Clinical Evaluation of a New Blood-Based Test for Colorectal Cancer Screening

Aasma Shaukat,^{1–3} Zhen Meng,⁴ Andy Piscitello,⁴ Chuanbo Xu,⁴ Lilian C. Lee,⁴ Lance Baldo,^{4,a} Theodore R. Levin^{3,5}

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INTRODUCTION

^aAffiliation at the time the study and/or analyses were conducted

- Colorectal cancer (CRC) is the second most common cause of cancer-related death in the US, but is treatable when detected early¹
- Despite the proven benefits of CRC screening, greater than 40% of eligible adults at average risk for CRC in the US in 2021 were not up-to-date with guidelines^{2–4}
- Low screening uptake can be partly attributed to the inconveniences associated with conventional screening methods, as well as disparities in access to medical care (including CRC screening) among certain demographic groups^{2,5,6}
- Specific challenges of conventional screening methods include the bowel preparation and invasiveness associated with colonoscopy and fecal aversion associated with stool-based tests^{7,8}
- Individuals may be more receptive to blood-based tests (BBTs) compared with conventional methods, which may help individuals overcome some barriers to screening^{9,10}
- PREEMPT CRC (NCT04369053¹¹), a prospective, multicenter observational study, was conducted to validate an investigational BBT designed to detect molecular signals associated with CRC using machine learning (ML) and artificial intelligence (AI) technologies in an average-risk, screening-eligible population

OBJECTIVE

 To provide an assessment of the clinical performance of an investigational BBT evaluating molecular signals for the early detection of CRC in an average-risk population

KEY FINDINGS AND CONCLUSIONS

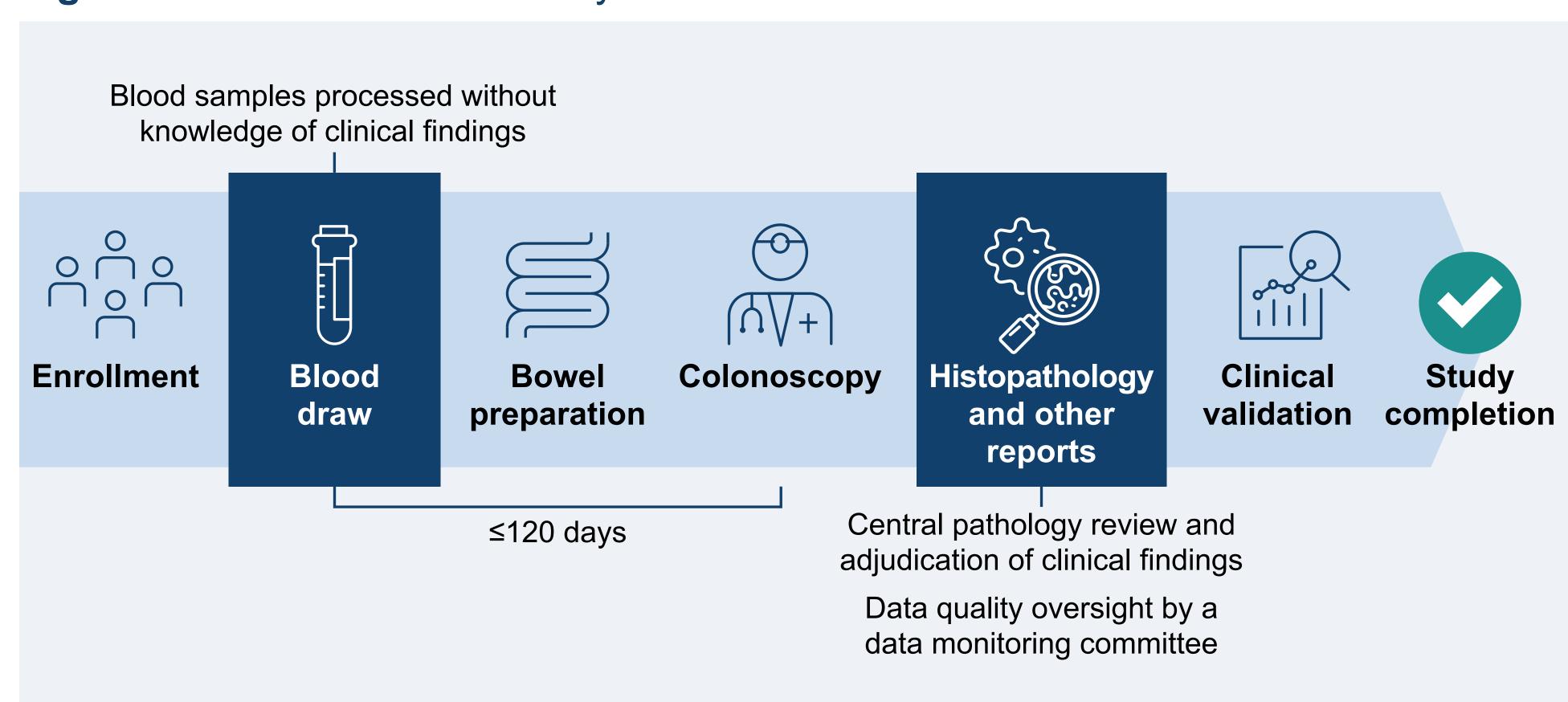
- PREEMPT CRC is the largest prospective study of a BBT for CRC in an average-risk population to date
- With a sensitivity for CRC of 79.2% and specificity for ACN of 91.5%, the investigational BBT met all primary endpoints
- Additionally, the investigational BBT displayed a sensitivity of 12.5% for advanced precancerous lesions
- Performance of the investigational BBT in PREEMPT CRC indicates that blood-based screening tests may offer an effective alternative to conventional methods for early CRC detection in average-risk individuals

METHODS

Study design

- Participants were 45 to 85 years of age, at average risk for CRC, and willing to undergo a standard-of-care screening colonoscopy to be eligible for enrollment
- Prior to bowel preparation for colonoscopy, participants provided a blood sample
- Colonoscopy was performed within 120 days of the blood draw (Figure 1)
- Colonoscopy and applicable histopathology reports underwent central review
- A data monitoring committee had oversight of data quality
- Blood samples were processed blind to clinical findings, and all participants, research physicians, and central pathologists remained blind to the results of the blood test

Figure 1. PREEMPT CRC study schema



Al/ML model training

- A classification model was established using ML and AI technologies to derive proprietary methylated-DNA signatures associated with advanced colorectal neoplasia (ACN)
- Plasma isolated from whole blood samples was analyzed to generate a binary result by comparing to a threshold learned during model training

Test validation

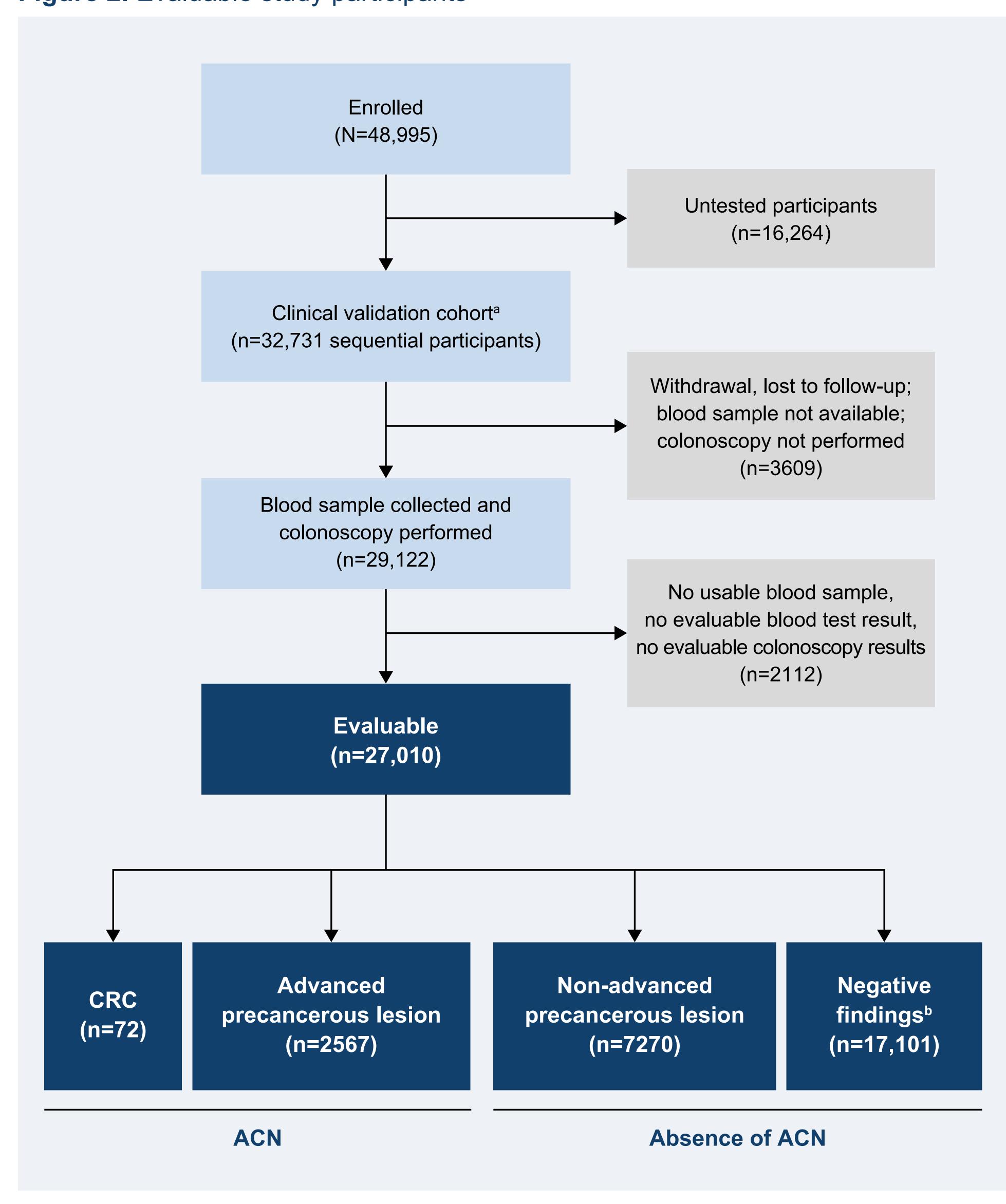
- The performance of the investigational BBT was assessed using screening colonoscopy with histopathology as the reference method
- The four prespecified primary endpoints included sensitivity for CRC, specificity for ACN, negative predictive value (NPV) for ACN, and positive predictive value (PPV) for ACN
- ACN was composed of CRC and advanced precancerous lesions
- Advanced precancerous lesions included carcinoma in situ or high-grade dysplasia, adenoma with villous growth pattern (≥25%), adenoma ≥1.0 cm, sessile serrated lesion with or without cytologic dysplasia ≥1.0 cm, and traditional serrated adenoma
- NPV for ACN was defined as the proportion of participants without a diagnosis of CRC or advanced precancerous lesion among those who had a negative test result
- PPV for ACN was defined as the proportion of participants with a diagnosis of CRC or advanced precancerous lesion among those who had a positive test result
- A secondary endpoint assessed the test's sensitivity for advanced precancerous lesions

RESULTS

Participant demographics

- Of 48,995 study participants originally enrolled in PREEMPT CRC between May 2020 and April 2022, a subset of 32,731 sequentially enrolled participants were included in the clinical validation cohort (Figure 2)
- Of these, 82.5% (n=27,010) had evaluable blood samples and colonoscopy results

Figure 2. Evaluable study participants



^aThe clinical validation cohort included 32,731 participants consecutively enrolled after a predetermined cutoff date that coincided with a study protocol amendment in which further COVID-19 mitigations were implemented and generally coincides with vaccine expansion to all adults in the United States. bNegative findings include non-neoplastic or no findings.

ACN, advanced colorectal neoplasia; CRC, colorectal cancer.

- The mean age of evaluable participants was 58.1 years, and 55.8% were female
- The study enrolled a diverse population, with 11.2% of evaluable participants identifying as Black or African American, 8.8% identifying as Asian, and 11.8% identifying as Hispanic or Latino (Table 1)

Table 1. Baseline demographics

Demographic characteristics	Evaluable participants ^a (N=27,010)
Age (years)	
Mean (SD)	58.1 (8.2)
Median	57
Age Group, n (%)	
45–49	2968 (11.0)
50-54	8899 (32.9)
55–64	8725 (32.3)
65–74	5604 (20.7)
≥75	814 (3.0)
Biological Sex, n (%)	
Female	15,076 (55.8)
Male	11,934 (44.2)
Race, n (%)	
White	19,707 (73.0)
Black or African American	3038 (11.2)
Asian	2381 (8.8)
American Indian or Alaskan Native	78 (0.3)
Native Hawaiian or Other Pacific Islander	72 (0.3)
More than one reported	136 (0.5)
Other/unknown	1598 (5.9)
Ethnicity, n (%)	
Hispanic or Latino	3189 (11.8)
Not Hispanic or Latino	22,421 (83.0)
Unknown	1400 (5.2)

Test performance for primary and secondary outcome measures

• PREEMPT CRC met all primary endpoints (Table 2)

Table 2. Test performance for primary and secondary outcome measures

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Evaluable participants (N=27,010)		ants (N=27,010)
Primary endpoints	Total evaluated (n/N)	% (95% CI)
Sensitivity for CRC	57/72	79.2% (68.4%–86.9%)
Specificity for ACN	22,306/24,371	91.5% (91.2%–91.9%)
NPV for ACN	22,306/24,567	90.8% (90.7%–90.9%)
PPV for ACN	378/2443	15.5% (14.2%–16.8%)
Secondary endpoint	Total evaluated (n/N)	% (95% CI)
Sensitivity for advanced precancerous lesions	321/2567	12.5% (11.3%–13.8%)
ACN advanced colorectal neoplasia: CRC colorectal cancer: NPV negative predictive value:		

ACN, advanced colorectal neoplasia; CRC, colorectal cancer; NPV, negative predictive value;

References

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Disclosures

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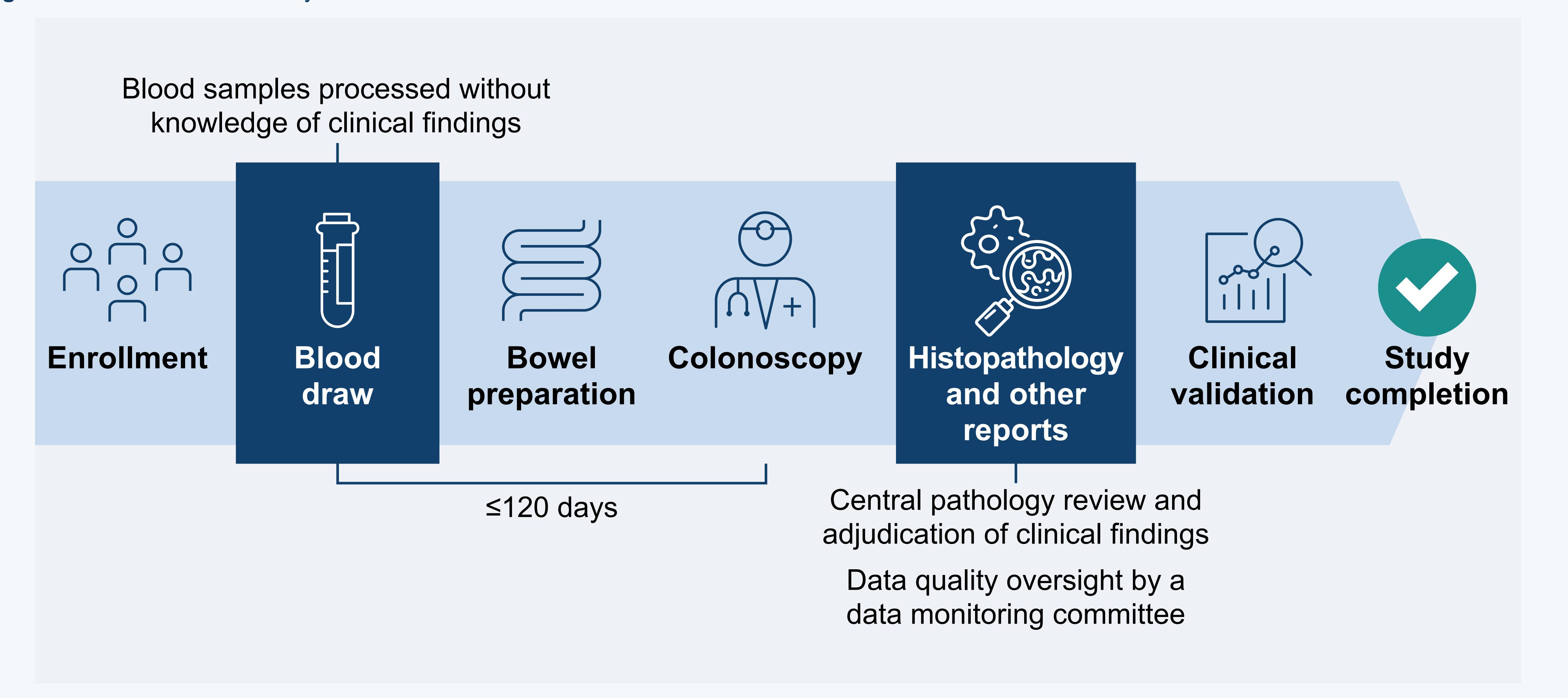
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	Evaluable participants ^a (N=27,010)
	58.1 (8.2) 57
	2968 (11.0) 8899 (32.9) 8725 (32.3) 5604 (20.7) 814 (3.0)
	15,076 (55.8) 11,934 (44.2)
ative ific Islander	19,707 (73.0) 3038 (11.2) 2381 (8.8) 78 (0.3) 72 (0.3) 136 (0.5) 1598 (5.9)
cause of rounding	3189 (11.8) 22,421 (83.0) 1400 (5.2)

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Evaluable participants (N=27,010)		
Total evaluated (n/N)	% (95% CI)	
57/72	79.2% (68.4%–86.9%)	
22,306/24,371	91.5% (91.2%–91.9%)	
22,306/24,567	90.8% (90.7%-90.9%)	
378/2443	15.5% (14.2%–16.8%)	
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BT evaluating molecular signals for the early detec average-risk population

Table 1. Baseline demographics

METHODS

Al/ML model training

- A classification model was established using ML and Al technologies to derive proprietary methylated-DNA signatures associated with advanced colorectal neoplasia (ACN)
- Plasma isolated from whole blood samples was analyzed to generate a binary result by comparing to a threshold learned during model training

Test validation

- The performance of the investigational BBT was assessed using screening colonoscopy with histopathology as the reference method
- The four prespecified primary endpoints included sensitivity for CRC, specificity for ACN, negative predictive value (NPV) for ACN, and positive predictive value (PPV) for ACN
- ACN was composed of CRC and advanced precancerous lesions
- Advanced precancerous lesions included carcinoma in situ or high-grade dysplasia, adenoma with villous growth pattern (≥25%), adenoma ≥1.0 cm, sessile serrated lesion with or without cytologic dysplasia ≥1.0 cm, and traditional serrated adenoma
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To provide an assessment of the clinical performance 3BT evaluating molecular signals for the early detec average-risk population

Table 1. Baseline demographics

RESULTS

Participant demographics

- Of 48,995 study participants originally enrolled in PREEMPT CRC between May 2020 and April 2022, a subset of 32,731 sequentially enrolled participants were included in the clinical validation cohort (Figure 2)
- Of these, 82.5% (n=27,010) had evaluable blood samples and colonoscopy results
- The mean age of evaluable participants was 58.1 years, and 55.8% were female
- The study enrolled a diverse population, with 11.2% of evaluable participants identifying as Black or African American, 8.8% identifying as Asian, and 11.8% identifying as Hispanic or Latino (Table 1)

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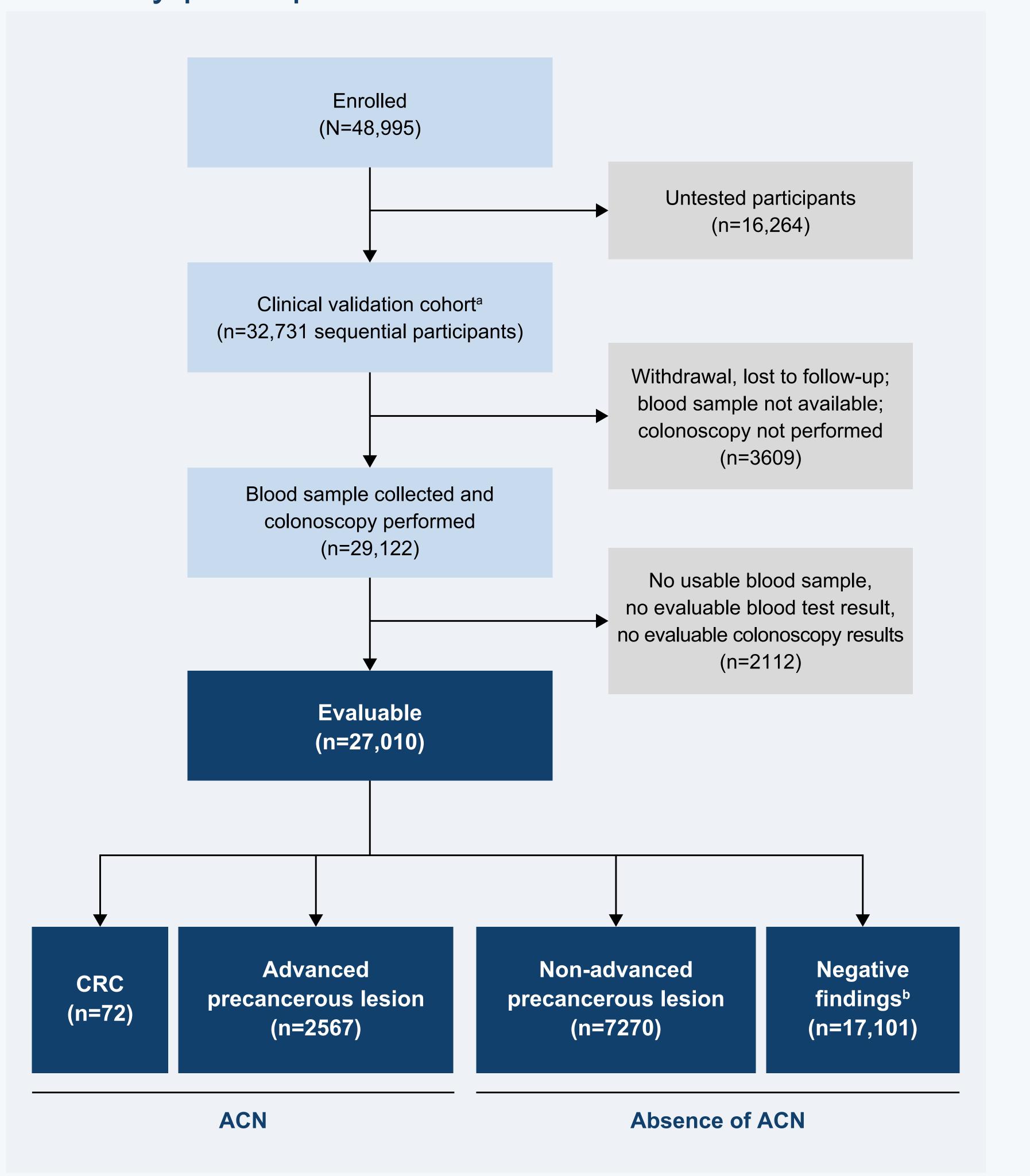
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Table 1. Baseline demographics

RESULTS

Figure 2. Evaluable study participants



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Table 1. Baseline demographics

RESULTS

Table 1. Baseline demographics

Demographic characteristics	Evaluable participants ^a (N=27,010)
Age (years)	
Mean (SD)	58.1 (8.2)
Median	57
Age Group, n (%)	
45–49	2968 (11.0)
50-54	8899 (32.9)
55–64	8725 (32.3)
65–74	5604 (20.7)
≥75	814 (3.0)
Biological Sex, n (%)	
Female	15,076 (55.8)
Male	11,934 (44.2)
Race, n (%)	
White	19,707 (73.0)
Black or African American	3038 (11.2)
Asian	2381 (8.8)
American Indian or Alaskan Native	78 (0.3)
Native Hawaiian or Other Pacific Islander	72 (0.3)
More than one reported	136 (0.5)
Other/unknown	1598 (5.9)
Ethnicity, n (%)	
Hispanic or Latino	3189 (11.8)
Not Hispanic or Latino	22,421 (83.0)
Unknown	1400 (5.2)

^aPercentages may not total 100 because of rounding.

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primary and secondary outcome measures

Evaluable participants (N=27,010)	
Total evaluated (n/N)	% (95% CI)
57/72	79.2% (68.4%–86.9%)
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Table 1. Baseline demographics

RESULTS

Test performance for primary and secondary outcome measures

PREEMPT CRC met all primary endpoints (Table 2)

Table 2. Test performance for primary and secondary outcome measures

	Evaluable participants (N=27,010)	
Primary endpoints	Total evaluated (n/N)	% (95% CI)
Sensitivity for CRC	57/72	79.2% (68.4%–86.9%)
Specificity for ACN	22,306/24,371	91.5% (91.2%–91.9%)
NPV for ACN	22,306/24,567	90.8% (90.7%–90.9%)
PPV for ACN	378/2443	15.5% (14.2%–16.8%)
Secondary endpoint	Total evaluated (n/N)	% (95% CI)
Sensitivity for advanced precancerous lesions	321/2567	12.5% (11.3%–13.8%)

ACN, advanced colorectal neoplasia; CRC, colorectal cancer; NPV, negative predictive value;

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