

ORIGINAL ARTICLE

Effect of Screening with Multicancer Early-Detection Test on Late-Stage Cancer Diagnosis

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ABSTRACT

BACKGROUND

Whether screening with blood-based early-detection tests for multiple cancers in addition to usual care has clinical utility is unknown.

METHODS

In a randomized, controlled trial conducted in England, we obtained peripheral blood from persons 50 to 77 years of age at up to three annual visits. After baseline blood collection, participants were randomly assigned in a 1:1 ratio to the intervention group (participants whose blood was tested) or the control group (participants whose blood was stored). Participants and trial personnel were initially unaware of the group assignments. The primary end point was stage III or IV cancer among 12 prespecified types of cancer, and a key secondary end point was stage IV cancer among the 12 prespecified types. The differences between the groups in the incidence rate (the number of first eligible events divided by person-years at risk) were measured after three screening rounds and at least 12 months of follow-up after the last participant's third visit.

RESULTS

Overall, 71,122 participants were randomly assigned to the intervention group and 71,128 to the control group. The incidence rate of stage III or IV cancer (primary end point) did not differ significantly between the groups (incidence rate ratio [intervention vs. control], 1.03; 95% confidence interval [CI], 0.92 to 1.14, $P=0.63$). The incidence rate ratio for stage IV cancer (a key secondary end point) after 3 screening rounds was 0.86 (95% CI, 0.74 to 1.00). Less than 1% of participants had trial-related adverse events; none were serious.

CONCLUSIONS

In this trial, we did not observe a lower incidence rate of stage III or IV cancers across 12 prespecified cancers after three screening rounds with multicancer early-detection testing plus usual care than with usual care alone. Further follow-up is warranted to assess the way in which findings for stage III or IV cancers and the between-group difference in stage IV cancers evolve over time. (Funded by Grail; NHS-Galleri ClinicalTrials.gov number, NCT05611632; ISRCTN number, ISRCTN91431511.)

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THE SURVIVAL ADVANTAGE ASSOCIATED with detection of cancer at earlier stages reflects broader eligibility for curative treatment and lower disease burden.¹ Standard-of-care screening contributes to earlier diagnosis and improved survival,² yet the recommended single-cancer screening accounts for less than 7% of all cancer diagnoses in England and less than 15% in the United States.^{2,3}

Multicancer early-detection testing offers a different approach by simultaneously screening for multiple cancer types in a biologic specimen (e.g., blood).⁴⁻⁶ One multicancer early-detection test that analyzes methylation patterns in cell-free DNA (cfDNA)⁶ to detect a cancer signal and predict the associated tissue type or organ (cancer signal origin) has shown the ability to detect cancer across a broad range of cancer types. The test has shown strong performance in case-control studies⁷ and in prospective clinical studies,^{8,9} as well as in real-world experience.¹⁰⁻¹²

Here, we report the primary results from the NHS-Galleri trial, a randomized, controlled trial evaluating the clinical utility of a clinically validated multicancer early-detection test when added to usual care in a national health care system among participants 50 to 77 years of age at invitation, over three annual screening rounds.

METHODS

TRIAL OVERSIGHT AND DESIGN

The NHS-Galleri trial (registered with ISRCTN on September 16, 2021 and at ClinicalTrials.gov on October 28, 2022), which is sponsored by Grail, is an ongoing, prospective, randomized, controlled trial to evaluate the clinical utility and effectiveness of a multicancer early-detection blood test (Galleri [Grail]) when added to usual care.⁶ Persons in eight participating English Cancer Alliance regions were eligible if they were 50 to 77 years of age, did not have a cancer diagnosis or treatment within the 3 years before enrollment, and were not being assessed for possible cancer (for more details, see the Supplementary Methods section in the Supplementary Appendix, available with the full text of this article at NEJM.org). Invitations, information sheets, and consent forms were developed with input from diverse members of the public, including persons from socioeconomically deprived neighborhoods and a range of ethnic backgrounds.¹³ This trial used data provid-

ed by participants and data collected by the National Health Service (NHS) as part of patient care and disease surveillance. The data were collated and maintained and quality was assured by the National Cancer Registration and Analysis Service, which is part of the NHS. NHS DigiTrials invited the majority of the participants in this trial. Further information on trial oversight and a list of author responsibilities are provided in the Supplementary Methods section. Details of the trial design (e.g., recruitment methods and trial objectives) have been published previously^{6,13} and are provided in the Supplementary Methods section.

Grail, in collaboration with the Cancer Research U.K. Cancer Prevention Trials Unit, was responsible for the design, conduct, and reporting of the trial and for analysis of the data. Data analysis was conducted independently by Queen Mary University of London and verified by Grail. The trial protocol, available at NEJM.org, received national ethical approval from Wales Research Ethics Committee 1. An independent data monitoring committee oversaw and assessed trial progress, reviewed clinical and safety data, and provided design and conduct recommendations to Grail. The chief investigators (the last two authors) take primary responsibility for the overall design, conduct, and reporting of the trial. The sponsor participated in drafting the manuscript and in approving submission of the manuscript for publication. The authors vouch for the completeness and accuracy of the data and for adherence of the trial to the protocol.

PROCEDURES

Initial appointments were conducted in mobile phlebotomy clinics. After participants provided written informed consent, a baseline peripheral blood sample was obtained by routine venipuncture, and participants were then randomly assigned in a 1:1 ratio to the intervention or control group (Fig. S1).⁶ All participants, except those for whom the trial team had received death notification, were invited to provide a blood sample at two further annual (12 months, with a window of ± 6 weeks) visits; participants missing the second visit could return for the third. Participants who had received treatment for cancer in the preceding year were advised to contact the trial team, because they may not have needed to attend the next screening visit. All participants and trial

staff were initially unaware of the group assignments; participants in the intervention group who had a positive result on a multicancer early-detection test (i.e., a cancer signal was detected) received the results in communications from trial nurses who became aware of the group assignment.¹³ Only statisticians who were aware of the group assignments reviewed unblinded safety data and presented results to the independent data monitoring committee in closed meetings conducted every 6 months.

Blood samples from participants in the intervention group were analyzed with the multicancer early-detection test. The trial team facilitated referral for diagnostic testing of participants who received a positive result through established NHS urgent cancer referral pathways that followed existing guidelines for anatomical site-specific suspected cancer based on the cancer-signal origin predicted by the multicancer early-detection test.^{6,14} All blood samples from participants in the control group and remaining plasma samples from the participants in the intervention group (kept in case of a processing error) were stored for future testing with the consent of the participants.

Cancer outcomes were obtained through linked national health care datasets. Participants were passively followed for cancer diagnoses and death until they emigrated or withdrew consent. Important protocol deviations are summarized in Tables S1 and S2.

SAFETY

Adverse events were reported by participants or recorded by qualified trial staff. Trial-related adverse events were those that were related to trial procedures and that occurred before referral to NHS; device-related adverse events were those that occurred after NHS referral and that had a reasonable temporal possibility of a causal relationship with the referral, the investigational device (i.e., the multicancer early-detection test), or its use, despite these activities occurring outside the trial. Adverse events were assessed for relatedness, expectedness, and severity, and their assessment was aligned with the medical safety and monitoring plan (Supplementary Methods section). Further information on anxiety among participants receiving a positive multicancer early-detection test result¹⁵ and data on radiation exposure and complications associated with diagnostic proce-

dures undergone outside the trial, are not included here.

STATISTICAL ANALYSIS

The statistical analysis plan is available with the protocol. Microsimulation indicated that a sample size of approximately 140,000 participants would be needed to provide the trial with at least 90% power for the primary end point after three screening rounds, with follow-up through 12 months after the last participant's third visit, across varied natural history assumptions¹⁶; an approximately 20% lower incidence rate of stage III or IV cancers among the 12 prespecified types (those that are responsible for more than 60% of cancer deaths^{6,7}: lung, head and neck, colon or rectum, pancreas, myeloma or plasma cell neoplasm, liver or bile duct, stomach, esophagus, anus, lymphoma, ovary, and bladder) was projected under the most likely scenario.⁶ Primary and secondary efficacy comparisons were conducted according to the intention-to-treat principle.

Cancer diagnoses that were registered by the National Cancer Registration and Analysis Service from randomization through July 12, 2025, were included for a follow-up period of three screening rounds plus 12 months after the last participant's third visit (primary analysis window). Person-years of follow-up were measured from randomization to the first event of interest (i.e., stage III or IV cancer diagnosis, death, consent withdrawal, or emigration).

Incidence rates were calculated as the number of first eligible events divided by person-years at risk, with 95% confidence intervals for incidence rates calculated with a Poisson distribution. Incidence rate ratios, 95% confidence intervals, and two-sided P values were calculated with exact Poisson methods. Unstageable cancers (i.e., cancers for which a staging system does not exist) and cancers with missing stage (Supplementary Methods section) were excluded from stage-specific analysis. The primary end point was stage III or IV cancer after three screening rounds and at least 12 months of follow-up after the last participant's third visit. Statistical testing followed a prespecified fixed conditional sequence. The comparison was performed first for the 12 prespecified cancer types, second for all routinely staged cancer types except prostate cancer, and third for all routinely staged cancer types. Testing stopped at the first nonsignificant step to

control the type I error. All routinely staged cancer types excluded those for which a staging system does not exist — brain cancers, leukemias, and cancers of unknown primary site. Testing stopped at the first nonsignificant step to control the type I error. Secondary end points (Supplementary Methods section), including stage IV cancer (a key secondary end point), were interpreted descriptively with 95% confidence intervals. The widths of the confidence intervals were not adjusted for multiple testing and should not be used for hypothesis testing.

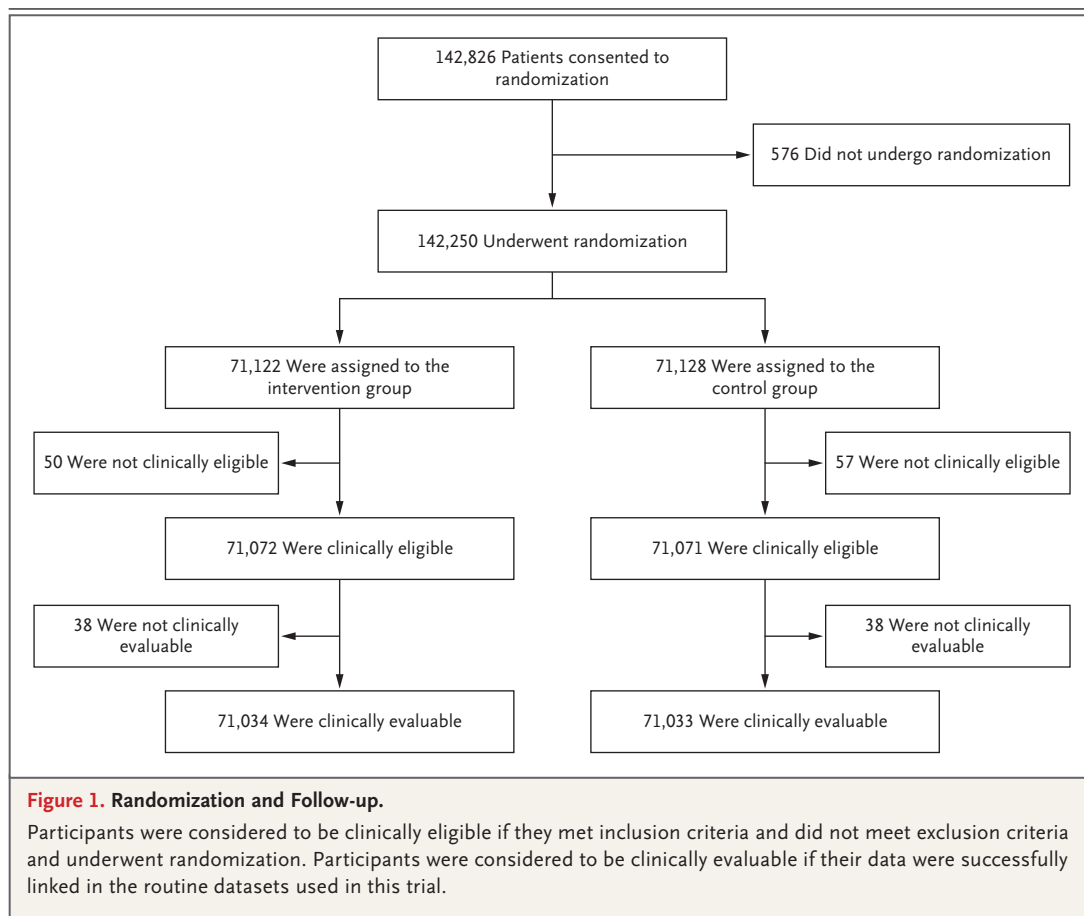
RESULTS

POPULATION

A total of 1,496,311 persons were invited to participate in the trial, and 142,826 persons consented to participate over the course of 10.5 months¹³; a blood sample was obtained in 142,250 participants (99.6%). Overall, 71,122 participants were randomly assigned to the intervention group and

71,128 to the control group (Fig. 1). A total of 64,888 participants (91.2%) in the intervention group and 65,066 (91.5%) in the control group returned to provide a blood sample at 12 months, and 62,867 (88.4%) and 63,101 (88.7%), respectively, returned to provide a blood sample at 24 months. Participants had 12 months of follow-up after each of the first two multicancer early-detection screening rounds, and a median of 17 months (range, 12 to 22) of follow-up after the third round.

By design, participants from the most socio-economically deprived areas were overrepresented (Table 1). Ethnic-group distribution broadly represented the equivalent-aged English population (Table S3).¹³ Most of the participants had never smoked (55.0%) and reported being up to date on standard-of-care screening (71.9%). The demographic and clinical characteristics of the participants were well balanced between the two groups at baseline and across screening rounds (Table 1 and Table S4).



LATE-STAGE CANCER OUTCOMES WITH MULTICANCER EARLY-DETECTION SCREENING

Overall, 3637 participants in the intervention group and 3400 participants in the control group received a diagnosis of cancer; 3431 and 3177, respectively, received a diagnosis of a routinely staged cancer, of whom 1421 and 1298 received a diagnosis of one of the 12 prespecified cancers (Tables S5 and S6). After three screening rounds, 706 participants in the intervention group and 688 participants in the control group had received a diagnosis of stage III or IV cancer among the 12 prespecified cancer types, which yielded an incidence rate per 100,000 person-years of 300.5 (95% confidence interval [CI], 278.7 to 323.5) in the intervention group and 292.5 (95% CI, 271.0 to 315.1) in the control group (Fig. 2 and Table 2). The incidence rate for stage III or IV cancer did not differ significantly between the intervention and control groups (incidence rate ratio, 1.03; 95% CI, 0.92 to 1.14; $P=0.63$). Participant-level descriptive counts (Table S7) revealed that with respect to the 12 prespecified cancer types, a greater number of stage III cancers were diagnosed in the intervention group than in the control group (360 vs. 287), which outweighed the lower number of stage IV cancers that were diagnosed in the intervention group (341 vs. 394). The overall result was driven by the higher incidence rate of stage III or IV cancers in the intervention group than in the control group in the first screening round (a post hoc analysis; incidence rate ratio, 1.19; 95% CI, 0.98 to 1.43). In contrast, the incidence rate ratio (intervention vs. control) for stage III or IV cancers in the second round (a post hoc analysis) was 0.95 (95% CI, 0.77 to 1.17), and the incidence rate ratio in the third round (a prespecified analysis) was 0.88 (95% CI, 0.73 to 1.07) (Table S8).

Among the 12 prespecified cancer types, after three screening rounds, the incidence rate of stage IV cancer per 100,000 person-years was 145.2 (95% CI, 130.2 to 161.4) in the intervention group and 168.5 (95% CI, 152.3 to 185.9) in the control group (incidence rate ratio, 0.86; 95% CI, 0.74 to 1.00) (Fig. 2 and Table 2). The incidence rate ratio for stage IV cancers was 0.91 (95% CI, 0.71 to 1.18) in the first round, 0.78 (95% CI, 0.57 to 1.06) in the second round, and 0.74 (95% CI, 0.57 to 0.95) in the third round (Table S9).

The observed incidence rate ratios for stage III or IV and for stage IV cancers appeared to be

similar between the 12 prespecified types and all routinely staged types, including or not including prostate cancer (Fig. 2, Fig. S2, Table 2, and Tables S8 and S9). Across all routinely staged cancers, the incidence rate ratio for stage IV cancer was 0.78 (95% CI, 0.61 to 1.00) in the second round and 0.80 (95% CI, 0.65 to 0.99) in the third round (Table S9).

In a prespecified secondary end-point analysis, we combined fatal cancers (defined as cancers that result in cancer-specific death during follow-up regardless of the stage at which the cancers were diagnosed) with stage III or IV cancers. With this definition, among all routinely staged cancer types, there were 1415 events in the intervention group and 1359 events in the control group after three screening rounds (incidence rate ratio, 1.04; 95% CI, 0.97 to 1.12) (Table S10). In an analysis in which we excluded cancers for which standard-of-care screening was available (i.e., breast, cervix, and colon or rectum), 1077 participants in the intervention group and 1030 participants in the control group received a diagnosis of stage III or IV cancer after three screening rounds (incidence rate ratio, 1.05; 95% CI, 0.96 to 1.14) (Table S11). In prespecified exploratory subgroup analyses, the greatest (relative and absolute) differences between the intervention and control groups in stage III or IV and in stage IV cancer rates were observed among men, among those with previous cancer history, and among those with lower education status; in a comparison of the between-group difference in stage IV cancer rates according to the index of multiple deprivation (a national indication of level of deprivation that is based on small geographic areas of residence, assessed in quintiles) the greatest difference was observed in quintile 1 (most deprived) (Fig. S3).

DETECTION OF EARLY-STAGE CANCERS WITH MULTICANCER EARLY-DETECTION SCREENING

The observed cancer-detection rate in the first screening round was higher in the intervention group than in the control group (cancer detection rate ratio, 1.21; 95% CI, 1.11 to 1.31) (Table S12). In the third screening round, the percentage of routinely staged cancers that were at stage I or II was 62.8% in the intervention group and 59.9% in the control group (Table S13). In a post hoc analysis of early-stage cancer diagnoses among the 12 prespecified types after three screening

Table 1. Demographic and Clinical Characteristics of the Participants at Baseline.*

Characteristic	Intervention (N=71,122)	Control (N=71,128)	Total (N=142,250)
Median age (IQR) — yr	66 (59–71)	66 (59–71)	66 (59–71)
Age group — no. (%)†			
50–59 years	18,791 (26.4)	18,889 (26.6)	37,680 (26.5)
60–69 years	28,596 (40.2)	28,792 (40.5)	57,388 (40.3)
70–79 years	23,734 (33.4)	23,447 (33.0)	47,181 (33.2)
Sex — no. (%)			
Female	35,723 (50.2)	35,739 (50.2)	71,462 (50.2)
Male	35,399 (49.8)	35,389 (49.8)	70,788 (49.8)
Race or ethnic group — no. (%)‡			
Asian or Asian British	2,360 (3.3)	2,365 (3.3)	4,725 (3.3)
Black, Black British, Caribbean, or African	1,016 (1.4)	1,038 (1.5)	2,054 (1.4)
White	66,552 (93.6)	66,566 (93.6)	133,118 (93.6)
Mixed	776 (1.1)	768 (1.1)	1,544 (1.1)
Other	318 (0.4)	309 (0.4)	627 (0.4)
Data missing	100 (0.1)	82 (0.1)	182 (0.1)
IMD quintile — no. (%)§			
1	16,071 (22.6)	16,062 (22.6)	32,133 (22.6)
2	13,942 (19.6)	13,980 (19.7)	27,922 (19.6)
3	15,034 (21.1)	14,956 (21.0)	29,990 (21.1)
4	14,372 (20.2)	14,476 (20.4)	28,848 (20.3)
5	11,469 (16.1)	11,414 (16.0)	22,883 (16.1)
Data missing	234 (0.3)	240 (0.3)	474 (0.3)
Previous history of cancer — no. (%)	5,328 (7.5)	5,355 (7.5)	10,683 (7.5)
Median time since previous cancer diagnosis (IQR) — yr¶	10.2 (6.7–15.0)	10.2 (6.7–14.8)	10.2 (6.7–14.9)
Participant-reported screening participation — no./total no. (%)			
Never heard of cancer screening	2,056/71,019 (2.9)	2,108/71,039 (3.0)	4,164/142,058 (2.9)
Heard of cancer screening but never been invited	13,955/71,019 (19.6)	13,871/71,039 (19.5)	27,826/142,058 (19.6)
Invited for cancer screening but never done it	861/71,019 (1.2)	883/71,039 (1.2)	1,744/142,058 (1.2)
Invited for cancer screening, but did not participate every time	2,428/71,019 (3.4)	2,361/71,039 (3.3)	4,789/142,058 (3.4)
Invited for cancer screening and participated every time	51,013/71,019 (71.8)	51,150/71,039 (72.0)	102,163/142,058 (71.9)
Don't know	655/71,019 (0.9)	608/71,039 (0.9)	1,263/142,058 (0.9)
Decline to answer	51/71,019 (0.1)	58/71,039 (0.1)	109/142,058 (0.1)
Data missing	103/71,019 (0.1)	89/71,039 (0.1)	192/142,058 (0.1)
Smoking history — no. (%)			
Current smoker	4,744 (6.7)	4,708 (6.6)	9,452 (6.6)
Former smoker	27,272 (38.3)	27,148 (38.2)	54,420 (38.3)
Never smoked	39,004 (54.8)	39,187 (55.1)	78,191 (55.0)
Data missing	102 (0.1)	85 (0.1)	187 (0.1)

Table 1. (Continued.)

Characteristic	Intervention (N = 71,122)	Control (N = 71,128)	Total (N = 142,250)
BMI — no. (%)			
<25	23,058 (32.4)	23,203 (32.6)	46,261 (32.5)
25 to <30	28,009 (39.4)	27,925 (39.3)	55,934 (39.3)
≥30	19,739 (27.8)	19,706 (27.7)	39,445 (27.7)
Data missing	316 (0.4)	294 (0.4)	610 (0.4)
History of selected medical diagnoses — no. (%)			
Barrett's esophagus	811 (1.1)	810 (1.1)	1,621 (1.1)
Chronic bowel disease	1,660 (2.3)	1,632 (2.3)	3,292 (2.3)
Chronic liver disease	1,167 (1.6)	1,056 (1.5)	2,223 (1.6)
Diabetes	7,091 (10.0)	7,129 (10.0)	14,220 (10.0)
Chronic pancreas disease	304 (0.4)	298 (0.4)	602 (0.4)
Systemic lupus erythematosus	129 (0.2)	140 (0.2)	269 (0.2)
Education level — no. (%)			
School up to 15 years of age	12,672 (17.8)	12,887 (18.1)	25,559 (18.0)
Completion of secondary education, e.g., CSEs, O-levels, or equivalent**	19,262 (27.1)	19,260 (27.1)	38,522 (27.1)
A-levels or equivalent††	6,517 (9.2)	6,509 (9.2)	13,026 (9.2)
Further education without a degree	14,776 (20.8)	14,570 (20.5)	29,346 (20.6)
Bachelor's degree or equivalent	11,953 (16.8)	11,970 (16.8)	23,923 (16.8)
Further degree, e.g., Masters or Ph.D.	5,842 (8.2)	5,850 (8.2)	11,692 (8.2)
Data missing	100 (0.1)	82 (0.1)	182 (0.1)

* Percentages may not total 100% because of rounding. IQR denotes interquartile range.

† Participants had to be 50 to 77 years of age at invitation; however, they could be 78 years of age by enrollment. One participant in the intervention group was younger than 50 years of age.

‡ Race and ethnic group were reported by the participant. "Mixed" includes White and Black Caribbean, White and Black African, White and Asian, and any other mixed or multiple racial or ethnic background. "Other" includes Arab and any other ethnic background not listed.

§ The index of multiple deprivation (IMD) is an area-based measure of relative deprivation ranging from 1 (most deprived) to 5 (least deprived).

¶ If a participant had multiple previous cancers, the number of years from the most recent previous cancer to the randomization date was used.

|| The body-mass index is the weight in kilograms divided by the square of the height in meters.

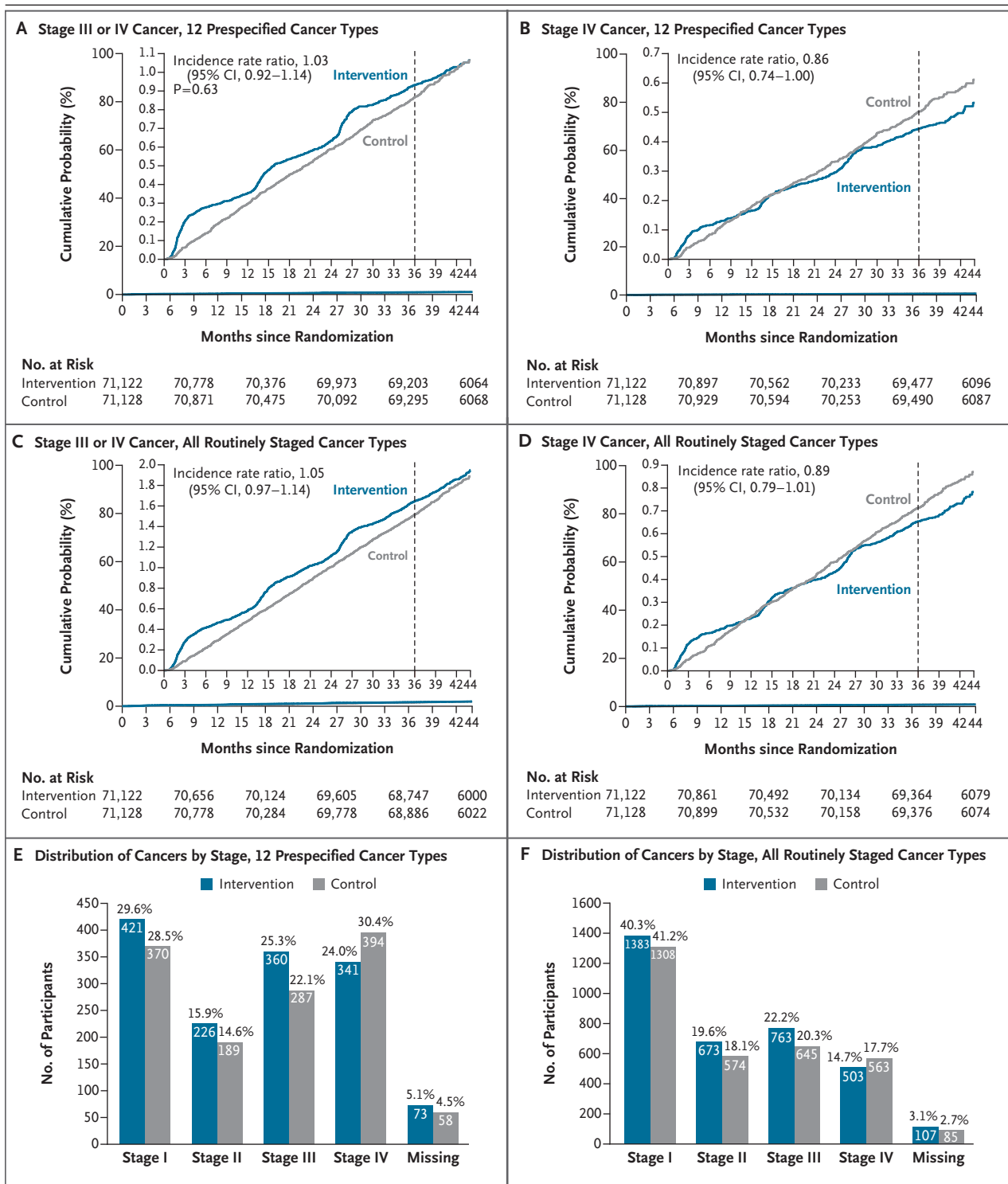
** CSEs (Certificates of Secondary Education) and O-levels (Ordinary Levels) are the predecessor examinations of the General Certificate of Secondary Education that is currently used in the United Kingdom.

†† A-levels (Advanced Levels) are the qualifications conferred as part of the General Certificate of Education to students completing secondary, pre-university education in the United Kingdom.

rounds, 647 stage I or II cancers were reported in the intervention group and 559 in the control group (relative risk, 1.16; 95% CI, 1.03 to 1.30), and stage I, II, or III cancers were reported in 1007 and 846, respectively (relative risk, 1.19; 95% CI, 1.09 to 1.30) (Table S14). Similar results were observed for participants with all routinely staged cancer types, including or not including prostate cancer (Table S14).

ROUTE TO CANCER DIAGNOSIS

The "route to diagnosis" (the categorization of the sequence of events and health care interactions that led to the diagnosis) was recorded by the cancer registry. After three screening rounds, the number of diagnoses after an urgent cancer referral (the referral route used for positive multi-cancer early-detection test results)¹⁴ was 18.9% higher in the intervention group than in the



control group (1775 vs. 1493), and the number of diagnoses after an emergency presentation was 21.3% lower (225 vs. 286) (Table S5).

In the intervention group, cancer was detected

by screening in 1173 of 3637 participants (32.3%) — 937 (25.8%) after a positive multicancer early-detection test result and 236 (6.5%) through NHS screening programs (Fig. 3). In the control group,

Figure 2 (facing page). Cumulative Probability of Stage III or IV Cancers and Stage IV Cancers According to Trial Group after Three Annual Screening Rounds.

Cumulative probability based on Kaplan–Meier estimates is shown for the risk of diagnosis of stage III or IV cancer among the 12 prespecified cancer types (Panel A), of stage IV among the 12 prespecified cancer types (Panel B); of stage III or IV among all routinely staged cancer types (Panel C), and of stage IV among all routinely staged cancer types (Panel D); these cumulative-probability displays were generated post hoc, whereas the corresponding incidence-rate analyses of these end points were prespecified. The inset in each panel shows the same data on an expanded y axis. Distribution of cancers according to stage and trial group are shown for the 12 prespecified cancer types (Panel E) (post hoc analysis) and for all routinely staged cancer types (Panel F). There were two participants with stage 0 cancer in each of the intervention and control groups; all these were Paget's disease, which is invasive at stage 0. Participant-level counts in Panels E and F were determined by assigning one cancer type and stage per participant on the basis of the cancer at the highest stage and, if tied, the earliest diagnosis; counts may therefore differ from those shown in Table 2, which shows the counts determined by the first qualifying cancer event. The 12 prespecified cancer types were lung, head and neck, colon or rectum, pancreas, myeloma or plasma cell neoplasm, liver or bile duct, stomach, esophagus, anus, lymphoma, ovary, and bladder.

cancer was detected through NHS screening programs in 290 of 3400 participants (8.5%). Thus, adding multicancer early-detection to standard-of-care screening was associated with an apparent increase in screening-detected cancers (1173 vs. 290) and in screening program sensitivity (32.3% vs. 8.5%) (Table S15).

There were 20.8% fewer clinically detected cancers (i.e., cancers detected neither by screening nor by multicancer early-detection testing) in the intervention group than in the control group — 2464 of 3637 participants (67.7%) in the intervention group as compared with 3110 of 3400 participants (91.5%) in the control group (Fig. 3). Similar results were observed across all three screening rounds (Fig. S4).

SAFETY

Across three screening rounds, 371 participants (0.52%) in the intervention group and 321 participants (0.45%) in the control group had adverse events that were trial related, device related, or both; none were serious (Tables S16 and S17). The excess was associated primarily with

anxiety after receipt of a positive multicancer early-detection test result. Among the participants in the intervention group, 337 (0.47%) had trial-related adverse events, 27 (0.04%) had device-related adverse events, and 11 (0.02%) had trial- and device-related adverse events (Table S16). Among the participants in the control group, 321 (0.45%) had trial-related adverse events. The most common trial-related adverse events were vessel bruises at the puncture site, syncope, dizziness, vessel hematomas at the puncture site, and anxiety. Participants reported high adherence to standard-of-care cancer screenings (Table S18).

DISCUSSION

NHS-Galleri is a randomized, controlled trial that evaluated the clinical utility of a multicancer early-detection test for population screening. After three annual multicancer early-detection screening rounds with 12 months of follow-up after the last participant's third visit, we did not observe a lower incidence rate in the intervention group than in the control group of stage III or IV cancers among the 12 prespecified cancer types (the primary end point). Although the prespecified hierarchical plan to adjust for multiple testing precluded any formal testing of secondary end points, the results suggested the possibility that the intervention was associated with fewer stage IV cancer diagnoses in the second and third screening rounds, in which observed trends would be expected to reflect those of a stable screening program with a routinely screened population. Stage IV cancer reduction is clinically important since stage IV disease confers worse survival than earlier-stage disease.¹

The observed lower incidence rate of stage IV cancer diagnosis was offset by a higher rate of stage III cancer diagnosis, which resulted in no overall difference between the intervention and control groups in stage III or IV cancers combined. Stage III cancers detected in the first screening round (also called the prevalent screening round) might be the major reason that the difference between the groups for the 12 prespecified types (primary end point) was not significant; the higher number in the intervention group may potentially reflect several non-mutually exclusive mechanisms, including earlier detection of cancers that might otherwise have manifested at stage IV and longer-than-anticipated lead-time effects. Addi-

Table 2. Stage III or IV and Stage IV Cancer Outcomes after Three Annual Screening Rounds.*

Outcome	12 Prespecified Cancers†		All Routinely Staged Cancers Except Prostate Cancer		All Routinely Staged Cancers	
	Intervention (N = 71,122)	Control (N = 71,128)	Intervention (N = 71,122)	Control (N = 71,128)	Intervention (N = 71,122)	Control (N = 71,128)
Stage III or IV Cancer						
No. of participants (%)	706 (1.0)	688 (1.0)	903 (1.3)	848 (1.2)	1266 (1.8)	1208 (1.7)
Person-years of follow-up	234,959	235,249	234,667	235,044	234,062	234,495
Incidence rate per 100,000 person-years (95% CI)	300.5 (278.7–323.5)	292.5 (271.0–315.1)	384.8 (360.1–410.7)	360.8 (336.9–385.9)	540.9 (511.5–571.5)	515.1 (486.5–545.0)
Incidence rate difference (95% CI)	8.0 (–23.1 to 39.2)		24.0 (–10.9 to 59.0)		25.7 (–15.9 to 67.4)	
Incidence rate ratio (95% CI)	1.03 (0.92–1.14)‡		1.07 (0.97–1.17)		1.05 (0.97–1.14)	
Stage IV Cancer						
No. of participants (%)	342 (0.5)	397 (0.6)	412 (0.6)	467 (0.7)	503 (0.7)	563 (0.8)
Person-years of follow-up	235,584	235,662	235,501	235,585	235,347	235,434
Incidence rate per 100,000 person-years (95% CI)	145.2 (130.2–161.4)	168.5 (152.3–185.9)	174.9 (158.5–192.7)	198.2 (180.7–217.1)	213.7 (195.5–233.2)	239.1 (219.8–259.7)
Incidence rate difference (95% CI)	–23.3 (–46.0 to –0.7)		–23.3 (–48.0 to 1.4)		–25.4 (–52.6 to 1.8)	
Incidence rate ratio (95% CI)	0.86 (0.74–1.00)		0.88 (0.77–1.01)		0.89 (0.79–1.01)	

* The primary end point was stage III or IV cancer after three screening rounds and at least 12 months of follow-up after the last participant's third visit. Person-years of follow-up were measured from randomization to the first qualifying stage III or IV cancer diagnosis, death, withdrawal of consent for passive follow-up, emigration, or the end of the follow-up period. Incidence rates were calculated as the number of first qualifying events divided by person-years at risk, with 95% confidence intervals for incidence rates calculated assuming a Poisson distribution. Counts may differ from descriptive analyses tables in which a single cancer or stage was assigned as the highest stage and earliest diagnosis if tied.

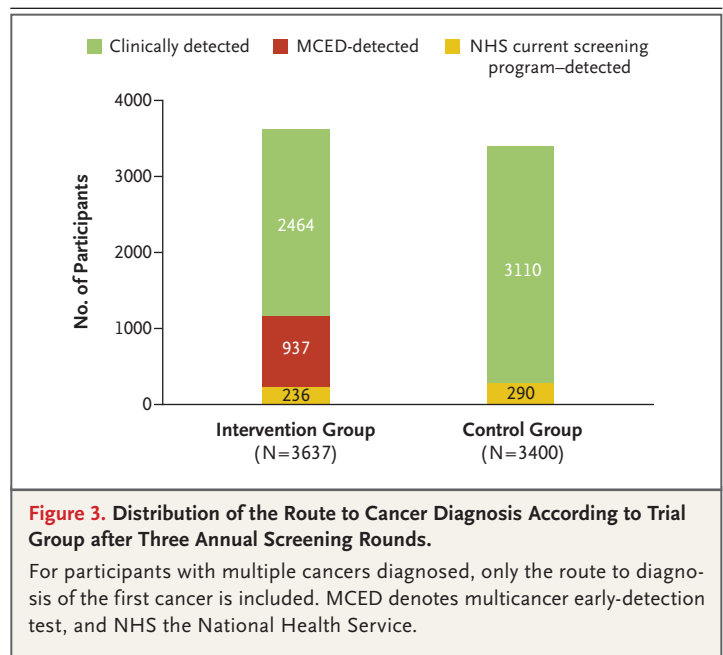
† The 12 prespecified cancers were lung, head and neck, colon or rectum, pancreas, myeloma or plasma cell neoplasm, liver or bile duct, stomach, esophagus, anus, lymphoma, ovary, and bladder.

‡ P = 0.63.

tional follow-up will provide more evidence about the effect of the intervention on the incidence of stage III or IV cancer over the long term. It is possible that the full clinical utility of multicancer early-detection screening will emerge over time, after depletion of the prevalent pool (i.e., undiagnosed cancers for which participants may never have been screened previously),¹⁷ a hypothesis consistent with published screening studies.¹⁸⁻²¹ Longer follow-up is needed to determine whether the excess of stage III cancers is transient and the observed stage distribution translates into lower cancer-specific mortality.

Late-stage cancer was chosen as the primary end point because it is clinically relevant and can be assessed earlier than cancer-specific mortality, although its value as a surrogate may vary by cancer type and screening context.²²⁻²⁴ A favorable result requires a lower late-stage cancer incidence rate, not merely more early-stage diagnoses and thus a lower proportion of late-stage cancers, which could reflect overdiagnosis without reducing advanced disease. At trial design, microsimulation enabled sample-size planning despite limited evidence on the duration of preclinical cancer and tumor-derived cfDNA detectability. These simplified assumptions projected a larger and quicker stage shift than observed. Subsequent model development has considered broader ranges in sojourn-time (i.e., the duration of the entire preclinical screening-detectable phase) and lower screening sensitivity.^{25,26} Further analyses incorporating trial data should better characterize these variables and inform the design of future studies. Data on cancer-specific and nested mortality analyzed at 3 and 6 years after final trial visit as secondary end points were not reported here; the trial was not powered for mortality end points.

The intervention group had more cancers diagnosed at earlier stages than the control group. The current analysis cannot distinguish between more cancers being diagnosed in the intervention group before the equivalent cancers were diagnosed in the control group and overdiagnosis. Given that circulating tumor-derived cfDNA shedding is a hallmark of more aggressive cancers, it is biologically unlikely that these excess cancers are indolent. Recent evidence suggests that cancers detected by multicancer early-detection tests based on circulating tumor-derived cfDNA are unlikely to be overdiagnosed, because



survival outcomes in case-control studies involving participants with positive multicancer early-detection results were consistent with population averages, even for cancers diagnosed in early stages.²⁷ Rather, the excess stage I or II cancers diagnosed in the intervention group were probably due to earlier detection of clinically significant disease. Longer follow-up would help address these questions. Future analysis to assess overdiagnosis is specified in the trial protocol.

The addition of multicancer early-detection testing increased the number of screening-detected cancers and decreased the number of clinically detected cancers. Diagnoses from emergency presentations were 21.3% lower in the intervention group than in the control group; such diagnoses are associated with poorer survival, even for the same cancer type and stage.^{2,28}

The performance characteristics of the multicancer early-detection test are the subject of another article.²⁹ In brief, positive multicancer early-detection tests were obtained in 722 participants (1.03%) in the first round, 518 (0.80%) in the second round, and 561 (0.90%) in the third round. Of the 1801 participants who had a positive multicancer early-detection test, 937 (52%) received a cancer diagnosis; of these, 815 (87.0%) had cancer that was located in the first-ranked site of origin predicted by the positive multicancer early-detection test.

The NHS-Galleri trial was a randomized, controlled trial designed to evaluate a multicancer early-detection test at a population level in order to provide robust evidence on the implementation of this approach in routine screening settings. The findings from this trial are consistent with those from the prospective PATHFINDER 2 study.⁹ The fact that these two independent prospective datasets show reproducibility across different health care settings (United Kingdom and United States) supports the feasibility of implementing this multicancer early-detection screening at scale. Future analyses of health economics and outcomes research end points that provide further insights are warranted.

The strengths of our trial include the randomized, double-blind design, ascertainment of outcome data from a quality-assured national cancer registry, socioeconomically diverse target population, high retention throughout the trial, and the use of existing standardized diagnostic pathways within the NHS,¹⁴ which ensured that clinical management was as close to usual care as possible. These features reduced bias and supported generalizability of the trial results.

Our trial had several limitations. The follow-up period was relatively short for a screening trial, and cancer incidence between the two groups has not yet converged, which suggests that the full effects of the multicancer early-detection intervention may not yet be mature. Continued follow-up is needed to assess how these effects evolve; for example, it is plausible that the excess of stage III cancers in the intervention group reflects earlier diagnosis of cancers that remain asymptomatic in the control group and may later manifest at stage III or IV. The combined stage III or IV primary end point may not capture all potentially clinically meaningful effects of screening, such as a shift from stage IV to stage III, diagnosis at an earlier substage within the same stage, and diagnosis before symptom onset. These findings suggest that future screening trials should carefully consider the primary and secondary end points, including the duration of follow-up after the last screening round. In addition, traditional stage categories should be complemented by end points that capture clinically meaningful effects within and beyond stage, such as the circulating tumor-derived cfDNA fraction. The trial was not powered to evaluate a reduction in cancer mortality. The trial was not

designed to assess different multicancer early-detection screening intervals or the likelihood of participation in a routine multicancer early-detection screening program. Negative multicancer early-detection test results were not reported to the participant (those participants remained unaware of their trial-group assignment) and individual medical records were unavailable, which limited assessment of effects on screening behavior and diagnostic workup. The trial was not powered to assess the clinical utility of multicancer early-detection screening within demographic subgroups or for individual cancer types. Adverse events in the trial were systematically collected until the participant was referred to the NHS system for diagnostic workup; thereafter, adverse events were captured only if they were reported directly by the participant or a clinician. As a result, this trial does not fully characterize the safety profile during diagnostic evaluation after a positive multicancer early-detection test result. This limitation is addressed with the PATHFINDER 2 study.⁹

In this large, randomized, controlled trial, annual multicancer early-detection testing added to usual care was not associated with a significantly lower incidence rate of stage III or IV cancer across 12 prespecified types after three screening rounds and at least 12 months of follow-up. Further follow-up is warranted to assess the way findings for stage III or IV cancers and the observed difference in stage IV cancers translate to clinical benefit over time.

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