Test Performance and Lesion Characteristics in a Large Clinical Validation Study of a Blood-Based Screening Test for the Early Detection of Colorectal Cancer

Aasma Shaukat,[1,2] Zhen Meng,[3] Chung-Kai Sun,[3] Chuanbo Xu,[3] Lilian C. Lee,[3] Lance Baldo,[3,a] Theodore R. Levin[4]

[1]*New York University Grossman School of Medicine, New York, NY, US;* [2]*University of Minnesota Twin Cities, Minneapolis, MN, US;* [3]*Freenome Holdings Inc., South San Francisco, CA, US;* [4]*Kaiser Permanente Division of Research, Pleasanton, CA, US*

[a]*Affiliation at the time the study and/or analyses were conducted*

INTRODUCTION

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- Colorectal cancer (CRC) is the second-leading cause of cancer-related death in the US, but is treatable when detected early[1]
- Despite the proven benefits of CRC screening, recent statistics revealed over 40% of eligible adults at average risk for CRC in the US were not up to date with guideline recommended screening in 2021[2–4]
- Low screening uptake can partly be attributed to the inconveniences associated with existing screening methods and disparities in access to medical care among certain demographic groups[2,5]
- Specific challenges of current screening modalities include bowel preparation and the invasiveness associated with colonoscopy (CS), and fecal aversion associated with stool-based tests[6]
- Ideally, comprehensive CRC screening should detect both small and large advanced colorectal neoplasia (ACN) and difficult-to-discern proximal lesions to increase the likelihood of achieving the best possible outcomes[7]
- Blood-based screening may offer a convenient alternative to traditional methods, and potentially increase screening uptake[8,9]
- PREEMPT CRC (NCT04369053[10]), a prospective, multicenter, observational study, was conducted to validate an investigational CRC early detection blood test designed to detect molecular signals associated with ACN in an average-risk population

OBJECTIVE

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- To analyze the performance of an investigational CRC early detection blood test by lesion location and size

METHODS

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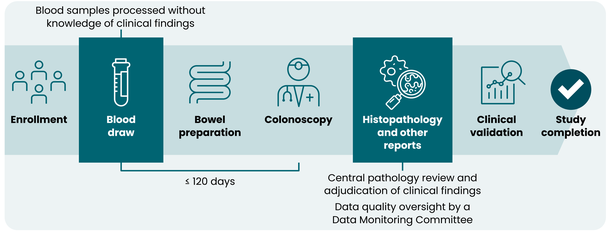
Study design

- Participants had to be 45 to 85 years of age, at average risk for CRC, and willing to undergo a standard-of-care screening CS to be eligible for enrollment
- Prior to bowel preparation for CS, participants provided a blood sample that was sent to Freenome for testing
- CS was performed within 120 days of the blood draw (**Figure 1**)
- CS and applicable histopathology reports underwent central review
- 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



Test validation

- The performance of the CRC early detection blood test was assessed using screening CS with histopathology as the reference method
- The prespecified four co-primary endpoints included sensitivity for CRC, specificity for ACN, negative predictive value (NPV) for ACN, and positive predictive value (PPV) for ACN
  - ACN comprised 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 cytological dysplasia ≥1.0 cm, and traditional serrated adenoma
- A prespecified multivariate logistic regression analysis was performed to assess the test positivity for CRC, adjusting for lesion location, lesion size, and demographic characteristics

RESULTS

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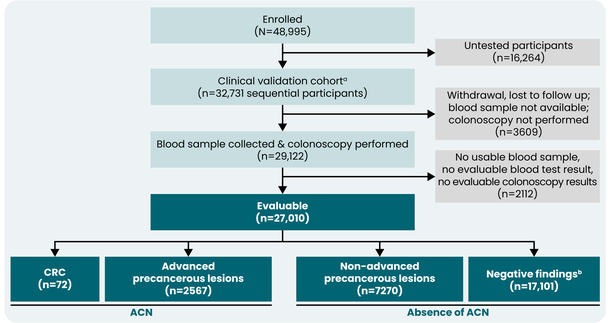
Participant demographics

- Out 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 CS results

Figure 2. Evaluable Study Participants



[a]The clinical validation cohort included 32,731 participants consecutively enrolled after a predetermined cutoff date that corresponded to expanded eligibility of COVID-19 vaccination for the overall population and a return to more normal office visits.
[b]Negative findings include non-neoplastic or no findings.
ACN, advanced colorectal neoplasia; CRC, colorectal cancer.

- The mean age of participants was 58.1 years and 55.8% were female
- The study enrolled a diverse population, with 11.2% of 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 of Evaluable Participants

Demographic characteristics	Evaluable participants (N=27,010)
Age, years	
Mean (SD)	58.1 (8.2)
Median	57.0
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)

Percentages may not total 100 because of rounding.

Test performance for primary outcome measures

- PREEMPT CRC met all primary endpoints (**Table 2**)

Table 2. Test Performance for Primary Outcome Measures in Evaluable Participants

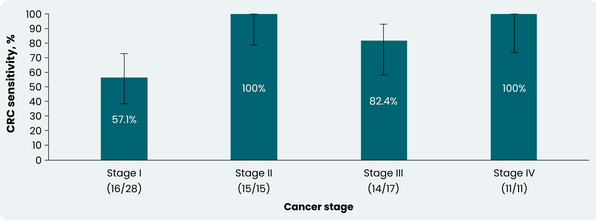
Endpoint	Evaluable participants (N=27,010)	
	Total evaluated (n/N)	% (95% CI)
Sensitivity for CRC	57/72	79.2% (68.4%–86.9%)
Specificity for ACN	22,306/24,371	91.5% (91.2%–91.9%)
NPV for ACN	22,306/24,567	90.8% (90.7%–90.9%)
PPV for ACN	378/2443	15.5% (14.2%–16.8%)

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

Test performance by CRC stage, lesion size, and lesion location

- Test sensitivity was 57.1% (95% CI, 39.1%–73.5%) for stage I, 100% (95% CI, 79.6%–100%) for stage II, 82.4% (95% CI, 59.0%–93.8%) for stage III and 100% (95% CI, 74.1%–100%) for stage IV (**Figure 3**)

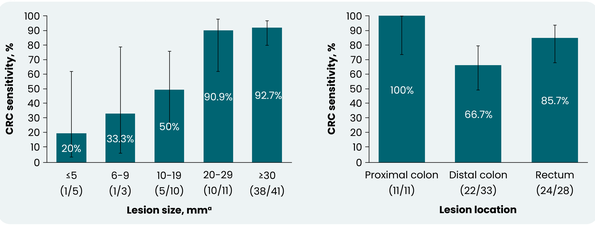
Figure 3. Test Sensitivity for CRC by Stage



Stage was reported for all except one CRC case, which was detected by the blood test. Stages were defined by the American Joint Committee on Cancer Staging System, 8th edition.[11] Error bars indicate 95% CIs.
CRC, colorectal cancer.

- Test sensitivity for CRC and lesion size were directly proportional, with sensitivity increasing as lesion size increased (**Figure 4**)
  - Sensitivity for CRC was 33.3% (95% CI, 6.1%–79.2%) for lesions of 6 to 9 mm, 50.0% (95% CI, 23.7%–76.3%) for lesions of 10 to 19 mm, 90.9% (95% CI, 62.3%–98.4%) for lesions of 20 to 29 mm, and 92.7% (95% CI, 80.6%–97.5%) for lesions ≥30 mm
- Sensitivity for CRC was 100% (95% CI, 74.1%–100.0%) for lesions located in the proximal colon, 66.7% (95% CI, 49.6%–80.2%) for lesions in the distal colon, and 85.7% (95% CI, 68.5%–94.3%) for lesions in the rectum (**Figure 4**)
- In the prespecified multivariate logistic regression analysis, no statistically significant difference in test sensitivity by lesion location was found when adjusting for demographic characteristics (age, sex, and race) and lesion size

Figure 4. Test Sensitivity for CRC by Lesion Size and Location



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KEY FINDINGS AND CONCLUSIONS

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- PREEMPT CRC is the largest prospective study to date of a blood-based screening test for CRC in an average-risk population
- With a sensitivity for CRC of 79.2% and specificity for ACN of 91.5%, the investigational CRC early detection blood test met all primary endpoints
- The test was able to detect CRC lesions across a wide range of sizes, with test sensitivity increasing as lesion size increased
- The test effectively detected CRC throughout the colon and displayed a 100% sensitivity for CRC lesions located in the proximal colon
  - When controlling for demographic characteristics and lesion size, lesion location was not found to be a variable contributing to test sensitivity for CRC
- Performance of the CRC early detection blood test in PREEMPT CRC indicates that blood-based screening tests may offer an effective alternative for early CRC detection in average-risk individuals

References

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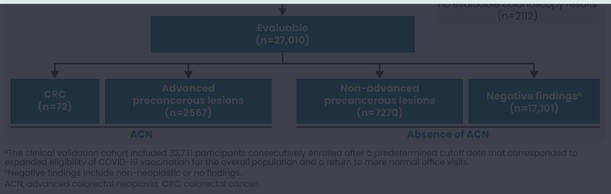

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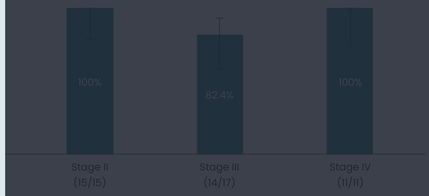
CRC by Stage



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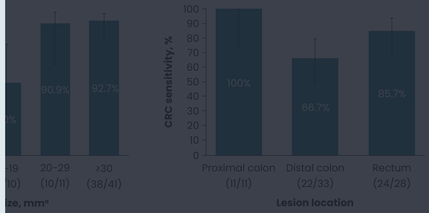

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- Specific challenges of current screening modalities include bowel preparation and the invasiveness associated with colonoscopy (CS), and fecal aversion associated with stool-based tests[6]
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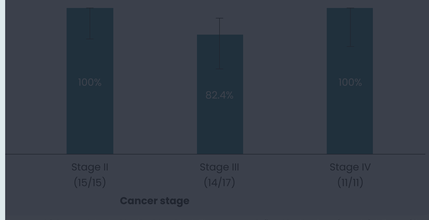

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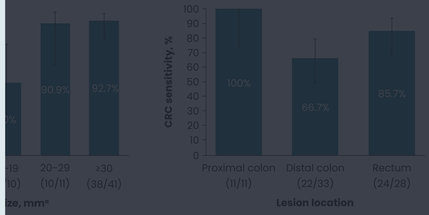

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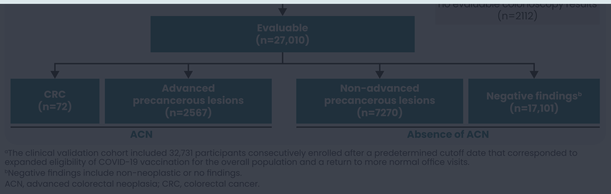

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INTRODUCTION

- Colorectal cancer (CRC) is the second-leading cause of cancer-
but is treatable when detected early[1]
- Despite the proven benefits of CRC screening, recent statistics re
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- Participants had to be 45 to 85 years of age, at average risk for C
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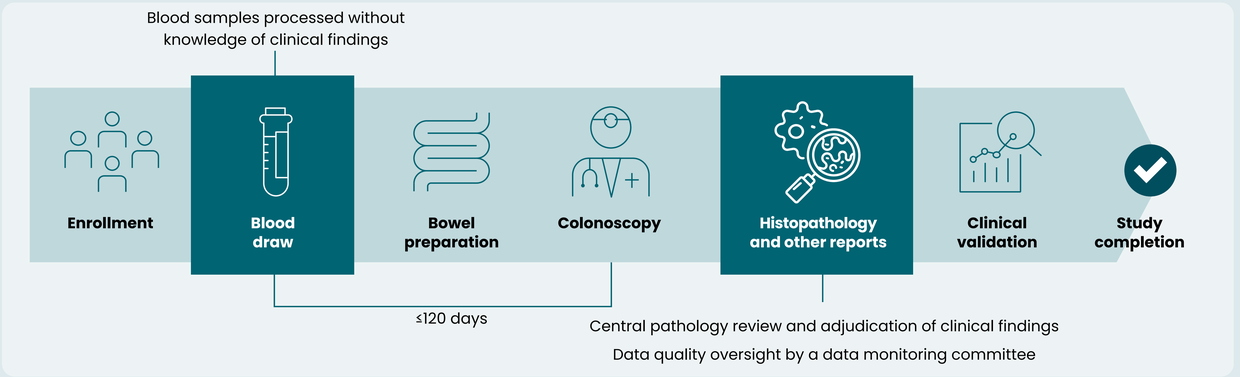
Back

METHODS

Study design

- Participants had to be 45 to 85 years of age, at average risk for CRC, and willing to undergo a standard-of-care screening CS to be eligible for enrollment
- Prior to bowel preparation for CS, participants provided a blood sample that was sent to Freenome for testing
- CS was performed within 120 days of the blood draw (**Figure 1**)
- CS and applicable histopathology reports underwent central review
- 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



1 of 2

CRC stage, lesion size, and lesion location

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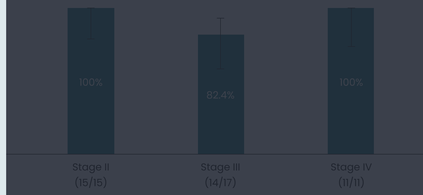
CRC by Stage



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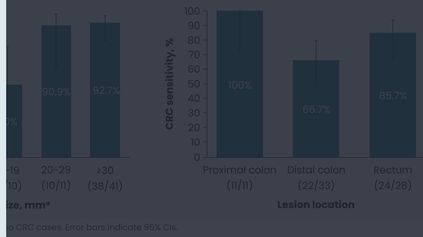

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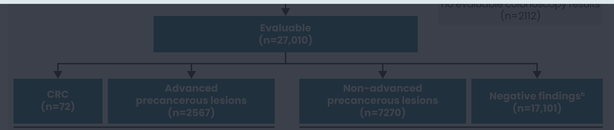

[a]The clinical validation cohort included 22,731 participants consecutively enrolled after a predetermined cutoff date that corresponded to expanded eligibility of COVID-19 vaccination for the overall population and a return to more normal office visits.
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METHODS

Test validation

- The performance of the CRC early detection blood test was assessed using screening CS with histopathology as the reference method
- The prespecified four co-primary endpoints included sensitivity for CRC, specificity for ACN, negative predictive value (NPV) for ACN, and positive predictive value (PPV) for ACN
  - ACN comprised 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 cytological dysplasia ≥1.0 cm, and traditional serrated adenoma
- A prespecified multivariate logistic regression analysis was performed to assess the test positivity for CRC, adjusting for lesion location, lesion size, and demographic characteristics

2 of 2

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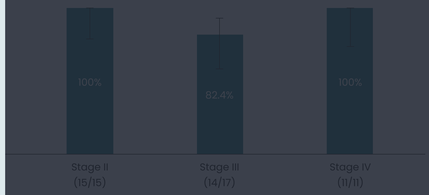

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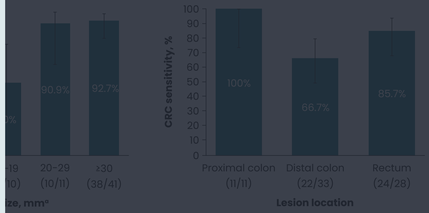

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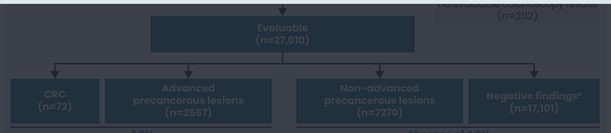

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KEY FINDINGS AND CONCLUSIONS

- PREEMPT CRC is the largest prospective study to date of a blood-based screening test for CRC in an average-risk population
- With a sensitivity for CRC of 79.2% and specificity for ACN of 91.5%, the investigational CRC early detection blood test met all primary endpoints
- The test was able to detect CRC lesions across a wide range of sizes, with test sensitivity increasing as lesion size increased
- The test effectively detected CRC throughout the colon and displayed a 100% sensitivity for CRC lesions located in the proximal colon
  - When controlling for demographic characteristics and lesion size, lesion location was not found to be a variable contributing to test sensitivity for CRC
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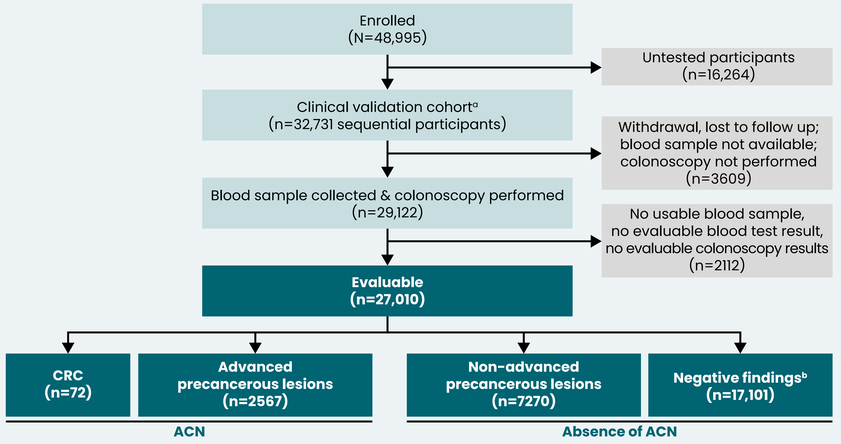
RESULTS

Participant demographics

- Out 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 CS results

Figure 2. Evaluable Study Participants



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- The mean age of participants was 58.1 years and 55.8% were female
- The study enrolled a diverse population, with 11.2% of 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 of Evaluable Participants

Demographic characteristics	Evaluable participants (N=27,010)
Age, years	
Mean (SD)	58.1 (8.2)
Median	57.0
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)

Percentages may not total 100 because of rounding.

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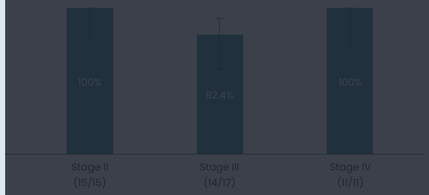

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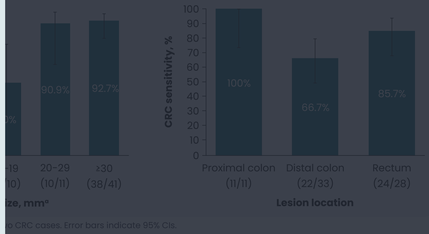

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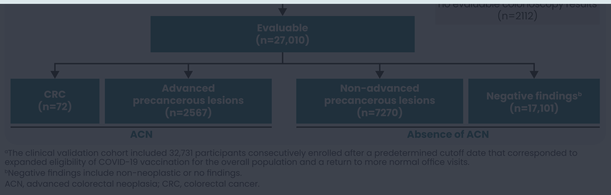

[a]The clinical validation cohort included 32,731 participants consecutively enrolled after a predetermined cutoff date that corresponded to expanded eligibility of COVID-19 vaccination for the overall population and a return to more normal office visits.
[b]Negative findings include non-neoplastic or no findings.
ACN, advanced colorectal neoplasia; CRC, colorectal cancer.

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Test Performance and Lesion Characteristics in a Large Clinical Validation Study of a Blood-Based Screening Test for the Early Detection of Colorectal Cancer

Aasma Shaukat,[1,2] Zhen Meng,[3] Chung-Kai Sun,[3] Chuanbo Xu,[3] Lilian C. Lee,[3] Lance Baldo,[3,a] Theodore R. Levin[4]

[1]*New York University Grossman School of Medicine, New York, NY, US;* [2]*University of Minnesota Twin Cities, Minneapolis, MN, US;* [3]*Freenome Holdings Inc., South San Francisco, CA, US;* [4]*Kaiser Permanente Division of Research, Pleasanton, CA, US*

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INTRODUCTION

- Colorectal cancer (CRC) is the second-leading cause of cancer-
but is treatable when detected early[1]
- Despite the proven benefits of CRC screening, recent statistics re
adults at average risk for CRC in the US were not up to date with
screening in 2021[2–4]
- Low screening uptake can partly be attributed to the inconvenier
existing screening methods and disparities in access to medical
demographic groups[4,5]
- Specific challenges of current screening modalities include bowe
invasiveness associated with colonoscopy (CS), and fecal aversi
stool-based tests[6]
- Ideally, comprehensive CRC screening should detect both small
colorectal neoplasia (ACN) and difficult-to-discern proximal lesi
likelihood of achieving the best possible outcomes[7]
- Blood-based screening may offer a convenient alternative to tra
potentially increase screening uptake[8,9]
- PREEMPT CRC (NCT04369053[10]), a prospective, multicenter, obser
conducted to validate an investigational CRC early detection blo
detect molecular signals associated with ACN in an average-risk

OBJECTIVE

- To analyze the performance of an investigational CRC early dete
location and size

METHODS

Study design

- Participants had to be 45 to 85 years of age, at average risk for C
a standard-of-care screening CS to be eligible for enrollment
- Prior to bowel preparation for CS, participants provided a blood s
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KEY FINDINGS AND CONCLUSIONS

- PREEMPT CRC is the largest prospective study to da
screening test for CRC in an average-risk populatio
- With a sensitivity for CRC of 79.2% and specificity fo
the investigational CRC early detection blood test m
primary endpoints
- The test was able to detect CRC lesions across a wi
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a 100% sensitivity for CRC lesions located in the pro
  - When controlling for demographic characteristics and lesion size, lesion location was not found to be a variable contributing to test sensitivity for CRC
- Performance of the CRC early detection blood test in PREEMPT CRC indicates that blood-based screening tests may offer an effective alternative for early CRC detection in average-risk individuals

RESULTS

Test performance for primary outcome measures

- PREEMPT CRC met all primary endpoints (**Table 2**)

Table 2. Test Performance for Primary Outcome Measures in Evaluable Participants

	Evaluable participants (N=27,010)	
Endpoint	**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%)
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PPV for ACN	378/2443	15.5% (14.2%–16.8%)

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

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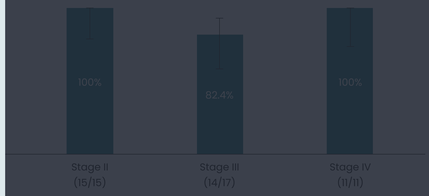
CRC stage, lesion size, and lesion location

(95% CI, 39.1%–73.5%) for stage I, 100% (95% CI, 79.6%–100%) for
3.0%–93.8%) for stage III and 100% (95% CI, 74.1%–100%) for stage IV

CRC by Stage



case, which was detected by the blood test. Stages were defined by the American Joint Committee
er bars indicate 95% CIs.

nd lesion size were directly proportional, with sensitivity increasing
(Figure 4)

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ns of 10 to 19 mm, 90.9% (95% CI, 62.3%–98.4%) for lesions of 20 to
% CI, 80.6%–97.5%) for lesions ≥30 mm

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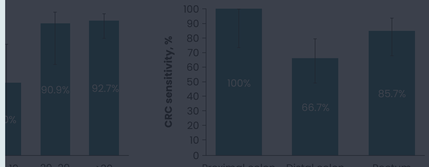
(Figure 4)

variate logistic regression analysis, no statistically significant
ity by lesion location was found when adjusting for demographic
and race) and lesion size

CRC by Lesion Size and Location



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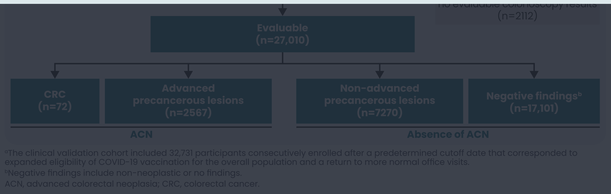

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- Performance of the CRC early detection blood test in PREEMPT CRC indicates that blood-based screening tests may offer an effective alternative for early CRC detection in average-risk individuals

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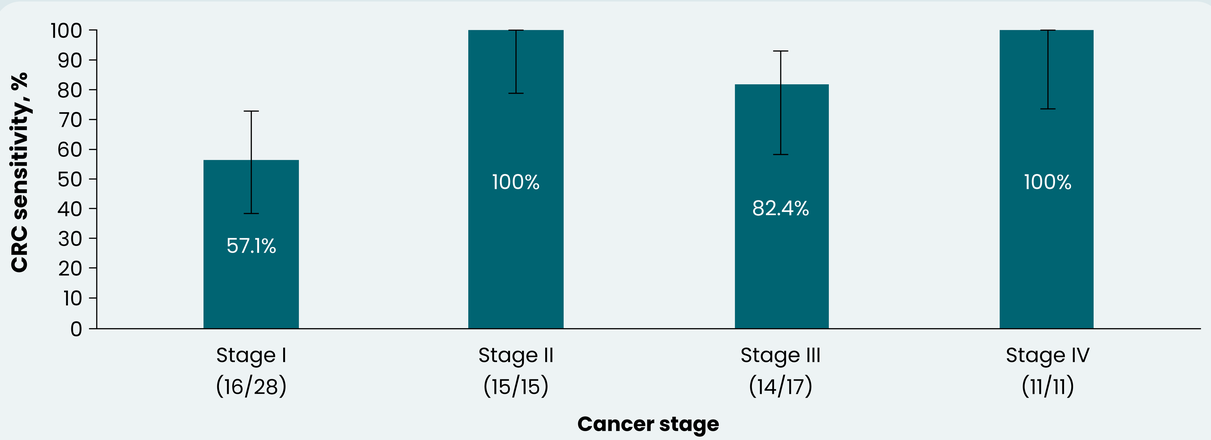
RESULTS

Test performance by CRC stage, lesion size, and lesion location

- Test sensitivity was 57.1% (95% CI, 39.1%–73.5%) for stage I, 100% (95% CI, 79.6%–100%) for stage II, 82.4% (95% CI, 59.0%–93.8%) for stage III and 100% (95% CI, 74.1%–100%) for stage IV (**Figure 3**)

Figure 3. Test Sensitivity for CRC by Stage



Stage was reported for all except one CRC case, which was detected by the blood test. Stages were defined by the American Joint Committee on Cancer Staging System, 8th edition.[11] Error bars indicate 95% CIs.
CRC, colorectal cancer.

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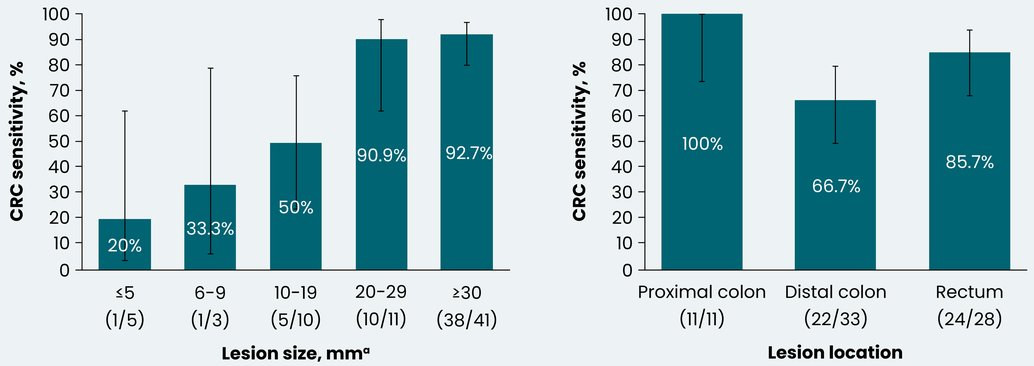
RESULTS

- Test sensitivity for CRC and lesion size were directly proportional, with sensitivity increasing as lesion size increased (**Figure 4**)
  - Sensitivity for CRC was 33.3% (95% CI, 6.1%–79.2%) for lesions of 6 to 9 mm, 50.0% (95% CI, 23.7%–76.3%) for lesions of 10 to 19 mm, 90.9% (95% CI, 62.3%–98.4%) for lesions of 20 to 29 mm, and 92.7% (95% CI, 80.6%–97.5%) for lesions ≥30 mm
- Sensitivity for CRC was 100% (95% CI, 74.1%–100.0%) for lesions located in the proximal colon, 66.7% (95% CI, 49.6%–80.2%) for lesions in the distal colon, and 85.7% (95% CI, 68.5%–94.3%) for lesions in the rectum (**Figure 4**)
- In the prespecified multivariate logistic regression analysis, no statistically significant difference in test sensitivity by lesion location was found when adjusting for demographic characteristics (age, sex, and race) and lesion size

Figure 4. Test Sensitivity for CRC by Lesion Size and Location



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