Supplemental Online Content

Atlas SJ, Tosteson ANA, Wright A, et al. A multilevel primary care intervention to improve follow-up of overdue abnormal cancer screening tests: a cluster randomized clinical trial. *JAMA*. Published October 10, 2023. doi:10.1001/jama.2023.18755

This supplemental material has been provided by the authors to give readers additional information about their work.

eMethods

Overview:

Details of the design, methods and analytic plan for the study have previously been described in a protocol manuscript.[1] The protocol manuscript provides a broad overview of the study and includes: Table 1: describing the clinically recommended follow-up intervals and eligibility windows for each organ (breast, cervical, colorectal, lung) based on screening abnormality (high-, med-, and low-risk), and Table 2: providing of summary of informatics implementations at the two sites (Mass General Brigham [MBG] and Dartmouth Health [DH]). Within MGB, two primary care networks affiliated with Massachusetts General Hospital (MGH) and Brigham and Women's Hospital (BWH) participated. This document is intended to provide additional information not included in this previous manuscript.

Study Design and Randomization:

To achieve balance in the cluster randomization of this pragmatic, primary care practice-based intervention across the four intervention groups, size of the practice, patient gender, and insurance status (receipt of Medicaid insurance) were collected. Since the sizes of the practices/clusters varied widely, as well as the other characteristics, the randomization was carried out within match group, as described below. Randomization was done separately for DH and MGB sites. Though not included in the randomization scheme, information was collected on the type of practice. This information is depicted in the following table stratified by intervention group.

	Combined MGB/DH Clinic Characteristics by Arm					
		All	**EHR+Outreach +Navigation (Arm 4)**	**EHR+Outreach (Arm 3)**	**EHR Reminder (Arm 2)**	**Usual Care (Arm 1)**
Patient Volume	**N**	463,905	122,219	108,155	121,887	111,644
Female	**N**	281,009	79,224	*60,175*	72,555	69,055
	%	60.6%	64.8%	*55.6%*	59.5%	61.9%
Medicaid	**N**	67,701	19,116	14,425	18,314	15,846
	%	14.6%	15.6%	13.3%	15.0%	14.2%
Type of Clinic						
Community based	**N**	23	5	6	4	8
	%	52.3%	45.4%	54.5%	36.4%	72.7%
Health center	**N**	6	1	2	1	2
	%	13.6%	9.1%	18.2%	9.1%	18.2%
Hospital based	**N**	6	2	2	2	0
	%	13.6%	18.2%	18.2%	18.2%	0.0%
Multi-specialty clinic	**N**	9	3	1	4	1
	%	20.5%	27.3%	9.1%	36.4%	9.1%

For each site, the number of practices was fortunately divisible by 4 and the randomization process was identical. First, each of the four practice characteristics was dichotomized at the median and each practice fell into 1 of the 8 strata that resulted (strata 1: Low volume; Low female percentage; Low Medicaid percentage; strata 2: low volume, low female percentage, high Medicaid percentage; strata 3: low volume, high female percentage, low Medicaid percentage; strata 4: low volume, high female percentage, high Medicaid percentage; strata 5: high volume, low female percentage, low Medicaid percentage; strata 6: high volume, low female percentage, high Medicaid percentage; strata 7: high volume high female percentage, low Medicaid percentage; strata 8: high volume, high female

percentage, high Medicaid percentage). From each stratum, 4 practices were chosen at random and formed a “stratified match group”. If less than 4 practices remained in a stratum, additional practices were chosen from the most similar stratum until 4 practices could be grouped together. Once all groups of 4 practices (i.e., all stratified match groups) were formed, random numbers generated in the SAS package by the study statistician (EJO) were used to assign a practice to an intervention arm. In this way each stratified matched group had one practice randomly assigned to each intervention arm. While this process yielded a valid randomization (i.e., each practice had a 25% of being assigned to any of the 4 arms), we were concerned about the coarseness of the strata and the arbitrariness of choosing practices to group together when 4 were not naturally available. Therefore, we developed a second process which used the exact patient volumes, percentages of female, and percentages of Medicaid patients to calculate the Mahalanobis distance of an index practice to each of the other practices. The index practice and the 3 practices with the smallest Mahalnobis distances formed a “Mahalanobis match group”. This was then repeated choosing a new index practice from the remaining unchosen practices, until all practices had been assigned to Mahalanobis match groups. The match groups formed using this process were remarkably similar, but not identical, to those using the dichotomized strata. As with the stratified match groups, each of the 4 practices within a Mahalanobis match group was randomly assigned to an intervention arm. Finally, to decide which set of match groups would yield a better balance of practice characteristics between the arms, we set aside the actual randomizations and simulated assigning randomization codes 100 times. We then looked at the variability in practice characteristics across the 4 arms and, for all characteristics, found greater balance with the stratified match groups. These stratified match groups are therefore the basis for the randomization of practices in the current study.

During the study enrollment period, two MGH practices (in intervention groups 1 and 3) closed and their patients and physicians moved to other locations within the network. For purposes of the research study, data systems that assigned patients to a specific practice location remained unchanged; patients from those practices were assigned to the original intervention arms. Since outreach activities were performed centrally by study staff, practice-level randomization remained unchanged.

Since this trial randomized practices rather than patients, the analysis accounted for the clustering/correlation within practices by including random effects for both practices and physicians within the mixed regression models. For the primary 120-day completion outcome, an intraclass correlation coefficient of 0.0060 was found for practices and 0.0080 for physicians.

Patient Eligibility:

Patients were eligible for the study as described in the methods section. Since one of the goals of the study was to identify patients with abnormal, overdue cancer screening test results using electronic systems, exclusion criteria from the primary, intention to treat population were based upon data obtained through the electronic health record (EHR) as detailed in the following table:

System-based Eligibility	Definition
Age	Based on the abnormal cancer organ type
Gender	Based on the abnormal cancer organ type
Language	Preferred language listed as English or Spanish
Prior cancer diagnosis	Problem list diagnosis prior to the abnormal screening test for the cancer organ type
Ulcerative colitis/Crohn's	Problem list diagnosis prior to the abnormal screening test
Not completed recommended follow-up during the specified time interval	No follow-up test was performed after the date of the abnormal screening test and before the follow-up time frame based on the cancer organ type and the severity of the abnormality
Insufficient information available to assess eligibility (MGB only)	A natural language processing (NLP)-based system was used to automatically classify an abnormal finding. The system was designed to flag patients with an unknown status when it did not have all the information that could be used to classify an abnormal finding. Study staff would be notified and would perform a review of the electronic health record to identify the missing data. Study staff would then assess eligibility and manually enter or exclude the patient from the study data base

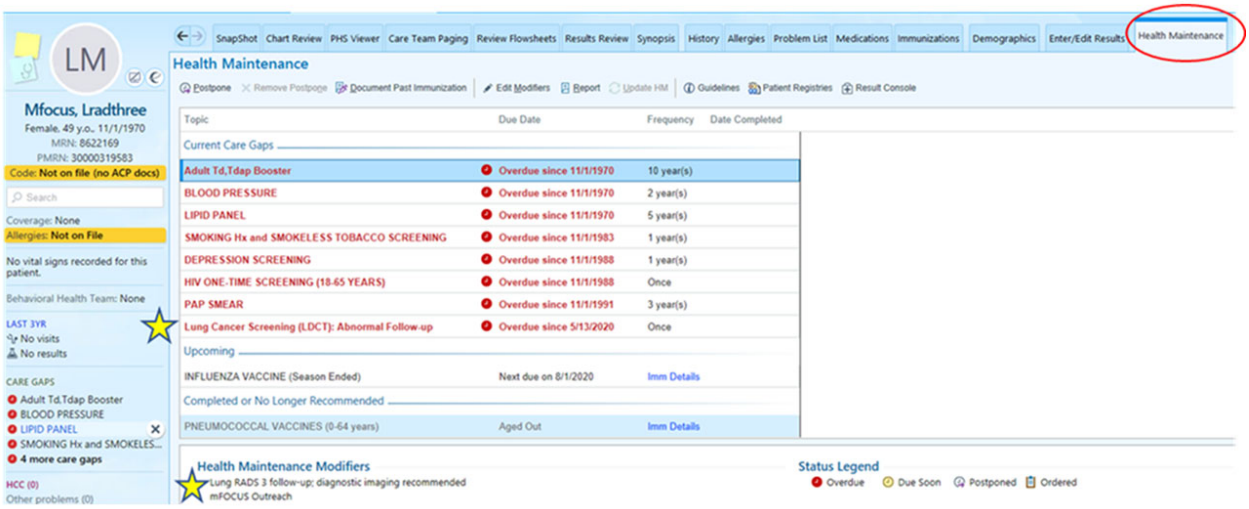
Definition of Abnormal Screening Results, Timing of Evaluation, Recommended Follow-up:

Definitions of the specific screening abnormalities and timing of diagnostic evaluation are based on guideline recommendations and expert opinion. The need for follow-up was determined by the lack of an appropriate clinical test or procedure within the specified time as documented in the EHR. **eTable 1** describes the test results, follow-up period, appropriate diagnostic follow-up, and estimated follow-up rates pre-trial for each cancer type.

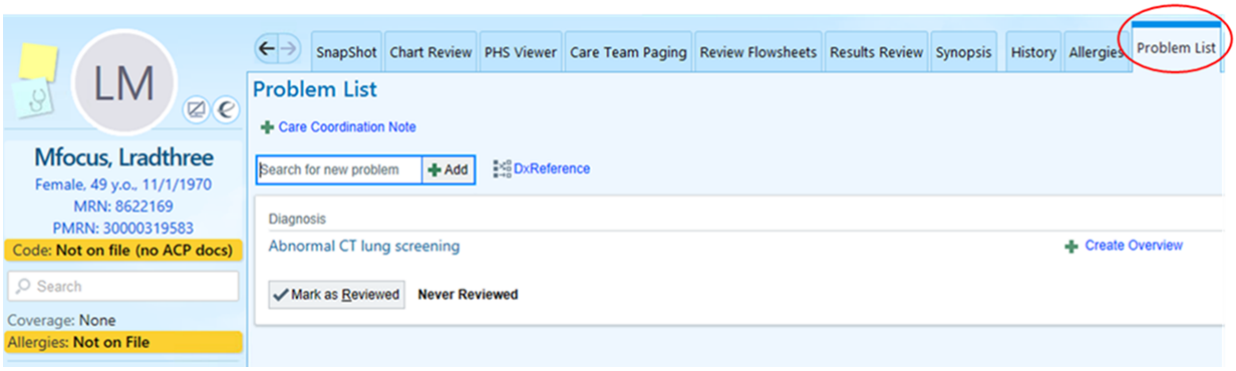
System Design:

DH and MGB both use the same EHR vendor (Epic Systems Corp, Verona, WI), but they are on separate Epic instances. Significant differences in EHR configuration led to variable implementation of the IT tools in this study at DH and MGB.

At DH, the identification and tracking of patients were performed within the EHR itself. Required data elements for eligibility determination (ie HPV results, mammogram dates) existed in the EHR database as defined values. Each night, patient registry functionality automatically queried the real-time database in order to identify patients potentially eligible for the study. The EHR then placed the appropriate health maintenance (HM) topic on patient charts based on the registry lists if the necessary follow-up test was not completed in a specified period (**see Figure below**). Study coordinators and patient navigators used a workbench report to see the registry list of eligible or enrolled patients. They used note templates with defined fields to manage the outcomes of coordination and navigation activities. If an enrolled patient received a completion test, the EHR updated the reports automatically. A separate daily report stored data about eligible and enrolled patients to a file that was encrypted and securely transferred to the mFOCUS research database, nicknamed DH SideCar. Encryption of data and transfer of data were completed manually throughout the study.



At MGB, data was extracted from the EHR into the mFOCUS research database server. Primary care patients with abnormal breast, cervical or lung cancer screening test results were identified using a natural language processing (NLP)-based system, which processed free-text procedure and pathology reports, extracted specific test results, and then classified abnormal results.[2] Colorectal cancer screening test results, as identified through the HM modifiers applied to the patient's chart, passed through an initial rule-based algorithm to identify qualifying results; subsequent review of the associated procedure and pathology report was used to verify eligibility. Based on the cancer type and specific abnormal result, a recommended follow-up test or procedure and time interval were established. Patients who did not complete the recommended follow-up in the specified time were enrolled into the study. The patient's EHR was subsequently updated with an addition to the problem list specifying the abnormal result (**see Figure below**); additionally, a HM reminder that included the abnormality and follow-up recommendation were added to the chart. Daily queries of the EHR were performed to identify new patients with abnormal results and to track the follow-up of patients who were already being followed in the mFOCUS research database.



In contrast to DH, the MGB system does not include structured data for cancer screening test results. This required use of the aforementioned NLP tool to identify new breast, cervical or lung cancer test results; however, this was performed contemporaneously relative to the date the test was performed, and thus identified patients with an abnormal result who did not yet meet the criterion of being "overdue" for follow-up. These patients entered and were tracked in the mFOCUS database but were labeled as "pending". If a "pending" patient received the recommended follow-up before their overdue

(eligible) date, they would be considered ineligible for the study. If a “pending” patient did not receive their follow-up before their designated eligibility date, they would be enrolled in the study.

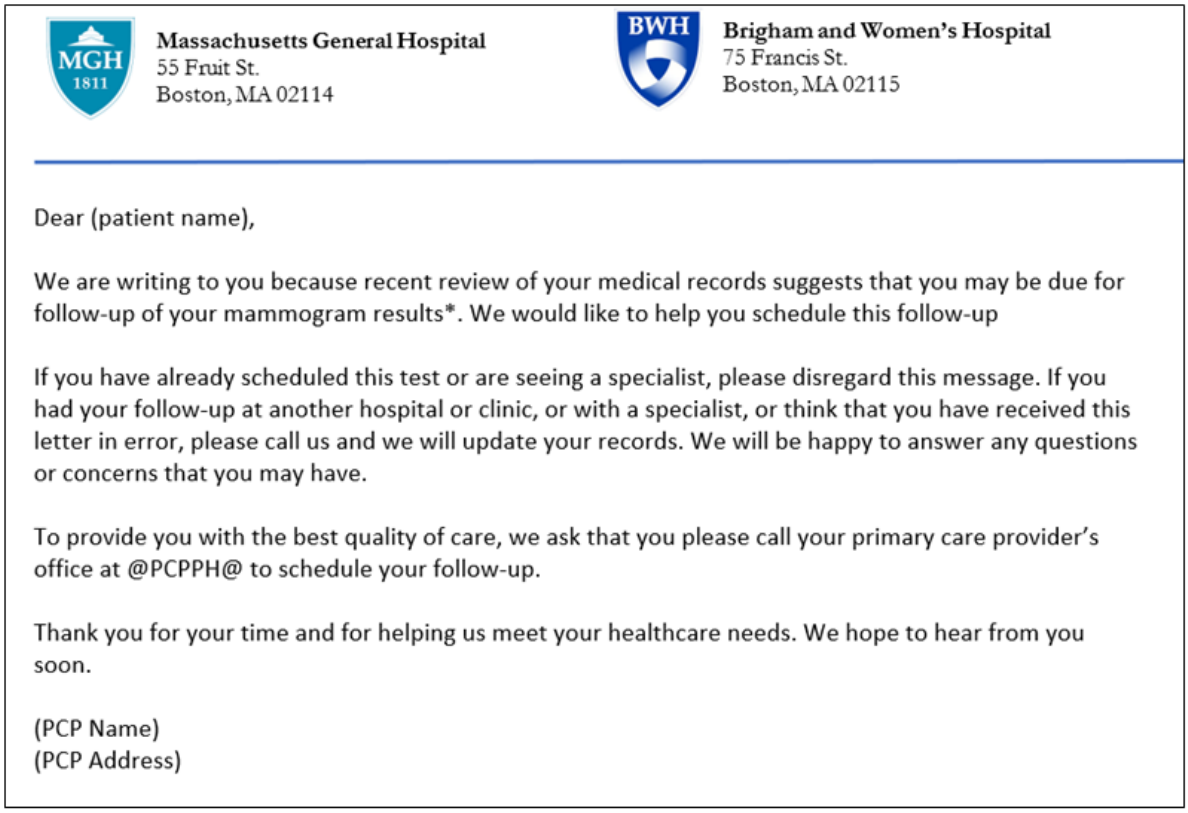
The mFOCUS research database, nicknamed SideCar, was built by study programmers at DH and MGB. Study teams at DH and MGB maintained two, independent instances of SideCar so that identified data were not shared. SideCar was a web-based application with a secure sign-on for only users assigned by the programmers. SideCar was populated with patient study information from secure, encrypted file transfer protocols from MGB or DH EHR database. Since patients could have more than one abnormal cancer screening test result over the study period, a primary flag was applied to all patients upon their first entry into mFOCUS. The flag was applied to the first eligible test for each patient. Patients with a primary flag were included in our analysis. If patients had multiple abnormal cancer screening test results that met study eligibility, only the first abnormality was included in analyses. However, all abnormal results were managed per the patient’s assigned intervention group.

Enrollment and Study Protocols:

Since the interventions were intended to function as a “fail-safe” system to supplement rather than replace usual care, a patient’s enrollment date included additional time, or “lead time,” beyond the due date for the abnormal result to allow for completion of recommended follow-up before a patient became eligible and was enrolled**. eFigure 1** depicts the flow of patients in the study.

Usual care: Given the heterogeneity within and among the participating health care systems, the study performed qualitative interviews with network and practice leaders as well as specialists to describe usual care. Since the study was designed as a “fail safe” system to take over after usual care did not result in the patient completing the recommended follow-up in a timely manner, all patients in each of the arms received usual care for their abnormal result. Our interviews revealed that systematic efforts to promote follow-up in the primary care practices were rare. All patients who received care in the participating practices have the option of having a patient portal to view their results as well as any outreach by their care team. Outreach and follow-up were at the discretion of the PCP. One primary care practice had a centralized system to track and follow-up abnormal cervical screening results. In the specialty care practices, there were system level efforts that varied according to the cancer type. The best described system is for follow-up of abnormal mammogram results, largely because of the requirements of the Mammography Quality Standards Act (MQSA).[6] Phone outreach occurred for BIRADS 4 and 5 results. Patients with BIRADS 3 results were contacted by mail to schedule a repeat exam. Similar outreach was in place for abnormal low dose chest CT results. For abnormal colorectal cancer screening results, patients typically received an initial mailed letter recommending follow-up. Finally, for cervical cancer, there was no systematic outreach effort other than an initial letter or phone call from the performing provider or PCP after the test result was received. The only exception was if the patient had the test performed in a high-risk clinic, there were systematic efforts to reach out to patients for high-risk abnormal results. **eTable 2** provides a high level summary of the range of practices that comprise usual care in the participating networks:

Intervention: The intervention was multilevel and had stepped care based on not completing recommended follow-up in the specified time period. Specifically, arms 2 (EHR Reminder), 3 (EHR Reminder+Outreach), and 4 (EHR Reminder+Outreach+Navigation) all received the same electronic health record reminders at the time of trial entry. For arms 3 and 4, in addition to the electronic health record reminders, patients also received a mailed or portal letter at trial entry (**see Figure below**).



Massachusetts General Hospital
55 Fruit St.
Boston, MA 02114

Brigham and Women's Hospital
75 Francis St.
Boston, MA 02115

Dear (patient name),

We are writing to you because recent review of your medical records suggests that you may be due for follow-up of your mammogram results*. We would like to help you schedule this follow-up

If you have already scheduled this test or are seeing a specialist, please disregard this message. If you had your follow-up at another hospital or clinic, or with a specialist, or think that you have received this letter in error, please call us and we will update your records. We will be happy to answer any questions or concerns that you may have.

To provide you with the best quality of care, we ask that you please call your primary care provider's office at @PCPPH@ to schedule your follow-up.

Thank you for your time and for helping us meet your healthcare needs. We hope to hear from you soon.

(PCP Name)
(PCP Address)

* customized based on organ, other variations were i.e. colonoscopy, lung CT scan screening, pap smear

At 4 weeks, if a patient in arms 3 and 4 had not completed recommended follow-up, they received a single phone call reminder from a study coordinator. For arm 4, in addition to the electronic health record reminders, mailed or portal letter and reminder phone call, patients who had not completed recommended follow-up received a phone call from the study navigator to assess for social determinants of health and to provide telephonic navigation to schedule and assist with completing the recommended follow-up by addressing any barriers identified. The following table provides details of the interventions received in the EHR Reminder+Outreach and the EHR Reminder+ Outreach+ Navigation arms. **eTable 4** summarizes the outreach activities in these intervention arms.

Initial patient enrollment occurred sequentially over time by cancer organ type beginning with breast and lung results at MGB sites in August 2020 and in November-December, 2020 at DH sites as depicted in the following table:

Table Organ	MGB launch date	DH launch date
Breast	8/24/2020	11/3/2020
Lung	8/24/2020	12/18/2020
Cervical	10/16/2020	5/10/2021
Colorectal (FIT, 1, 2, 3-year follow-up)	1/19/2021	2/10/2021
Colorectal (5-year follow-up)	4/5/2021	4/26/2021

Due to a large number of patients overdue for 5-year colonoscopy screening follow-up, this arm was rolled out in two phases. The first phase included patients with Positive FIT tests, 1-year, 2-year and 3-year follow-up. In the second phase, patients with 5-year follow-up intervals were added to the enrollment process.

Chart Review During the Study Period:

Dartmouth Hitchcock (DH):

- **Cervical:** A study team member with the supervision of a study Co-I (MD) performed a clinical chart review of all medium and high-risk cervical patients using ASCCP Management Guidelines (web application found at https://app.asccp.org/) and searching for missing colposcopy data.

Mass General Brigham (MGB):

- **Cervical:** After the study began, patients enrolled due to an abnormal cervical cancer screening test result requiring a colposcopy were commonly misidentified as overdue, because many colposcopy procedures are performed *within* the same patient encounter and not as a subsequent encounter. Since these patients were not eligible and did not require follow-up, a manual chart review process was established to review all medium- and high-risk cervical patients from October 2020 through April 2021 when a programmatic fix to the NLP tool could be developed, tested, and implemented. From April 2021 to the end of enrollment in December 2021, only high-risk patients were reviewed to ensure eligibility for the study.

- **Colorectal:** Eligibility was based upon patients with a 1, 2, 3, or 5 year follow-up interval specific in the HM section of the EHR for colonoscopy or an abnormal stool test result. In reaching out to patients in intervention groups 3 and 4, research coordinators identified many individuals as having specified follow-up intervals that differed from the result letter or post-procedure discharge papers provided to the patient. As a result, chart review for all CRC patients were performed in intervention groups 3 and 4 prior to research coordinator or navigator outreach.

At DH and MGB, patients were identified who met study eligibility but the responsible clinician and designated an alternate care plan or potentially had recommended care that was not consistent with guideline recommendations. For patients who appeared to have received care that was not consistent with guideline recommendations, a study physician contacted the patient's PCP to notify them of the patient, their results, and recommended care. Care remained under the direction of the PCP with assistance provided at their direction for patients in intervention groups 3 and 4. Most of these involved the responsible clinician misapplying guideline recommendations (mainly for cervical findings). For patients with a stated alternate care plan that correctly recognized the nature of the abnormal result, patients were not contacted and this was noted in the study database.

Chart Review Process to Ascertain modified Intention-to-Treat Cohort:

As noted in the manuscript, the primary intention to treat population included all patients who met protocol eligibility criteria for at least one abnormal cancer screen. The eligibility criteria were based on information derived from the EHR since one of the study's objectives was to use an automated system to identify patients for inclusion and outreach. We anticipated that patients in the intention to treat population may in fact not be truly eligible because of inaccuracies in the available electronic

data or the algorithms used. As a result, a secondary as treated population was planned that would exclude those patients who were subsequently found to be ineligible after study enrollment.

We anticipated that since patients in intervention groups 3 and 4 would have clinical research coordinators (CRCs) and navigators calling patients, a manual chart review process was designed as part of their workflow prior to contacting patients to ensure that they were in fact eligible (see previous section). For this reason, a similar manual chart review process was planned for intervention groups 1 and 2 after all enrolled patients had completed 120-day follow-up.

After the end of the study enrollment period, CRCs performed a retrospective review of all colonoscopy results in arms 1 and 2 and the remaining medium-risk cervical tests that the MDs did not review in arms 1 and 2 (see table on following page). A retrospective review was not done for low-risk breast, lung, or cervical test results, or positive FIT results, in arms 1 and 2 because of the relatively low volume of results and low number of ineligible results in arms 3 and 4.

- **Dartmouth Hitchcock**: Two study team members completed clinical review of all medium to high-risk cervical patients at DH for missing colposcopies under the supervision of a second study co-I (MD). Two study team members completed chart review for all cervical and CRC patients in arms 1 and 2 after study enrollment closed. They focused on if the patient was accurately identified as eligible including if follow-up of the qualifying abnormal screen happened in the time captured by DH IT infrastructure.

- **Mass General Brigham**: Two study team members completed chart review for medium-risk cervical and all CRC patients with colonoscopies in arms 1 and 2 after study enrollment closed. The review ascertained the accuracy of the patient's "eligible" status, and accuracy of capture of any appropriate follow-up procedures occurring within the patient's eligibility window. Patients identified as having non-standard care plans were passed to study PIs for additional clinical review.

References:

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3. Tosteson AN, Beaber EF, Tiro J, et al. Variation in Screening Abnormality Rates and Follow-Up of Breast, Cervical and Colorectal Cancer Screening within the PROSPR Consortium. *J Gen Intern Med.* 2015
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5. Wiener RS, Gould MK, Slatore CG, Fincke BG, Schwartz LM, Woloshin S. Resource use and guideline concordance in evaluation of pulmonary nodules for cancer: too much and too little care. *JAMA Intern Med.* 2014;174(6):871-880
6. Destouet JM, Bassett LW, Yaffe MJ, Butler PF, Wilcox PA. The ACR's Mammography Accreditation Program: ten years of experience since MQSA. *J Am Coll Radiol*. Jul 2005;2(7):585-94. doi:10.1016/j.jacr.2004.12.005.

Chart Review Process to Ascertain Exclusions to Intention to Treat Population in Deriving As-Treated Population

BREAST	Arm 1	Arm 2	Arm 3	Arm 4
BIRADS 3	Not reviewed	Not reviewed	Prospective review	Prospective review
Reviewed by:			CRCs	CRCs
BIRADS 4/5	Prospective review	Prospective review	Prospective review	Prospective review
Reviewed by:	MDs	MDs	MDs + CRCs	MDs + CRCs

CERVICAL	Arm 1	Arm 2	Arm 3	Arm 4
High risk	Prospective review	Prospective review	Prospective review	Prospective review
Reviewed by:	MDs	MDs	MDs + CRCs	MDs + CRCs
Medium risk	Prospective/retrospective review	Prospective/retrospective review	Prospective review	Prospective review
Reviewed by:	MDs (pro) + CRCs (retro)	MDs (pro) + CRCs (retro)	MDs + CRCs	MDs + CRCs
Low risk	Not reviewed	Not reviewed	Prospective review	Prospective review
Reviewed by:			CRCs	CRCs

COLORECTAL	Arm 1	Arm 2	Arm 3	Arm 4
Colonoscopy	Retrospective review	Retrospective review	Prospective review	Prospective review
Reviewed by:	CRCs	CRCs	CRCs	CRCs
FIT	Not reviewed	Not reviewed	Prospective review	Prospective review
Reviewed by:			CRCs	CRCs

LUNG	Arm 1	Arm 2	Arm 3	Arm 4
LRADS 3	Not reviewed	Not reviewed	Prospective review	Prospective review
Reviewed by:			CRCs	CRCs
LRADS 4A / 4B / 4X / 5	Prospective review	Prospective review	Prospective review	Prospective review
Reviewed by:	MDs	MDs	MDs + CRCs	MDs + CRCs

eTable 1. Description of included test results, follow-up period, appropriate diagnostic follow-up, and estimated follow-up rates pre-trial

Screening Test – Breast	Abnormal Result	Recommended follow-up period	Enter mFOCUS Study	Lookback period [a]	Appropriate diagnostic follow-up	Estimated Follow-up Rates
Unilateral or bilateral screening mammography or DBT *If 12-month recommended follow-up, study entry at 15 months	BI-RADS 5	1 month	3 months	6 months	Biopsy (FNA, core, surgical), lumpectomy, mastectomy	87-94%[1]
	BI-RADS 4	1 month	3 months	6 months	Biopsy (FNA, core, surgical), lumpectomy, mastectomy	87-94%[1]
	BI-RADS 3*	6 months	9 months	12 months	Unilateral or bilateral mammography/ DBT, Breast US, Breast MRI	54-83%[1]
Breast Imaging-Reporting and Data System (BI-RADS). Digital breast tomosynthesis (DBT), ultrasound (US), fine needle aspiration (FNA), magnetic resonance imaging (MRI						

Screening Test – Cervical	Abnormal Result	Recommended follow-up period	Enter mFOCUS Study	Lookback period [a]	Appropriate diagnostic follow-up	Estimated Follow-up Rates
Primary HPV	Positive/ no reflex genotyping	3 months	6 months	12 months	Pap AND 16/18 genotype	50-76%[1,2]
Primary HPV	Positive/ reflex 16/18 genotyping positive	3 months	6 months	12 months	Colposcopy – with or without biopsy	
Pap +hrHPV cotesting	Pap normal/ HPV + with reflex 16/18 genotyping positive	3 months	6 months	12 months	Colposcopy – with or without biopsy	
Pap +hrHPV cotesting	ASCUS HPV +	3 months	6 months	12 months	Colposcopy – with or without biopsy	

Screening Test – Cervical	Abnormal Result	Recommended follow-up period	Enter mFOCUS Study	Lookback period [a]	Appropriate diagnostic follow-up	Estimated Follow-up Rates
Pap +hrHPV cotesting	Any higher abnormality (LSIL including HPV changes, ASC-H, HSIL)	3 months	6 months	12 months	Colposcopy – with or without biopsy	
Pap	ASCUS/ reflex HPV positive 25+ years	3 months	6 months	12 months	Colposcopy – with or without biopsy	
Pap	ASCUS/ reflex HPV positive 21-24 years, 16-18 genotype positive	3 months	6 months	12 months	Colposcopy – with or without biopsy	
Pap	Any higher abnormality (LSIL including HPV changes, ASC-H, HSIL)	3 months	6 months	12 months	Colposcopy – with or without biopsy	
Pap	Endometrial cells over age 50	3 months	6 months	12 months	Endometrial biopsy	62-73%
Pap +hrHPV cotesting	Endometrial cells over age 50	3 months	6 months	12 months	Endometrial biopsy	
Pap	AGC	3 months	6 months	12 months	Colposcopy – with or without biopsy AND endometrial biopsy if over age 35	
Pap +hrHPV cotesting	AGC	3 months	6 months	12 months	Colposcopy – with or without biopsy AND ECC AND endometrial biopsy if > age 35	
Pap	ASCUS/ reflex HPV positive 21-24 years, 16-18 genotype negative or not done	12 months	15 months	24 months	Pap with reflex HPV OR colposcopy with or without biopsy	43-69%[1,2]
Pap	ASCUS/ reflex HPV unknown or not done	12 months	15 months	24 months	Pap with reflex HPV	

Screening Test – Cervical	Abnormal Result	Recommended follow-up period	Enter mFOCUS Study	Lookback period [a]	Appropriate diagnostic follow-up	Estimated Follow-up Rates
Pap +hrHPV cotesting	Pap normal/ HPV + with reflex 16/18 genotyping negative	12 months	15 months	24 months	Pap + cotest OR colposcopy with/ without biopsy	
Pap +hrHPV cotesting	Pap normal/ HPV + with reflex 16/18 genotyping not done or unknown	12 months	15 months	24 months	Pap + cotest OR colposcopy with/ without biopsy	
Primary HPV	Positive/reflex 16/18 genotyping and reflex PAP (if done) negative	12 months	15 months	24 months	Pap with cotest OR colposcopy with/without biopsy	
Pap	ASCUS/ reflex HPV negative	36 months	42 months	48 months	Pap with reflex HPV	17-43%[12]
Pap +hrHPV cotesting	ASCUS/ HPV negative	36 months	42 months	48 months	Pap with or without HPV	
Papanicolaou (Pap), human papillomavirus (HPV), high risk HPV (hrHPV), atypical squamous cells of undetermined significance (ASCUS), low grade squamous intraepithelial lesion (LSIL), atypical squamous cells cannot exclude high-grade squamous intraepithelial lesions (ASC-H), high-grade squamous intraepithelial lesions (HSIL), endocervical curettage (EEC). All sites do reflex HPV testing for ASCUS so there will not be individuals who are ASCUS without an HPV result.						

Screening Test – Colorectal	Abnormal Result	Recommended follow-up period	Enter mFOCUS Study	Lookback period [b]	Appropriate diagnostic follow-up	Estimated Follow-up Rates
FOBT/ FIT	Positive	3 months	6 months	-	Colonoscopy	33-48%[1]
Colonoscopy	Colonoscopy HM modifier 1 year + Colonoscopy procedure 6 months – 1.5 years prior	1 year	1.5 years	-	Colonoscopy	31-41%

	Colonoscopy HM modifier 3 years + Colonoscopy procedure 2.5 – 3.5 years prior	3 years	3.5 years	-	Colonoscopy	31-41%
	Colonoscopy HM modifier set at 5 years 5 years ago + Colonoscopy procedure 4.5 – 5.5 years prior	5 years	5.5 years	-	Colonoscopy	41-48%
Fecal occult blood test (FOBT), Fecal immunochemical test (FIT), health maintenance (HM)						

Screening Test – Lung	**Abnormal Result**	**Recommended follow-up period**	**Enter mFOCUS Study**	**Lookback period [a]**	**Appropriate diagnostic follow-up**	**Estimated Follow-up Rates**
LDCT	Lung-RADs 4b & 4x	1 month	3 months	6 months	Chest CT (with or without contrast), PET/ CT or tissue sampling (CT guided FNA/percutaneous needle biopsy, bronchoscopy, thoracotomy), thoracoscopy	95%
	Lung-RADs 4a	3 months	6 months	9 months	LDCT, Chest CT, PET/ CT	95%
	Lung-RADs 3	6 months	9 months	12 months	LDCT, Chest CT, PET/CT	55%[3]
Low dose computed tomography scan (LDCT). Lung CT Screening Reporting and Data System (Lung-RADS). Diagnostic chest CT (DCT). Positron emission tomography-computed tomography (PET-CT)						

[a] The lookback period was used as part of the NLP algorithms and clinical decision support system to identify patients with abnormal results prior to becoming due for recommended follow-up. The amount of time was varied depending on the risk of the abnormal result. A shorter period was used for higher risk findings. The purpose was to avoid enrolling patients who were so long overdue for follow-up that the mFOCUS intervention may be less likely to be relevant.

[b] There was no lookback period for colorectal cancer screening test results. Patients were identified from the electronic health record's health maintenance section that identified patients with an abnormal result and the date that the patient was due for follow-up.

eTable 2. Overview of Usual Care Outreach by Organ Type and Risk Status

Organ/Risk Status	Initial Outreach: Specialty Care	Initial Outreach: Primary Care
Breast		
BIRADS 5	Initial patient phone call and notify ordering provider with subsequent tracking and outreach as required by MQSA [6]	Any additional outreach and follow-up at PCP discretion
BIRADS 4	Initial patient phone call and notify ordering provider with subsequent tracking and outreach as required by MQSA [6]	Any additional outreach and follow-up at PCP discretion
BIRADS 3	Patient letter and notify ordering provider	Any additional outreach and follow-up at PCP discretion
Cervical		
High risk (need for colposcopy/treatment)	Patient phone call or letter at the discretion of ordering provider or staff	Patient phone call or letter at the discretion of PCP
Medium risk (repeat Pap/HPV in 1 year)	Patient letter at the discretion of ordering provider or staff	Patient letter at the discretion of PCP
Low risk (repeat Pap/HPV in 3 years)	Patient letter at the discretion of ordering provider or staff	Patient letter at the discretion of PCP
Colorectal		
FIT	N/A	Patient letter or phone call at the discretion of PCP
1-, 3-, 5- year	Patient letter with PCP cc'ed at the discretion of performing provider	None or at follow-up PCP visit
Lung		
LRADS 4b/x	Critical alert notifying ordering provider with tracking and outreach to ordering provider	Any additional outreach at PCP discretion or at follow-up PCP visit
LRADS 4a	Notify ordering provider with tracking and outreach to ordering provider	Any additional outreach at PCP discretion or at follow-up PCP visit
LRADS 3	Notify ordering provider	Patient letter at the discretion of PCP or at follow-up PCP visit

eTable 3. Assignment of Risk Status to Screening Test Results by Cancer Type [a]

Organ	High-risk	Medium-risk	Low-risk
Breast	BIRADS 5	BIRADS 4	BIRADS 3
Cervical	• Any pap cytology with HPV genotypes +16/18/45 • LSIL or ASCUS pap with HPV+, age 25 years or above • ASCH, HSIL pap with any HPV result • LSIL pap with no HPV test, age 25 years or above; • AGC pap with any HPV result • Endometrial cells with any HPV result, age 50 years or above	• LSIL or ASCUS pap with HPV +, under age 25 years • LSIL pap with HPV – • ASCUS pap with no HPV test • LSIL pap with no HPV test, under age 25 years; • Normal pap with HPV +	• ASCUS pap with HPV -
Colorectal	FIT or 1-year	3-year	5-year
Lung	LRADS 4b/x	LRADS 4a	LRADS 3

AGC – Atypical Glandular Cells
ASC-H – Atypical Squamous Cells, Cannot Rule Out High-Grade Squamous Intra-epithelial Lesion
ASCUS - Atypical Squamous Cells of Undetermined Significance
HPV – Human Papillomavirus
LSIL – Low-grade Squamous Intraepithelial Lesion
HSIL - High-grade Squamous Intraepithelial Lesion
[a] For exploratory subgroup analyses based on risk of the abnormal test result, findings were classified as low, medium, or high, for each cancer organ type.

eTable 4. Outreach Activities for Intervention Arms 4 (EHR Reminders + Outreach + Navigation) and 3 (EHR Reminders + Outreach)

Number (%)	EHR + Outreach + Navigation (Arm 4)	EHR + Outreach (Arm 3)
Patient population	3455 (100%)	2569 (100%)
Outreach 1: Mailed or portal letter at trial entry		
Portal letter	1579 (45.7)	1137 (44.2)
Mailed letter	506 (14.6)	441 (17.2)
Portal followed by mailed letter	884 (25.6)	648 (25.2)
No letter	486 (14.1)	343 (13.4)
Not eligible on manual review	376 (10.9)	269 (10.5)
Completed follow-up test prior to scheduled outreach time	101 (2.9)	64 (2.5)
Outreach missed	9 (0.3)	10 (0.4)
Outreach 2: Phone call from study coordinator		
Phone call attempted	1830 (53.0)	1531 (59.6)
Left voicemail message	913 (26.4)	782 (30.4)
Spoke with patient	724 (21.0)	605 (23.6)
No answer	112 (3.2)	84 (3.3)
Left message with other person	48 (1.4)	36 (1.4)
Other [a]	33 (1.0)	24 (0.9)
No phone call	1625 (47.0)	1038 (40.4)
Not eligible on manual review	1060 (30.7)	645 (25.1)
Completed follow-up test prior to scheduled outreach time	533 (15.4)	374 (14.6)
Outreach missed	32 (0.9)	19 (0.7)
Outreach 3: Phone call from study navigator [b]		
Phone call attempted	1421 (41.1)	[redacted]
Spoke with patient	775 (22.4)	
Screened for social determinants	315 (9.1)	
Not screened	460 (13.3)	
Left voicemail message	511 (14.8)	
No answer	50 (1.4)	
Left message with other person	58 (1.7)	
Other [a]	27 (0.8)	
No phone call	2034 (58.9)	
Not eligible on manual review	1178 (34.1)	
Completed follow-up test prior to scheduled outreach time	820 (23.7)	
Outreach missed	36 (1.1)	

[a] Other – disconnected, wrong number, number not in service
[b] More than one phone call could be made by the study navigator

eTable 5. Primary 120-day follow-up and secondary 240-day follow-up completion outcomes from the partially adjusted model by study population and intervention arm

	Proportion Completing Follow-up				
	EHR Reminders + Outreach + Navigation (Arm 4)	**EHR Reminders + Outreach (Arm 3)**	**EHR Reminders (Arm 2)**	**Usual Care (Arm 1)**	**Overall *P* value** [b]
Primary Intention-to-Treat Population	(n=3455)	(n=2569)	(n=3254)	(n=2702)	
120-day follow-up completion					
Partially adjusted proportion [a]	31.4	31.1	23.0	23.2	<0.0001
240-day follow-up completion					
Partially adjusted proportion [a]	43.7	42.6	35.0	34.3	<0.0001
Secondary As Treated Population [c]	(n=2094)	(n=1855)	(n=2348)	(n=1883)	
120-day follow-up completion					
Partially adjusted proportion [a]	38.9	33.8	24.1	22.7	<0.0001
240-day follow-up completion					
Partially adjusted proportion [a]	53.8	46.8	37.7	36.0	<0.0001

[a] The partially adjusted models were performed using mixed logistic regression models (SAS Proc GLIMMIX) with the patient as the unit of analysis and included indicator variables for study arms 2, 3 and 4 as the primary exposure, random effects for practices and physicians, and fixed effects for cancer type, study site, enrollment time period, and the interaction between enrollment time period and study site.
[b] Overall p value was derived from the adjusted model.
[c] A secondary as treated population included all patients in the primary intention to treat population, but excluded those who were found to be ineligible based upon manual chart review (see eMethods in Supplement 3 for details).

eTable 6. Adjusted [a] odds ratios of 120-day follow-up completion for primary intention to treat subgroups among study arms

	Odds Ratio (95% Confidence Interval)						
	Arm 4 vs. Arm 1	**Arm 3 vs. Arm 1**	**Arm 2 vs. Arm 1**	**Arm 4 vs. Arm 2**	**Arm 3 vs. Arm 2**	**Arm 4 vs. Arm 3**	**P value[b]**
Type of screening test							0.051
Breast (n=1005)	1.41 (0.93, 2.13)	1.05 (0.71, 1.57)	0.82 (0.56, 1.20)	1.72 (1.16, 2.54)	1.32 (0.88, 1.87)	1.34 (0.89, 2.01)	
Cervical (n=2596)	1.28 (0.93, 1.77)	1.51 (1.09, 2.09)	0.79 (0.57, 1.09)	1.63 (1.18, 2.25)	1.92 (1.38, 2.67)	0.85 (0.61, 1.17)	
Colorectal (n=8245)	1.68 (1.32, 2.16)	1.71 (1.33, 2.19)	1.16 (0.91, 1.48)	1.45 (1.15, 1.84)	1.47 (1.16, 1.87)	0.99 (0.78, 1.25)	
Lung (n=134)	2.16 (0.70, 6.61)	1.31 (0.34, 5.07)	1.52 (0.33, 7.09)	1.42 (0.32, 6.22)	0.86 (0.17, 4.48)	1.64 (0.45, 6.04)	
Risk of screening result [c]							0.22
Low (n=6082)	1.66 (1.36, 2.02)	1.58 (1.28, 1.95)	1.09 (0.89, 1.33)	1.53 (1.27, 1.84)	1.46 (1.20, 1.77)	1.05 (0.87, 1.27)	
Medium (n=3712)	1.57 (1.25, 1.96)	1.55 (1.23, 1.96)	1.04 (0.82, 1.31)	1.51 (1.22, 1.87)	1.49 (1.19, 1.86)	1.01 (0.81, 1.26)	
High (n=2186)	1.13 (0.77, 1.66)	1.46 (0.99, 2.15)	0.74 (0.50, 1.10)	1.52 (1.02, 2.26)	1.97 (1.32, 2.94)	0.77 (0.52, 1.14)	

[a] The adjusted models were performed using mixed logistic regression models (SAS Proc GLIMMIX for each of the subgroups, respectively) with the patient as the unit of analysis and included indicator variables for study arms as the primary exposure, random effects for practices and physicians, and fixed effects for cancer type, severity of the abnormality, marital status, having a primary care visit in the past year, race, ethnicity, study site, enrollment time period, and interaction term between study arm and subgroup variable

[b] Overall p value for the interaction term was derived from the adjusted model

[c] Risk of the screening abnormality was based on guidelines or specialist consensus as detailed in the eMethods in Supplement 3.

Arm 4 - EHR Reminder + Outreach + Navigation
Arm 3 - EHR Reminder + Outreach
Arm 2 - EHR Reminder
Arm 1 - Usual Care

eTable 7. Patient Characteristics for As-Treated Population by Study Arm

	EHR + Outreach + Navigation (Arm 4)	EHR + Outreach (Arm 3)	EHR Reminders (Arm 2)	Usual Care (Arm 1)
Patient Characteristics, n (%)	**(n=2094)**	**(n=1855)**	**(n=2348)**	**(n=1883)**
Age, Median (q1, q3), years	62 (54, 69)	62 (53, 69)	61 (52, 69)	59 (50, 68)
Sex [a]				
Female	1267 (60.5%)	1185 (63.9%)	1503 (64.0%)	1221 (64.8%)
Male	827 (39.5%)	670 (36.1%)	845 (36.0%)	662 (35.2%)
Race [a]				
American Indian or Alaska Native	8 (0.4%)	5 (0.3%)	5 (0.2%)	4 (0.2%)
Asian	63 (3.1%)	42 (2.3%)	64 (2.9%)	64 (3.5%)
Black	134 (6.6%)	130 (7.3%)	195 (8.7%)	97 (5.3%)
Native Hawaiian or other Pacific Islander	1 (0.0%)	1 (0.1%)	1 (0.0%)	2 (0.1%)
Other	182 (8.9%)	122 (6.8%)	138 (6.2%)	112 (6.1%)
White	1652 (81%)	1490 (83.2%)	1829 (81.9%)	1546 (84.7%)
Ethnicity, [a] Hispanic or Latino	214 (10.2%)	168 (9.1%)	236 (10.1%)	152 (8.1%)
Primary Language, Spanish	146 (7.0%)	83 (4.5%)	131 (5.6%)	57 (3.0%)
Marital status, [a] Married/Life Partner	1252 (59.8%)	1056 (56.9%)	1419 (60.4%)	1039 (55.2%)
Primary insurance [b]				
Commercial	1063 (50.8%)	1000 (53.9%)	1324 (56.4%)	1048 (55.7%)
Medicare	654 (31.2%)	551 (29.7%)	610 (26.0%)	490 (26.0%)
Dual/Medicaid	340 (16.2%)	284 (15.3%)	378 (16.1%)	310 (16.5%)
Self pay/No or other insurance	37 (1.8%)	20 (1.1%)	36 (1.5%)	35 (1.9%)
Charlson score [c]				
0	965 (46.1%)	884 (47.7%)	1120 (47.7%)	934 (49.6%)
1	463 (22.1%)	389 (21.0%)	510 (21.7%)	400 (21.2%)
2+	666 (31.8%)	582 (31.4%)	718 (30.6%)	549 (29.2%)
Type of cancer screening				
Breast	1520 (72.6%)	1287 (69.4%)	1567 (66.7%)	1170 (62.1%)
Cervical	359 (17.1%)	335 (18.1%)	490 (20.9%)	450 (23.9%)
Colorectal	185 (8.8%)	218 (11.8%)	279 (11.9%)	233 (12.4%)
Lung	30 (1.4%)	15 (0.8%)	12 (0.5%)	30 (1.6%)
Risk of screening test abnormality [d]				
Low	1062 (50.7%)	967 (52.1%)	1257 (53.5%)	899 (47.7%)
Medium	741 (35.4%)	612 (33.0%)	782 (33.3%)	651 (34.6%)
High	291 (13.9%)	276 (14.9%)	309 (13.2%)	333 (17.7%)
Covid-19 Pandemic Enrollment Period				
Pre-vaccine (August-December 2020	292 (13.9%)	285 (15.4%)	384 (16.4%)	344 (18.3%)
Vaccine rollout (January-June 2021)	1301 (62.1%)	1125 (60.6%)	1353 (57.6%)	1058 (56.2%)
Post-vaccine (July-December 2021	501 (23.9%)	445 (24.0%)	611 (26.0%)	481 (25.5%)
Primary care visit in past year [e]	1415 (67.6%)	1211 (65.3%)	1516 (64.6%)	1204 (63.9%)

[a] Patient demographic variables including sex, race, ethnicity, and marital status were patient self-reported in open ended questions collected as part of routine care during patient registration. Other is a self-reported option for race.
[b] Insurance status is collected from patients as part of routine care during patient registration and updated at visits.
[c] Charlson scores (range 0-17, higher scores indicate increasing comorbidity) calculated using ICD-10 diagnosis codes from electronic health record data in the last two years that are active on the problem list and prior to patient enrollment for the following conditions: myocardial infarction, congestive heart failure, peripheral vascular disease,

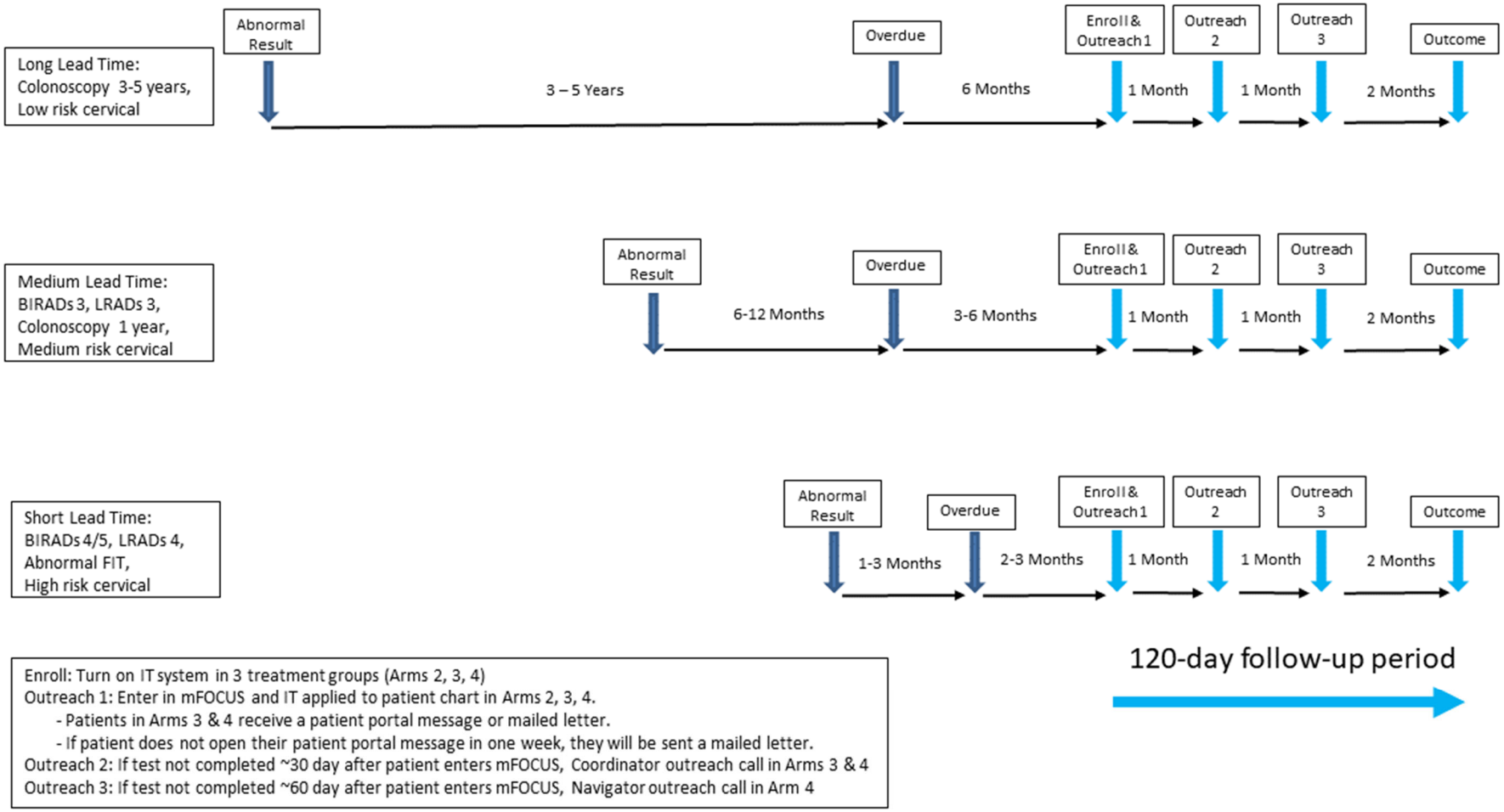
cerebral vascular disease, dementia, chronic pulmonary disease, rheumatic disease, peptic ulcer, liver disease, diabetes, hemi/paraplegia, malignancy, metastatic solid tumor, HIV/AIDS.[44]

[d] Risk of the screening abnormality was based on guidelines or specialist consensus as detailed in the eMethods in Supplement 3.

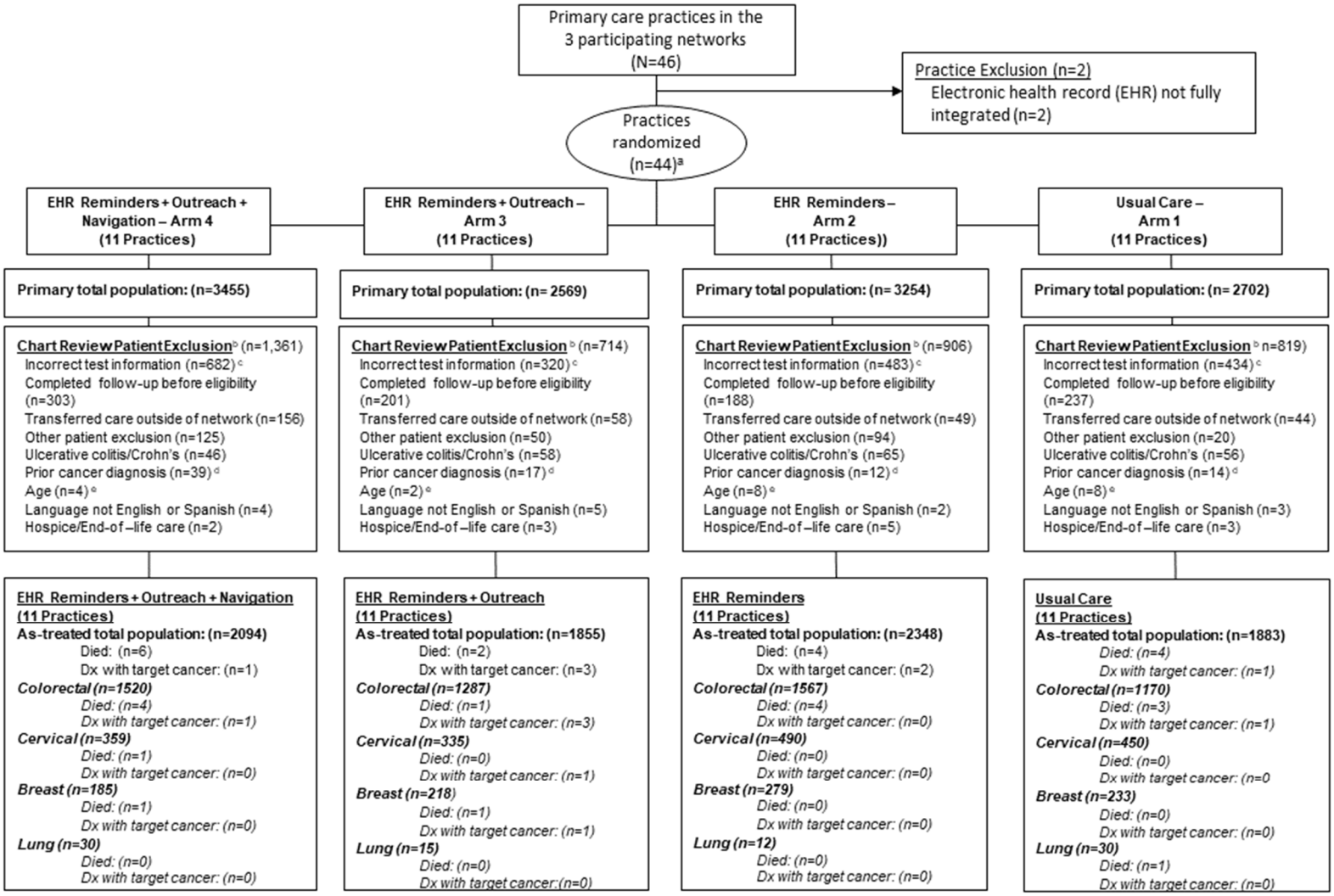
[e] Primary care visit in the same health care system as abnormal screening test.

eFigure 1. Flow of patients in the study

The first horizontal arrow represents the “lead time” that preceded enrollment.

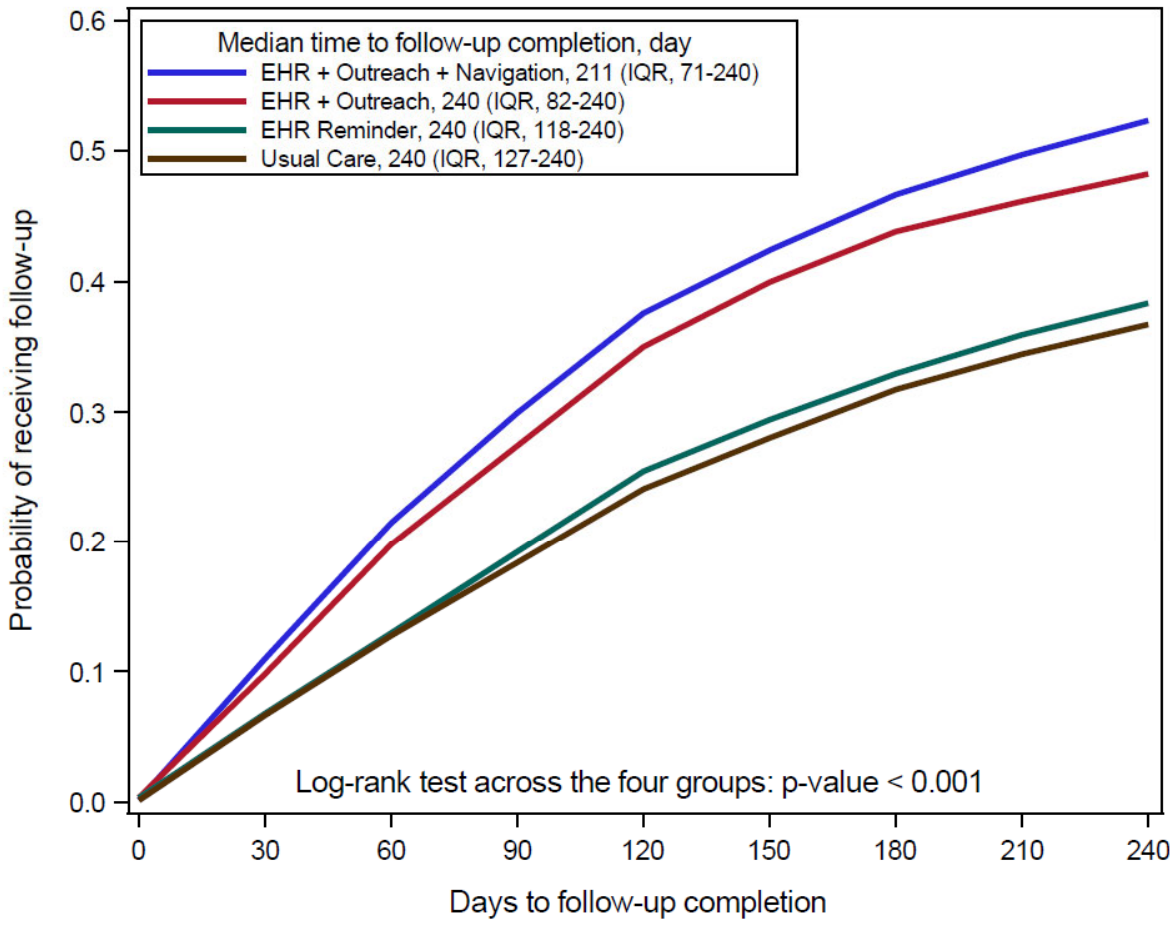


eFigure 2. Consort Diagram for As Treated Population



[a] Practices were randomized based on practice size, and number of patients who were female or had Medicaid insurance.
[b] Patient post-hoc enrollment exclusions were identified based on manual chart review as described in the eMethods section of Supplement 3.
[c] Incorrect test information includes patients who had an incorrect test date or who had a normal test result.
[d] Prior cancer diagnosis refers to a target organ cancer before the abnormal test of interest was performed.
[e] Eligibility by age based on abnormal cancer type; breast: women 40-80 years old, cervical: women 21-65 years old, colorectal: adults 40-80 years old, lung: adults 55-80 years old.

eFigure 3. Cumulative follow-up completion rates (Kaplan-Meier estimates) and KM plot for As Treated Population



No. at risk (As-Treated population)									
EHR + Outreach + Navigation	2094	1872	1653	1469	1312	1209	1116	1055	998
EHR + Outreach	1855	1680	1495	1352	1208	1115	1043	1000	963
EHR Reminder	2348	2194	2048	1902	1755	1661	1576	1507	1449
Usual Care	1883	1760	1645	1546	1433	1359	1287	1235	1192