorithm Combining Fecal Immunochemical Test, Blood-Based Cancer-Associated Proteins and Demographics to Reduce Colonoscopy Burden

Mathias M. Petersen,[1,2] Jakob Kleif,[1,2,3] Lars N. Jørgensen,[2,4] Jakob W. Hendel,[5] Jakob B. Seidelin,[5] Mogens R. Madsen,[6] Jesper Vilandt,[3] Søren Brandsborg,[7] Jørn S. Rasmussen,[7] Lars M. Andersen,[8] Ali Khalid,[10] Linnea Ferm,[1] Susan H. Gawel,[11] Frans Martens,[12] Berit Andersen,[8,9] Morten Rasmussen,[2] Gerard J. Davis,[11] Ib J. Christensen,[1] Christina Therkildsen[1]

Abstract

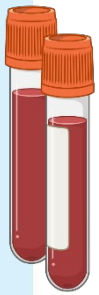
This study aimed to investigate if a 2-step algorithm using fecal immunochemical test, blood-based biomarkers and demographics of a subject could enhance screening for colorectal cancer. Our results indicate that the algorithm could reduce the number of colonoscopies by up to 11% without compromising colorectal cancer detection.

Background: Fecal Immunochemical Test (FIT) is widely used in population-based screening for colorectal cancer (CRC). This had led to major challenges regarding colonoscopy capacity. Methods to maintain high sensitivity without compromising the colonoscopy capacity are needed. This study investigates an algorithm that combines FIT result, blood-based biomarkers associated with CRC, and individual demographics, to triage subjects sent for colonoscopy among a FIT positive (FIT^+) screening population and thereby reduce the colonoscopy burden. **Materials and methods:** From the Danish National Colorectal Cancer Screening Program, 4048 FIT^+ (≥100 ng/mL Hemoglobin) subjects were included and analyzed for a panel of 9 cancer-associated biomarkers using the ARCHITECT *i*2000. Two algorithms were developed: 1) a predefined algorithm based on clinically available biomarkers: FIT, age, CEA, hsCRP and Ferritin; and 2) an exploratory algorithm adding additional biomarkers: TIMP-1, Pepsinogen-2, HE4, CyFra21-1, Galectin-3, B2M and sex to the predefined algorithm. The diagnostic performances for discriminating subjects with or without CRC in the 2 models were benchmarked against the FIT alone using logistic regression modeling. **Results:** The discrimination of CRC showed an area under the curve (AUC) of 73.7 (70.5-76.9) for the predefined model, 75.3 (72.1-78.4) for the exploratory model, and 68.9 (65.5-72.2) for FIT alone. Both models performed significantly better ($P < .001$) than the FIT model. The models were benchmarked vs. FIT at cutoffs of 100, 200, 300, 400, and 500 ng/mL Hemoglobin using corresponding numbers of true positives and false positives. All performance metrics were improved at all cutoffs. **Conclusion:** A screening algorithm including a combination of FIT result, blood-based biomarkers and demographics

1533-0028/$ - see front matter © 2023 The Authors. Published by Elsevier Inc. This is an open access article under the CC BY license (http://creativecommons.org/licenses/by/4.0/)
https://doi.org/10.1016/j.clcc.2023.02.001

Clinical Colorectal Cancer June 2023

Blood-based biomarkers combined with FIT

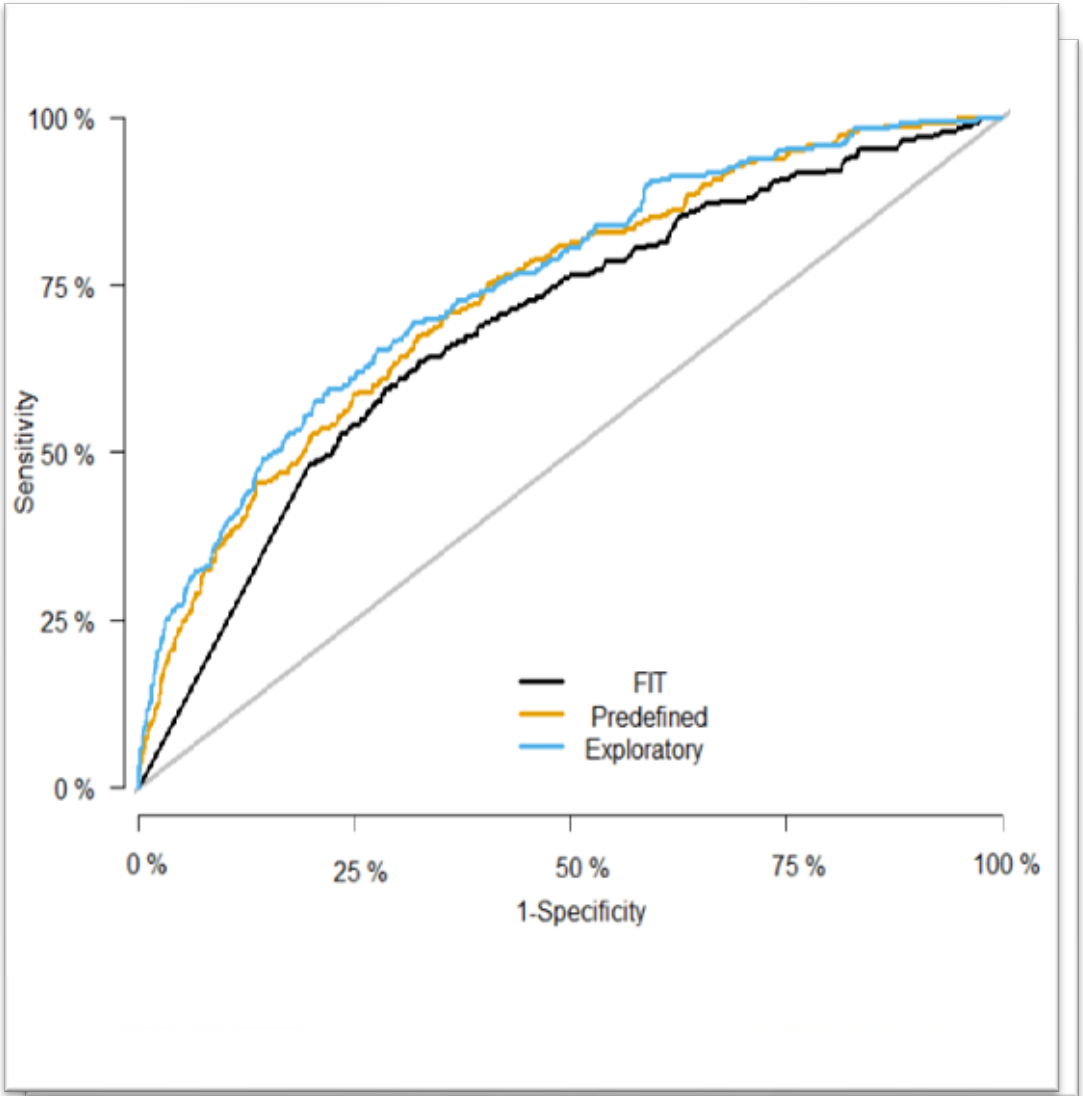


Ferritin, CEA, TIMP-1, hsCRP, Galectin-3, HE-4, CyFra-21, B2M, Pepsinogen-2 and FIT

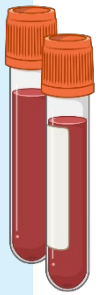
+

Combined in two algorithms

CRC vs remaining



Blood-based biomarkers combined with FIT

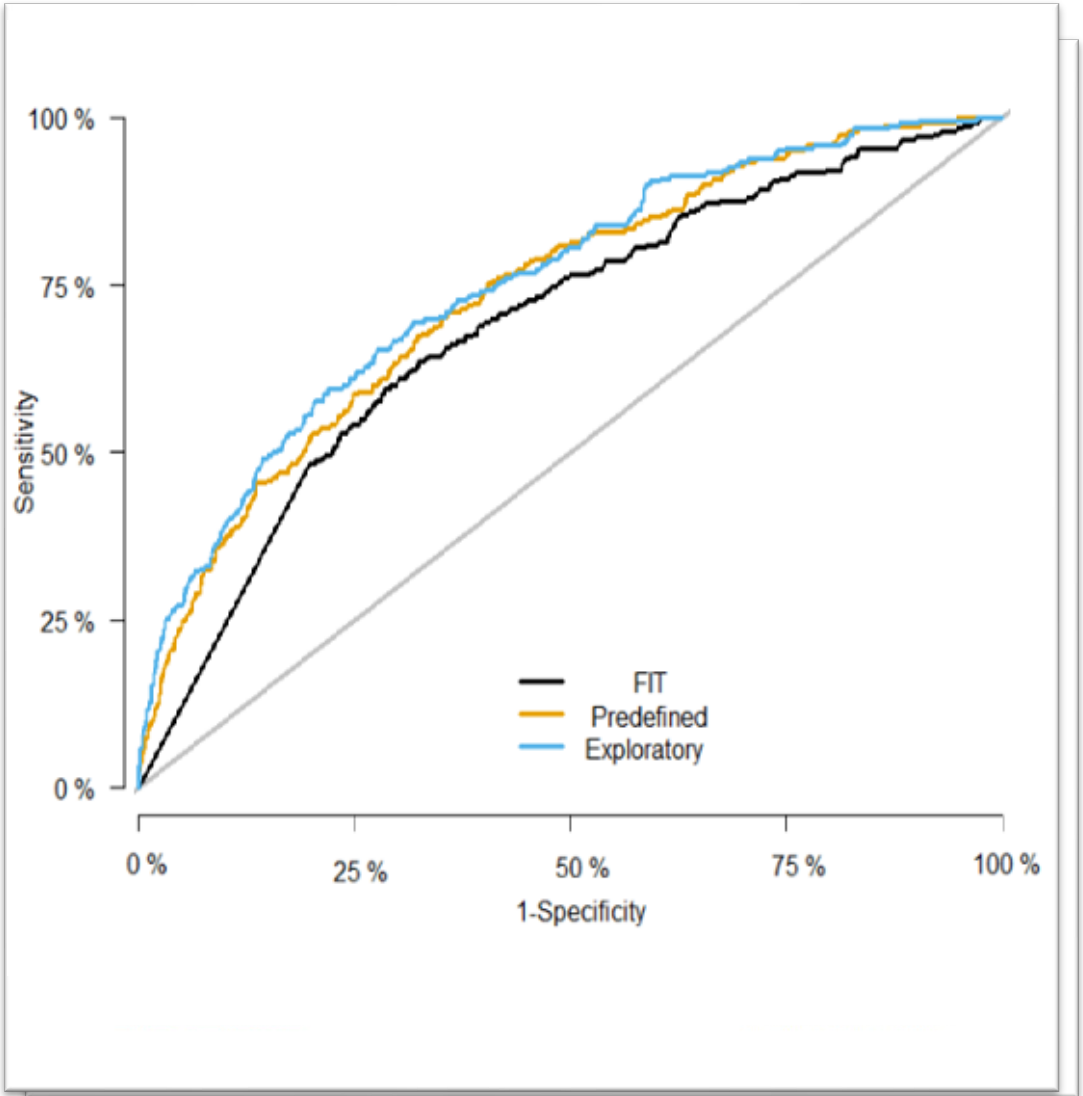


Ferritin, CEA, TIMP-1, hsCRP, Galectin-3, HE-4, CyFra-21, B2M, Pepsinogen-2 and FIT

+

Combined in two algorithms

CRC vs remaining



Algorithm
AUC = 0.75 (95% CI 0.72-0.77)
AUC = 0.74 (95% CI 0.71-0.78)

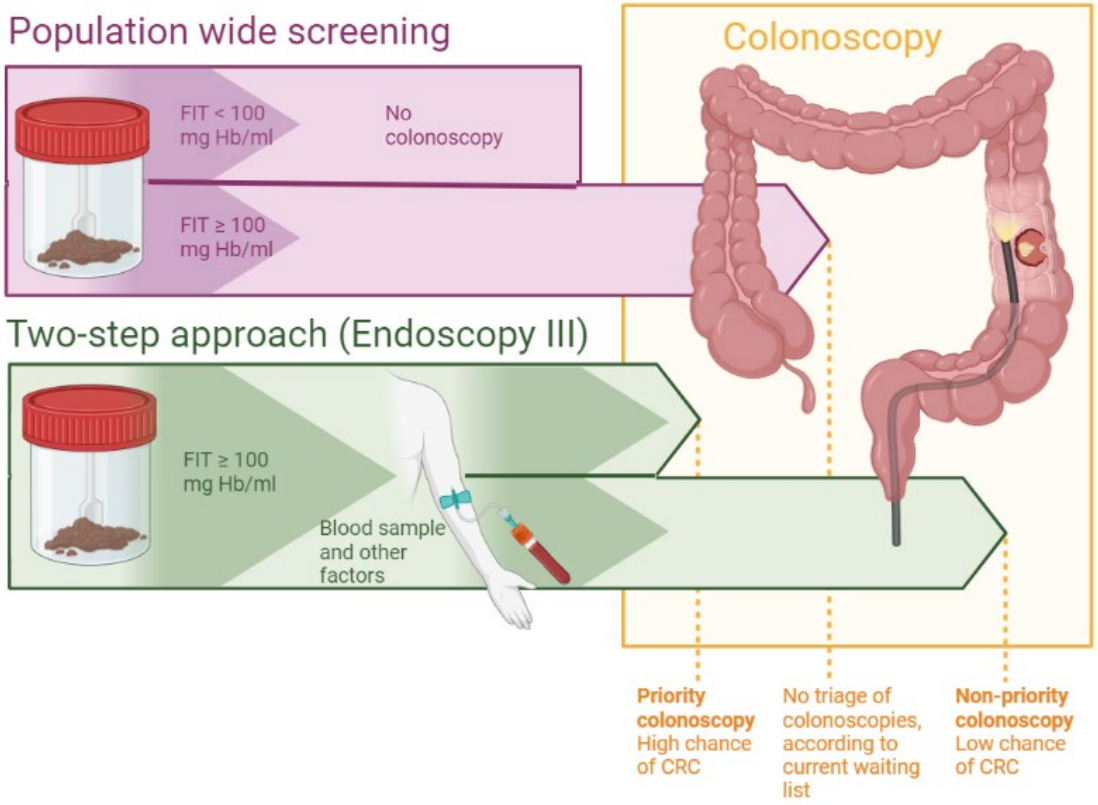
FIT
AUC = 0.69 (95% CI 0.66-0.72)

The algorithm at different FIT cut-offs

The algorithm at different FIT cut-offs

Missed CRC	150 ng Hb/mL France	235 ng Hb/mL Netherlands	400 ng Hb/mL Scotland	600 ng Hb/mL England
FIT only	8%	20%	33%	42%
With use of algorithm	1%	9%	22%	31%

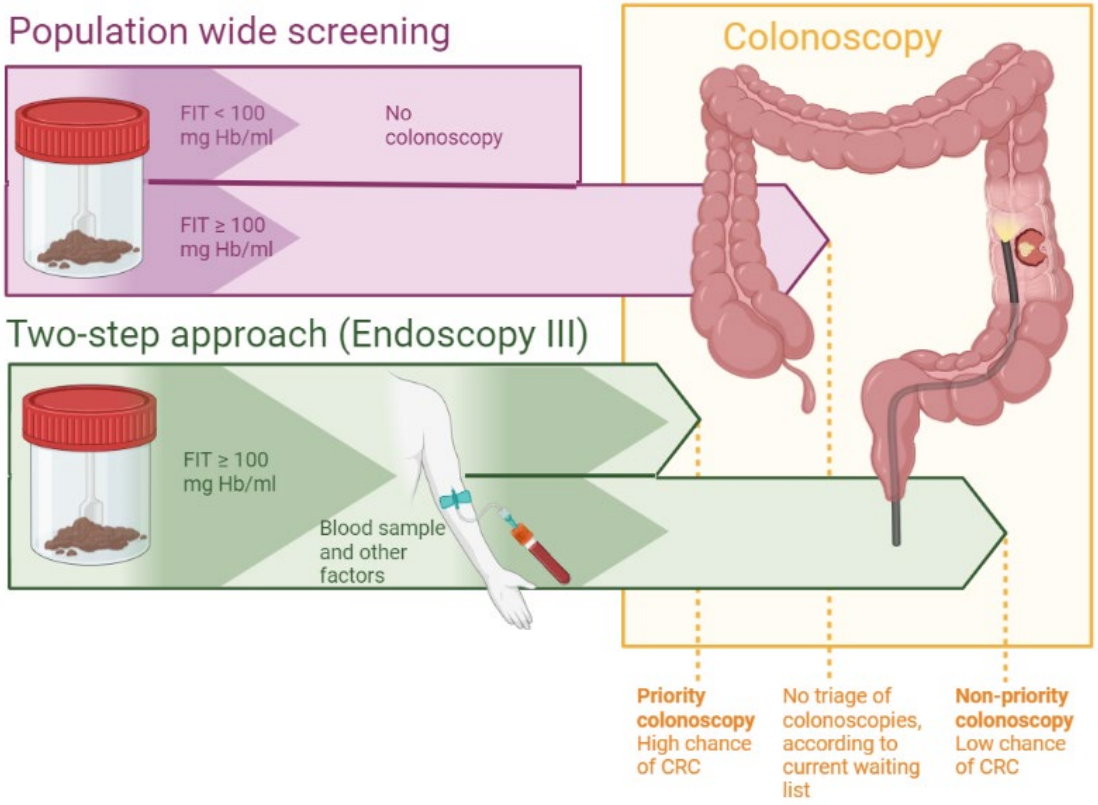
Endoscopy III cohort



Endoscopy III cohort

Cohort

- 13343 total
- 8132 FIT +
  - Training set 4048
- 31% stage III & IV CRC

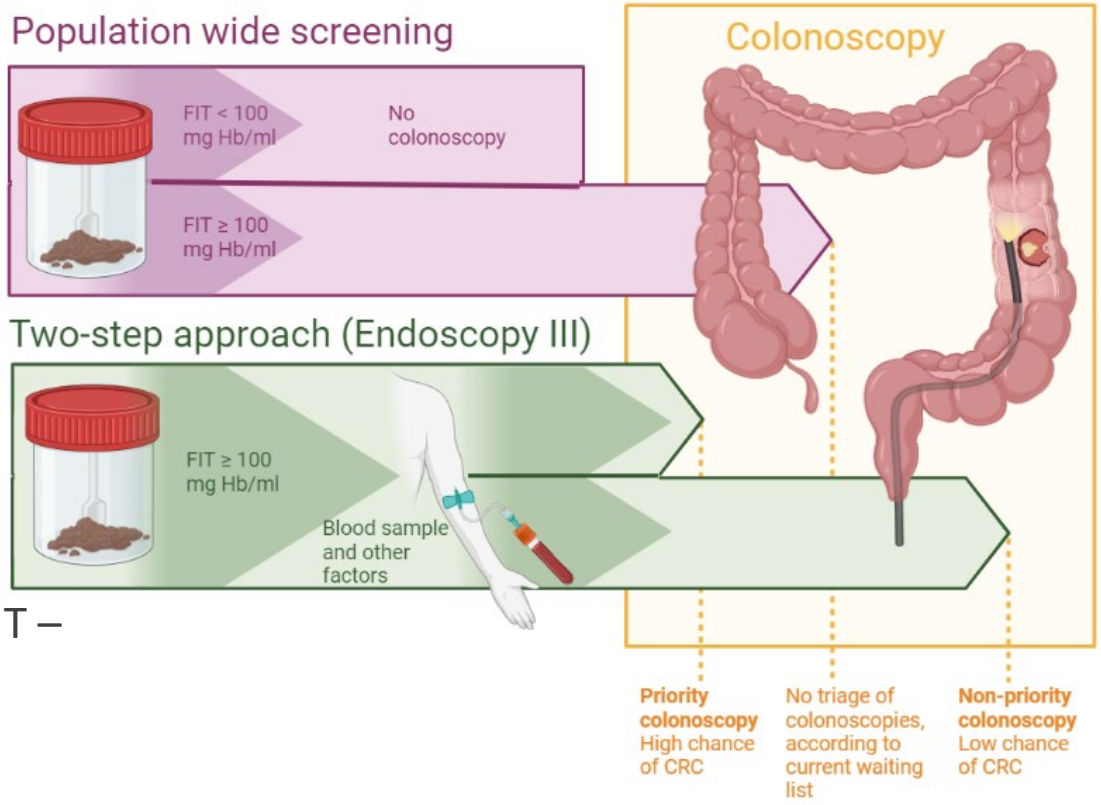


Endoscopy III cohort

Cohort

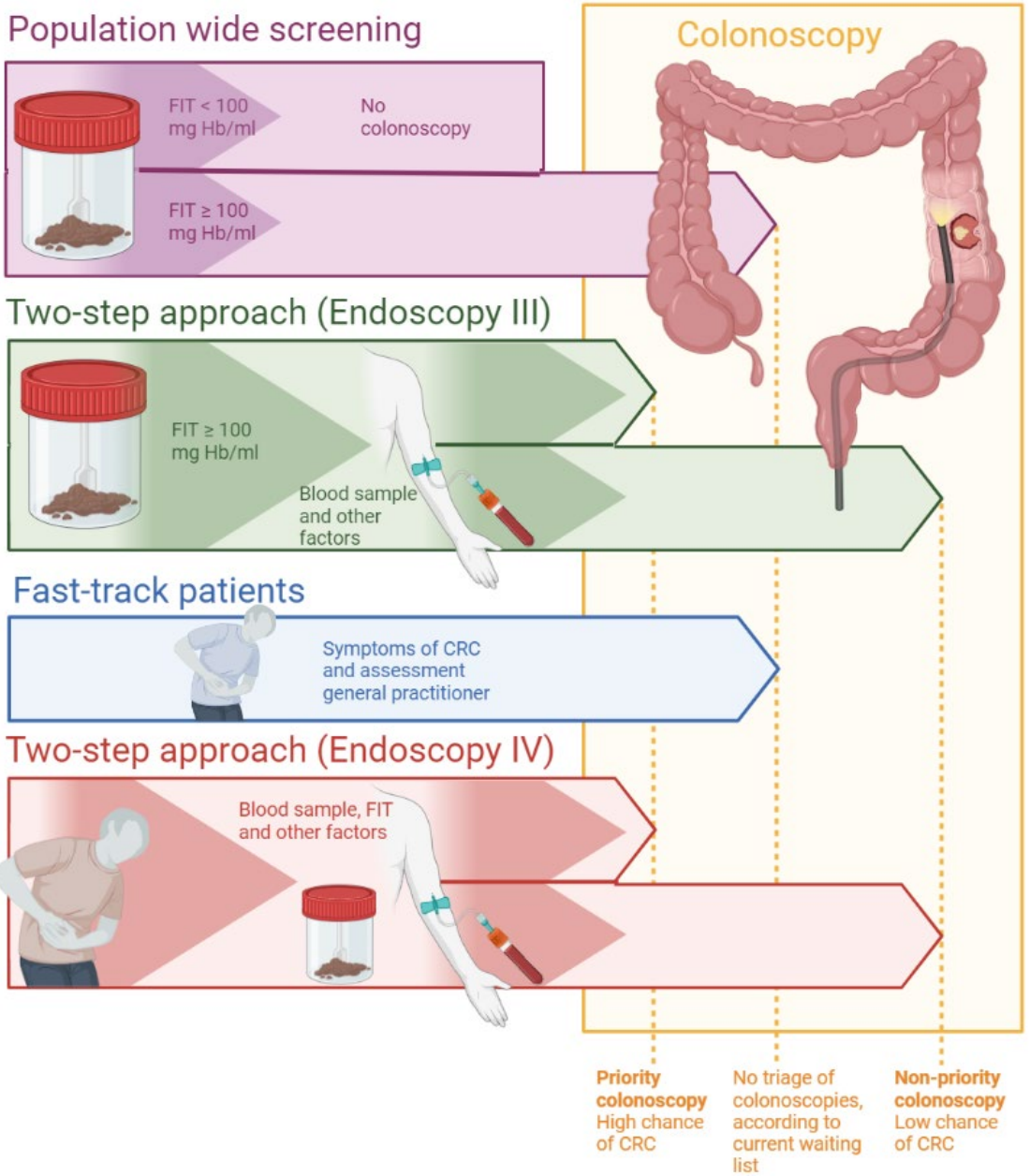
- 13343 total
- 8132 FIT +
  - Training set 4048
- 31% stage III & IV CRC

- Only colonoscopy on FIT –



Endoscopy III cohort

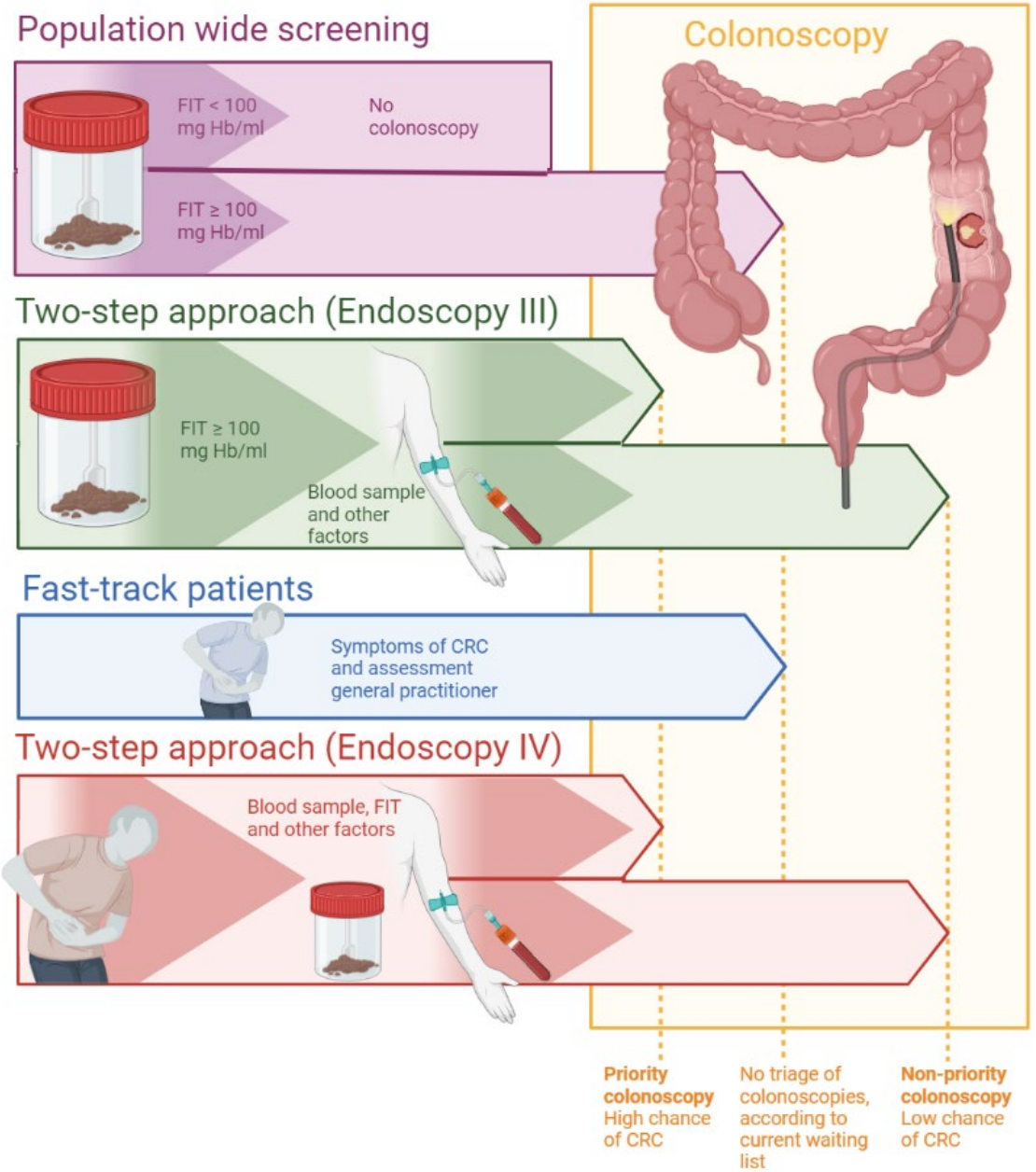
Endoscopy IV cohort



Endoscopy III cohort

Endoscopy IV cohort

Symptomatic patients
1723 total
Colonoscopy on all



Thank you for listening

FACULTY OF HEALTH AND MEDICAL SCIENCES
UNIVERSITY OF COPENHAGEN

WEO
World Endoscopy Organization

REGION H

Hvidovre Hospital

Endoscopy III project
Mathias M. Petersen, Jakob Kleif & Christina Therkildsen

Abbott

Gerard J. Davis & Susan H. Gawel

Steering committee
Lars N. Jørgensen, Jakob W. Hendel, Jakob B. Seidelin, Morgens R. Madsen, Jesper Vilandt, Søren Brandsborg, Jørn S. Rasmussen, Lars M. Andersen, Ali Khalid, Linnea Ferm, Frans Martens, Berit Andersen, Morten Rasmussen & Ib J. Christensen

This work was supported by The Andersen-Isted Foundation, The Augustinus Foundation, The Beckett Foundation, The Inger Bonnéns Fund, The Hans & Nora Buchards Fund, The Walter Christensen Fund, The P.M. Christiansen Fund, The Kong Chr. X's Fund, The Aase & Ejnar Danielsens Fund, The Family Erichsens Fund, The Knud & Edith Eriksens Fund, The Svend Espersens Fund, The Elna & Jørgen Fagerholts Cancer Research Foundation, The Sofus Carl Emil Friis Scholarship, The Torben & Alice Frimodts Fund, The Eva & Henry Frænkels Fund, The Gangsted Foundation, Thora & Viggo Groves Memorial Scholarship, The H-Foundation, Erna Hamiltons Scholarship, Søren & Helene Hempels Scholarship, The Sven & Ina Hansens Fund, The Henrik Henriksen Fund, Carl & Ellen Hertz' Scholarship, Jørgen Holm & Elisa F. Hansen Memorial Scholarship, The Jochum Foundation, The KID Foundation, The Kornerup Foundation, The Linex Foundation, The Dagmar Marshalls Fund, The Midtjyske Fund, The Axel Muusfeldts Fund, The Børge Nielsens Fund, Michael Hermann Nielsens Memorial Scholarship, The Arvid Nilssons Fund, The Obelske Family Fund, The Krista & Viggo Petersens Fund, The Willy & Ingeborg Reinhards Fund, The Kathrine & Vigo Skovgaards Fund, The Toyota Foundation, The Vissing Foundation, The P. Carl Petersen Fund, The Danish Cancer Research Foundation, Hvidovre Hospitals Research Pool.