mFOCUS Detailed Protocol

TITLE: mFOCUS (multilevel Follow-up of Cancer Screening)

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GRANT NUMBER: U01CA225451

VERSION DATE: 3/16/2022

I. BACKGROUND AND SIGNIFICANCE

A.1. Strong Support for Evidence-Based Screening. Cancer is currently the 2nd leading cause of death in the US and is projected to surpass heart disease as the leading cause of death by 2030.[1] Together, breast, cervical, colorectal (CRC), and lung cancer result in 634,460 new diagnoses and 250,950 deaths a year.[2]

Screening reduces cancer-specific mortality for breast,[3] cervical,[4] and CRC,[5] and more recent evidence supports lung cancer screening (LCS) in high-risk patients.[6] In addition to early detection, cervical and CRC screening can prevent cancer by removing pre-cancerous lesions.[4,5] Routine screening is recommended by the US Preventive Services Task Force (USPSTF) and other national guidelines.[3,7-11] Cancer screening is a process and not a discrete event. Even among individuals who receive screening, the benefits are only fully realized if coupled with timely and appropriate follow-up of abnormal screens.

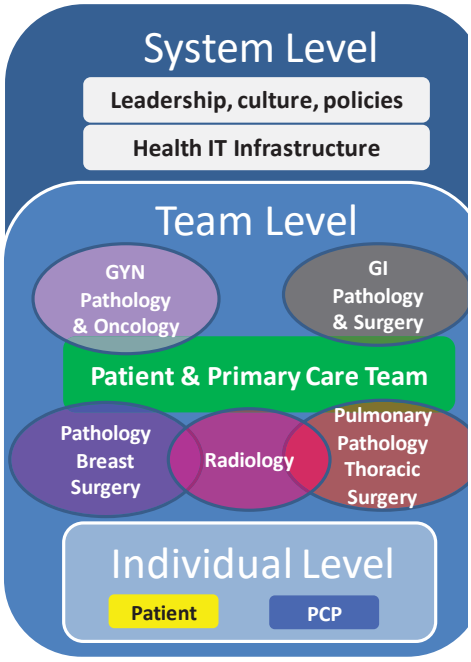
A.2 Many Screening Tests Require Diagnostic Evaluation but there is Variation in Timely Follow-up. Our recent study within the NCI-funded Population-Based Research Optimizing Screening through Personalized Regimens (PROSPR) consortium reported significant rates of screening abnormalities that required additional evaluation, including; 11% of breast cancer, 8% of cervical and 5% of fecal occult blood test (FOBT)/ fecal immunochemical test (FIT) screens,[12] consistent with other studies.[13-16] The abnormality rates for colonoscopy screening (~20% adenomas)[17] and LCS with low dose computed tomography (LDCT)'s are also high (~25%).[18] Our work also demonstrates wide variation in follow-up rates across primary care clinics.[12] Apart from the legislated requirement for radiologists to follow-up abnormal mammograms, responsibility for comprehensive screening follow-up falls to the ordering provider, typically a primary care provider (PCP). Unfortunately, few PCPs/ primary care practices have systems to track abnormalities and promote follow-up. **PCPs face the challenge of responsibility for managing the diagnostic evaluation for populations of patients for each of these cancers, each with differing requirements and timeframes for completion**.

A.3. Diagnostic Evaluation Barriers. The transition from screening to diagnostic evaluation often requires a transfer of role/ responsibility between primary and specialist care.[19,20] Depending on the test and finding, a patient and their care team may need to track when follow-up testing is needed, from several months to many years. For example, abnormal Pap follow-up often entails specialist referral for colposcopy while colorectal abnormality follow-up may require further testing immediately or years in the future. Failure to receive appropriate diagnostic testing after an **abnormal cancer screening test result** (**hereafter called an "abnormal screen")** undermines the benefits of screening, and violates the trust that patients place in their providers and health systems.[21,22] **Barriers to follow-up of abnormal screens exist at multiple levels**; in this application, we focus on the **individual** (patient, PCP), care **team**, and health **system** levels (**Figure 1**).

Patient barriers often begin with not being informed about how and when they will be notified of screening results. Phone messages mailed or emailed results may not be acknowledged. Patients may not understand the importance of a result or have difficulty negotiating the process for obtaining additional evaluation. Patient barriers such as language, literacy, financial resources, anxiety, logistical challenges such as transportation and scheduling, and knowledge and beliefs about tests and treatments have been shown to result in delays in follow-up of abnormal screens.[23-26]

For PCPs, follow-up of abnormal screens is difficult, time consuming, and frequently uncoordinated. Though PCPs often order screening, specialists often perform the screening test (e.g., radiology for breast and lung); there can be uncertainty about responsibility for management. Though high-risk abnormalities may entail direct communication, most often the PCP receives mailed, faxed, or electronic result notification. EHRs often provide visit-based reminders for screening, but there are fewer reminders for follow-up of abnormal screens and any such reminders are often tied to office visits. Even if an EHR delivers non-visit based results to the ordering provider, there are rarely tools to facilitate a standard, easily actionable next step.

Figure 1: Multilevel factors



While patients and providers may take **individual** responsibility, effective follow-up requires that the patient and PCP function effectively with practice staff and relevant specialists who together comprise a **care team**. The World Health Organization defines a team as "a distinguishable set of two or more people who interact dynamically, interdependently and adaptively towards a common and valued goal, who have been assigned specific roles or functions to perform, with specialized and complementary knowledge and roles, and act as a collective unit."[27] Effective team function can benefit the patient (improved outcomes and satisfaction), PCP and specialist (greater role clarity and job satisfaction), and health system (efficient resource use).[28] Individuals and care teams function within the context of a **health system**, with unique leadership, culture and policies. Systems include infrastructure to support care through health information technology (IT), which can help or hinder the individual and team functions. Systems adopt varied approaches to measurement and incentives that may directly or indirectly influence the follow-up of abnormal screens.[29]

A.4. Rationale for Interventions to Improve Follow-up of Abnormal Screens. Our prior documentation of incomplete follow-up of abnormal screens, and variation across organ types and settings, highlights the importance of developing systematic, multilevel interventions to improve care.[12] We propose leveraging several key advances to provide a multilevel approach to improving follow-up of abnormal screens including:

Population Management (PM), a team-based approach widely adopted in primary care whereby staff members identify and reach out to patient groups with unmet care needs, often outside of visits, to improve adherence.[30-33] EHR-integrated registries facilitate identification and tracking of patient groups, but registries alone are unlikely to result in improvements as busy PCPs may develop "registry fatigue." PM tasks can be performed by non-clinical personnel, using pre-defined algorithms with two main purposes, to: 1) improve care for patients regardless of whether they have a visit, and 2) redistribute work so that clinicians have more time for complex functions.[34] PM programs are often "low touch," using patient registries coupled with emails or letters to remind patients that they are due for care. PM systems typically address use of cancer screening;[35,36] to our knowledge few PM systems have focused on the follow-up of abnormal screens as we propose here.[37]

New EHR-integrated ***health information technology (IT) platforms*** can support PM and promote completion of diagnostic evaluation following an abnormal screen. These include: patient portals to inform patients of their results, provide education and reminders;[38,39] clinical decision support and registries for providers;[40] promote communication between PCPs and specialists,[41] and improve the accuracy of EHR problem lists.[39,42] Despite these advances, infrastructure alone is likely insufficient to address barriers to follow-up of abnormal screens.

Patient Navigation (PN), an evidence-based strategy for coordinating care designed to ensure that necessary care is delivered to all patients, seeks to identify and remove barriers, including logistical, psychosocial and educational.[25,37,43-47] Services offered by PN programs are flexible and focus on individual problem-solving rather than providing a pre-defined set of services. PN has been shown to improve rates of cancer screening, particularly for vulnerable populations.[44,48] As a part of a NCI-initiated PN Research Program, RCTs have found modest improvements in time to diagnosis and treatment initiation.[25,49-56] PN is traditionally delivered by a combination of phone calls and face-to-face visits,[25,37] often making programs difficult for individual clinical sites to maintain.[25,57] Models of PN that incorporate centralized PN in a stepped care model, such as we propose, are needed to reduce costs and promote sustainability. **Integration of health IT-enabled PM platforms with personalized PN that can address social-contextual barriers to care may be best able to address the needs of patients at increased risk of delayed follow-up of an abnormal screen.**

A.4. Potential Impact of Proposed Study. Though considerable progress has been made in advancing use of cancer screening, evidence supports an opportunity to improve follow-up of abnormal screens.[12] We hypothesize that the optimal strategy to ensure follow-up will: 1) coordinate care for diagnostic evaluation leveraging a system level health IT platform for PM; 2) offer a stepped care approach that individually engages patients and PCPs, and enhances team-functioning with increasing intensity over time (**Figure 2).** Accordingly, we propose to develop, implement, and rigorously test **mFOCUS** (multilevel FOllow-up of Cancer Screening), directed at abnormal breast, cervical, CRC and LCS screens within three primary care practice networks.

B. Innovation and Scientific Premise

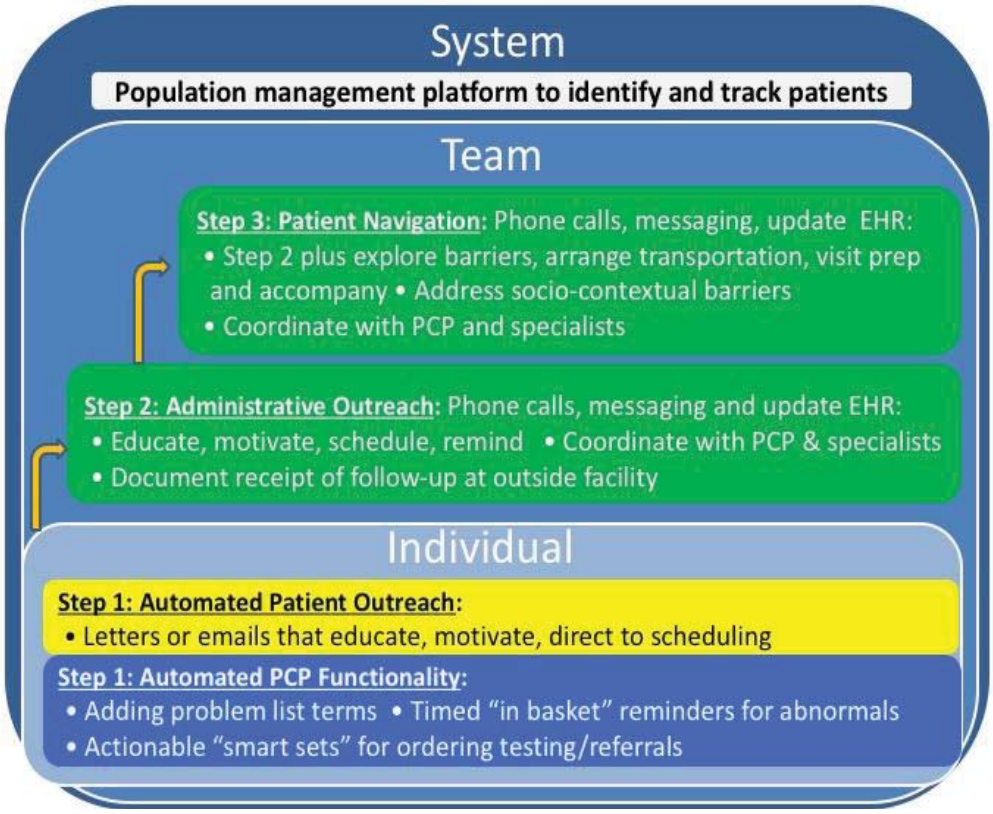
While historically research has examined diagnostic evaluation barriers for organ-specific screening, PCPs take a "whole person" approach. The number of abnormal results that PCPs are responsible for is staggering. PCPs review over 900 test results per week;[58] the sheer volume of results supports the need to have a unified management approach. Our PROSPR work demonstrates that PCPs lack and want team-based systems to manage abnormal screens.[59,60] Thus, our "whole person" approach to follow-up of abnormal screens is innovative and timely. Our study design will allow us to examine the effect of intervention components at the individual, team, and system levels (**Figure 2**). Changes in health care financing provide opportunities for innovation in care delivery outside of an office visit. PCPs and health systems are also increasingly taking responsibility for population health through new care delivery models, such as patient centered medical homes (PCMHs), "medical neighborhoods" (delivery models with standards for the integration of primary and specialty care, with feedback loops for referrals), and accountable care organizations (ACOs).[61-63] As new financing and delivery models are implemented, the integration of primary and specialty services is a key area for care redesign. For comprehensive cancer detection, this will require coordinating the responsibility for cancer screening that resides with PCPs to the diagnostic evaluation that often involves specialists.

Our **scientific premise** builds from the literature, relevant conceptual models and our strong preliminary studies; these support the following key concepts to improve follow-up of abnormal screens: 1) comprehensive follow-up of breast, cervical, CRC and LCS is best organized using a primary care focus;[50] 2) a system-level, population-based health IT platform to power the underlying infrastructure and support culture change; 3) PM to efficiently allocate resources by consistently targeting interventions to the most appropriate patients at the right time; 4) workflow that promotes multilevel engagement of individual patients and providers with coordinated care teams; 5) stepped care approach to promote efficiency; and 6) a program that can be successfully deployed across different health systems. **Key innovations** of our approach include: 1) taking a patient- and PCP-centered "whole person" perspective to integrate follow-up management for four cancers; 2) stratifying patients based upon abnormality risk; 3) a health IT platform for PM based in primary care with pre-defined information exchange to support multilevel team engagement; and 4) applying a 4-arm randomized design to evaluate the effectiveness of mFOCUS components at the system, team, and individual levels.

Preliminary Studies. Our multiple-PI leadership team has a history of successful collaboration.[12,64-74] Jennifer Haas, MD, MSc, is a PCP at BWH with research expertise in practice-based interventions focused on cancer screening, behavior change, and reducing disparities.[75-78] Together with Dr. Tosteson, Dr. Haas is PI of an

NCI-funded PROSPR research center.[12,59,64,65,67,68,71,72,79,80] Steven Atlas, MD, MPH is a PCP at MGH and as director of its primary care practice-based research network developed and implemented IT-enabled PM platforms used at BWH and MGH.[26,35,37,81-84] Anna Tosteson, ScD is a decision scientist at Dartmouth/DH whose research addresses how programs affect outcomes of care.[85-92] Along with Dr. Haas, she has evaluated screening follow-up for breast, cervical and CRC.[12,68,71] We describe our most relevant preliminary studies:

Figure 2. Multilevel components of mFOCUS



Defining Episodes of Cancer Screening and Diagnostic Evaluation. We have extensive expertise defining data elements and extracting information from EHRs about the cancer screening continuum, including diagnostic evaluation following abnormal screenings.[12,65,68] This work uses natural language processing (NLP) to define coded data fields with good validity.[68,93-97] As PROSPR PIs, we have access to the common data elements defined by PROSPR. In addition to our PROSPR work documenting variation in follow-up of abnormal screens,[12] Dr. Adam Wright (co-I), a medical informatician, has developed and validated algorithms for EHR decision support to improve the follow-up of high risk results, including abnormal cancer screens.[40,93] **This work demonstrates our ability to define, measure and operationalize the needed data elements to assess to follow-up of abnormal screens.**

RCTs of Multilevel Interventions in Practice. Our team has strong experience conducting pragmatic, cluster-RCTs in primary care exemplified by the following studies: 1) In a study of 6,730 women overdue for breast cancer screening, providers in intervention practices used a PM platform to review lists of overdue patients, order screening or document deferral reasons.[82,83] Patients in standard care and intervention practices had EHR reminders available during visits. Mammography screening rates were significantly higher in the intervention vs. control arm at 1- and 3-year follow-up. We next examined receipt of screening for breast, cervical, and/or CRC by comparing different contact mechanisms.[35] Cost analysis favored automated outreach without PCP involvement.[60] 2) In a trial of 3,703 adults, we evaluated a brief, individualized health risk assessment (HRA) including breast cancer and CRC.[98] Intervention patients underwent systematic risk factor collection via an IT-platform that offered automated calls and/ or secure internet survey and received a 1-page HRA. Intervention patients were more likely to report PCP discussion of changes to improve their health and had greater improvement in the accuracy of self-perceived disease risk. These studies demonstrate our ability to implement large, system-wide, multilevel (system; individual patient- and provider-level) interventions.

Patient Navigation (PN). We have demonstrated that culturally-tailored PN programs improve equity in cancer screening.[48,99] Among 1,223 low income, mostly non-English speaking patients eligible and overdue for CRC screening, patients randomized to PN were more likely to undergo screening than controls (27% vs. 12%, $p<0.001$).[100] Embedding PN in a PM system to improve screening, 1,612 patients randomized to the

intervention were more likely to complete breast, cervical, and CRC screening than standard care.[37] In a trial of PN to promote LCS, screening was completed in 24% of navigated vs. 9% in standard care ($p<0.001$).[101] These studies demonstrate our ability to deploy and evaluate PN programs.

II. SPECIFIC AIMS (Research Objectives)

Specific Aim 1: To evaluate the *effectiveness* of the system, team and individual components of mFOCUS vs. standard care by conducting a 4-arm cluster randomized controlled trial (RCT) of individuals who are due for follow-up of an abnormal cancer screening test. Standard care consists of well-characterized existing decision support and systems for follow-up in these three participating primary care networks and their affiliated integrated delivery systems (Brigham and Women's Hospital and Massachusetts General Hospital, both members of Partners HealthCare System, Massachusetts's largest integrated health care delivery system, and Dartmouth Hitchcock Health, the largest health care provider in New Hampshire). The primary outcome will be whether an individual receives follow-up, defined based on the type of screening abnormality and organ type, within 120 days of becoming eligible for mFOCUS. Secondary comparisons will assess multi- and cross-level (individual, team, system) outcomes**.** Because the Coronavirus pandemic impacted access to health care, we will also assess whether an individual receives follow-up, defined based on the type of screening abnormality and organ type, within 240 days of becoming eligible for mFOCUS. The study design will allow us to examine the marginal effectiveness of system, team and individual-level enhancements, and exploratory analyses will address subgroups defined by race/ ethnicity, socioeconomic status and cancer type.

Hypothesis: mFOCUS will significantly increase the proportion of individuals who receive follow-up testing, thereby reducing time to follow-up vs. standard care.

Specific Aim 2: To evaluate facilitators and barriers to the *Reach, Adoption, Implementation and Maintenance* of mFOCUS. The impact of any intervention depends on its ability to be implemented in clinical practice.

Hypothesis (***Reach***): Individuals who are due for follow-up can be reached by mFOCUS irrespective of patient sociodemographic characteristics and "severity" of the screening result. Patient surveys will be used to examine barriers and facilitators.

Hypothesis (Adoption, Implementation, and Maintenance): mFOCUS will be *adopted* across providers/ practices and consistently *implemented*. Provider, team and system-level surveys will be used to examine barriers and facilitators to adoption, implementation and maintenance.

NOTE: This protocol involves patients who receive care at Partners (MGH and BWH) as well as Dartmouth. Dartmouth will be a relying site on the Partners IRB review that will be added in an amendment once the Partners protocol is approved.

III. SUBJECT SELECTION

Inclusion criteria: Individuals who have an abnormal screen that is due for follow-up including:

- Breast: women 40-80 years with an *incident* (i.e., newly detected) abnormal screening mammogram or digital breast tomosynthesis (DBT) exam.
- Cervical: women 21-65 years with an *incident* abnormal screening Pap.
- Colorectal: adults 40-80 years with an abnormal screen, including *incident* FOBT/ FIT, or *prevalent* colonoscopy. Because of the long periods of time required for follow-up of colonoscopies, we will look back over a 5-year period and will therefore find *prevalent* abnormalities that become due for follow-up.
- Lung: adults 55-80 years, current and former smokers, with an *incident* abnormal LDCT result.

Definition of the specific screening abnormalities and timing of diagnostic evaluation are based on our prior work, expert opinion, and the literature. Need for follow-up will be determined by the lack of an appropriate clinical test within the specified time as documented in the EHR.

Exclusion criteria: We will exclude patients who: 1) are not English or Spanish-speaking, or 3) have had prior cancer of the organ for each screening test (i.e., women with prior breast cancer will not be tracked for breast cancer screening abnormalities) as these individuals may have non-standard follow-up care recommendations.

IV. SUBJECT ENROLLMENT

AIM 1:

RCT: We will recruit 3324 participants who fit the eligibility criteria defined above (are overdue for follow-up of an abnormal cancer screening test result). Because randomization will be done at the practice level, we will not be able to recruit exactly 3324 individuals (patients will be in process of recruitment since they will be recruited in batches) – this is the number suggested by our sample size calculation. We will not exceed recruitment of 12,000 eligible individuals. Because the trial is testing a "care enhancement," and is minimal risk, we are requesting a waiver of informed consent given the large number of subjects distributed over 44 primary care practices. Randomization will be done at the practice level and individual patients will not be approached for recruitment. The outcomes for the main trial will be assessed using data from the electronic health record. Subjects in the main trial will not receive remuneration.

We anticipate that this calculations will need to be updated due to the impact of COVID-19 and that our recruitment number will be higher because of the back log of testing that will occur as hospitals reopen for screening procedures. We anticipate that we could possible recruit up to 9,000 eligible patients at MGHBWH, and 12,000 eligible patients study wide. We will not exceed recruitment of 12,000 eligible individuals. Due to the way our IT system is configured, we anticipate that we could review up to 20,000 patient charts study wide. Not all of the patient charts reviewed will be deemed eligible.

Surveys: Some of the outcomes of the study will be measured by PCP, practice administrator and patient surveys:

PCP Surveys: A brief, self-administered survey will be administered to PCPs, excluding trainees, just before the trial in launched and 3 months after recruitment ends. Prior to fielding the survey, we will request that the primary care network director send an email to PCPs in his/ her network informing them about the purpose to the survey (attached with the survey); PCPs will then receive an email from one of the study investigators with a link to a Redcap survey. PCP surveys will be administered using RedCap (up to 5 email contacts with a RedCap link over 4 weeks)

PCPs who are eligible for the survey will receive a $50 gift card code for Amazon with the initial delivery of the survey as the survey literature supports the use of "up front" incentives for health care providers.

Patient surveys: As noted above, we will randomly sample 15% of participants. Patient surveys will be administered 4-12 weeks after their individual follow-up period has been completed, so surveys will be conducted throughout the enrollment period. *Survey procedures* will include: 1) an introductory letter from the clinical director of each primary care network paired with a letter from the PI that explains the study purpose and opportunities to opt out/ participate of the survey (attached). Patients will be given the opportunity to go to a unique Redcap url from the letter or will receive a link via PG or the un-secured email that is recorded in the electronic health record (if available). The letter will include contact directions to email/ phone study staff if they do not wish to opt-out of the survey or do not wish to receive un-secured email. Those who do not opt-out within 2 weeks will be contacted by phone and asked to complete the survey by phone or RedCap. If the patients opt for the later, they will receive the survey link via un-encrypted email (and asked for the email where they would like to receive it). Patients will receive up to 5 email/mail attempts over 4 weeks followed by up to by one phone call. All mail surveys will be sent with a pre-addressed envelope with pre-paid postage.

Patients who are sampled for the survey and complete the survey will receive a $50 gift card from their choice of Amazon or a regional grocery store.

No additional remuneration will be provided as this study does not incur any out-of-pocket expenses for participating.

V. STUDY PROCEDURES

Definition of the specific screening abnormalities and timing of diagnostic evaluation are based on our prior work, expert opinion, and the literature. Need for follow-up will be determined by the lack of an appropriate clinical test within the specified time as documented in the EHR. Example logic is shown in the following Table:

Table 1. Description of included test results, follow-up period and appropriate diagnostic follow-up.

Screening Test	Abnormal Result	Guideline Recommended follow-up period	Enter mFOCUS Study	Lookback period	Appropriate diagnostic follow-up
BREAST:					
Unilateral or Bilateral screening mammography or DBT, excluding women with prior cancer *Patients will 12 month recommended follow up will enter the study at 15 months	Birads 3*	6 months	9 months	12 months	Unilateral or bilateral Mammo/ DBT, Breast US, Breast MRI
	Birads 4	1 month	3 months	6 months	Biopsy (FNA, core, surgical), lumpectomy, mastectomy
	Birads 5	1 month	3 months	6 months	Biopsy (FNA, core, surgical), lumpectomy, mastectomy
LUNG:					
LDCT	Lung-RADs 3	6 months	9 months	12 months	LDCT, Chest CT, PET/CT
	Lung-RADs 4a	3 month	6 months	9 months	LDCT, Chest CT, PET/ CT
	Lung-RADs 4b & 4x	1 month	3 months	6 months	Chest CT (with or without contrast), PET/ CT, visit with surgeon or pulmonary nodule clinic, or tissue sampling (CT guided FNA/percutaneous needle biopsy, bronchoscopy, , thoracotomy), thoracoscopy
COLORECTAL:					
FOBT/ FIT	Positive	3 months	6 months	12 months	Colonoscopy
Colonoscopy	Colonoscopy HM modifier set at 5 years 5 years ago +	5 years	5.5 years	6.5 years	Colonoscopy

	Colonoscopy procedure 4.5 – 5.5 years prior				
	Colonoscopy HM modifier 3 years + Colonoscopy procedure 2.5 – 3.5 years prior	3 years	3.5 years	4.5 years	Colonoscopy
	Colonoscopy HM modifier 1 year + Colonoscopy procedure 6 months – 1.5 years prior	1 year	1.5 years	2.5 years	Colonoscopy

CERVICAL					
Primary HPV	Positive/ no reflex genotyping	3 months	6 months	12 months	Pap AND 16/18 genotype
Primary HPV	Positive/ reflex 16/18 genotyping positive	3 months	6 months	12 months	Colpo – with or without biopsy
Pap +hrHPV cotesting	Pap normal/ HPV + with reflex 16/18 genotyping positive	3 months	6 months	12 months	Colpo – with or without biopsy
Pap +hrHPV cotesting	ASCUS HPV +	3 months	6 months	12 months	Colpo – with or without biopsy
Pap +hrHPV cotesting	Any higher abnormality (LSIL including HPV changes, ASCH, High grade SIL, HSIL)	3 months	6 months	12 months	Colpo – with or without biopsy
Pap +hrHPV cotesting	AGC	3 months	6 months	12 months	Colpo – with or without biopsy AND ECC AND endometrial biopsy if over age 35
Pap +hrHPV cotesting	Endometrial cells over age 50	3 months	6 months	12 months	endometrial biopsy
Pap	ASCUS/ reflex HPV positive 25+ years	3 months	6 months	12 months	Colpo – with or without biopsy

Pap	Any higher abnormality (LSIL including HPV changes, ASCH, High grade SIL, HSIL)	3 months	6 months	12 months	Colpo – with or without biopsy
Pap	AGC	3 months	6 months	12 months	Colpo – with or without biopsy AND endometrial biopsy if over age 35
Pap	Endometrial cells over age 50	3 months	6 months	12 months	endometrial biopsy
Pap	ASCUS/ reflex HPV positive 21-24 years, 16-18 genotype positive	3 months	6 months	12 months	Colpo – with or without biopsy
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 Colpo with or without biopsy
Pap	ASCUS/ reflex HPV unknown or not done	12 months	15 months	24 months	Pap with reflex HPV
Pap +hrHPV cotesting	Pap normal/ HPV + with reflex 16/18 genotyping negative	12 months	15 months	24 months	Pap + cotest OR colpo 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 colpo 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 colpo with/without biopsy
Pap	ASCUS/ reflex HPV negative	36 months	42 months	48 months	Pap with reflex HPV
Pap +hrHPV cotesting	ASCUS/ HPV negative	36 months	42 months	48 months	Pap with or without HPV

Exclusion criteria: Patients who: 1) have an abnormality not listed above (e.g., incidental findings); 2) undergo one of these tests for diagnostic evaluation; 3) those with a prior cancer of the target organ for each test and 4) are not English or Spanish-speaking.

Intervention Design and Randomization Scheme. We will perform a 4-arm cluster RCT with randomization done at the practice-level, across the ~44 participating practices. We have chosen this level of randomization as it would be logistically complicated for the practices to have different patients randomized to different intervention components (i.e., reduced contamination). Randomization will be stratified based on: (1) primary care network, (2) practice type (e.g., community health center), and (3) practice size. Practices within each stratum will be randomly allocated; practice characteristic data are available from each primary care network's administration. Prior RCTs with randomization at the practice level have resulted in good balance of patient and provider characteristics across arms.[35,78,82,103,104] The 4-arm design is summarized in **Table 2** and will allow us to compare "standard care" to three intervention arms that represent the sequential addition of: visit based reminders that the patient is overdue for followup directed at the PCP, visit based reminders + population based reminders (both PCP and patient), including sending letters, patient portal, and phone reminders outside of a visit, and patient navigation Given our stepped care approach, this randomization scheme will allow us to compare the cumulative addition of each level of intervention to standard care as well as the marginal effect of each additional level to the prior group.

Table 2. Four-Arm Design

		Study Arm			
		1	**2**	**3**	**4**
	Standard care	x	x	x	x
Level of Intervention	**Visit-based reminders**		x	x	x
	Population based reminders			x	x
	Patient navigation				x

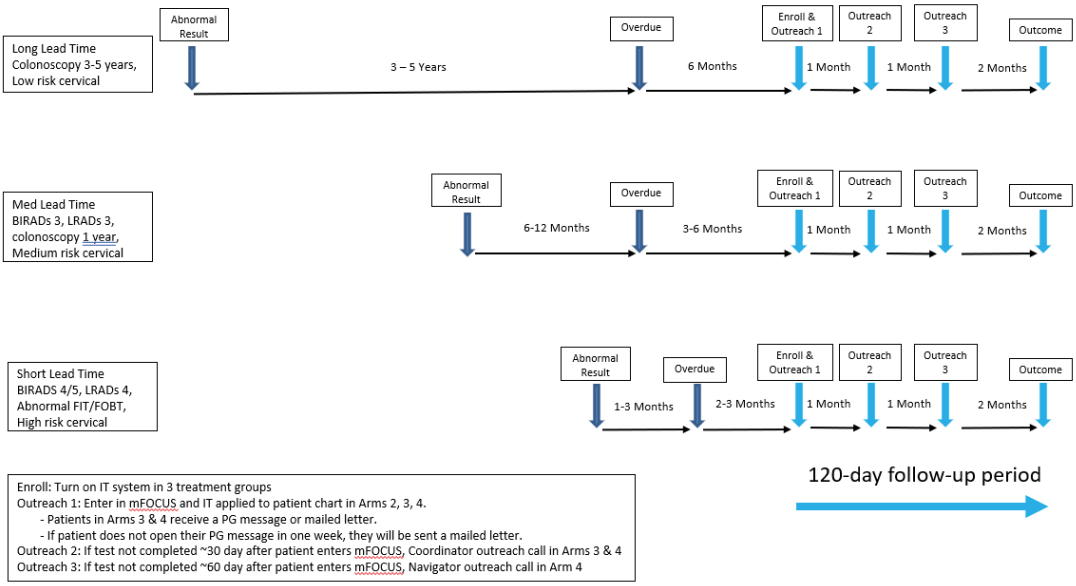
Recruitment and Enrollment. Key organizational components of the study will involve:

(1) Practice and Provider Engagement. We have support of network leadership for the study and providers from each network involved in the application. Investigators have/ will attend practice meetings at intervention sites to integrate work flow with practice routines and educate staff about the study and its procedures.[37,76,78,81,83,100] PCPs will not be required to do recruitment; this will be done centrally through each sites population management program. We therefore anticipate a high level of practice and PCP participation since the intervention does not constrain usual practice but adds additional systems beyond those currently available. Practices will be given the opportunity to opt-out of the study before practices are randomized.

Patient Identification and Enrollment. The development and implementation of the mFOCUS platform will incorporate algorithms for identification of eligible patients and patient-practice attribution. All patients will remain under the direction of their personal PCP/ practice and the intervention components will facilitate the delivery of care in addition to the current standard of care. Based on historical data from our primary care networks, we expect approximately 14,000 eligible patients over the course of the study period (this number may be higher due the impact of COVID-19, we will adjust accordingly), with a goal of enrolling 3324 eligible patients because of personnel capacity required to deliver the patient-engagement intervention (see **Analysis/ Power**).

Control Arm (Standard Care) patients will receive the usual care provided by their PCP, practice, and/or specialists. For each cancer type, the ordering provider receives a report of the abnormal screen viewable in the lab results section of each patient's EHR and in an "In-Basket queue" (i.e., all results of any type, normal or abnormal, are sent to this queue). From the In-Basket queue, the ordering provider may choose, at their discretion, to send a letter to the patient, document a phone call, and/ or order additional testing. If the ordering provider is not the PCP, the PCP often does not receive any additional information (left to the discretion of the ordering provider). Beyond this, systems vary by organ type and by provider/ practice. For breast cancer screening, the radiologist is typically more involved in the follow-up of abnormal screens than for any of the other organs, particularly for BIRADS 4, and 5 results (with algorithms for phone calls and certified letters).

While less established, lung results are often followed by radiology using algorithms that parallel breast. Result communication and management for cervical and CRC are much more variable.



Intervention Arm Components. mFOCUS will include components that address individual (patient, PCP), team, and system-level barriers that will be tested using the 4-arm design noted above that allows for the sequential addition of these multilevel components. This multilevel design allows us to evaluate changing the responsibility for "opportunistic" follow-up, typically by the PCP at the time of a visit, to a systematic, multilevel approach, examining the cumulative and marginal effects of each subsequent level of intervention. Patients in Arm 1 will receive the standard of care. Arm 2 will include the implementation of a system-level, appointment-based intervention: an IT platform that will facilitate updates to Health Maintenance modifiers and problem lists within the EHR that will be visible to the provider at the time of a visit. Practices/ providers will receive training for the new platform. In addition to the visit based reminders, Arm 3 will include automated population level reminders (based on when a patient is due for follow-up regardless of whether he/ she comes for a visit) which target PCPs (In-Basket reminders) and patients (with Patient Gateway messages or letters, and one brief phone call or voice message). Arm 4 will include all previous components in addition to the team-level intervention which consists of administrative outreach to patients (i.e. up to 3 phone calls) and a patient navigator to assist with scheduling and addressing social barriers to care. The engagement algorithm will take a "stepped care" approach with increasing level of intensity of engagement (**Figure 2**). Step 1 will start on the follow-up date listed in the table above for the cancer-specific abnormality. In practices randomized to the team-level intervention, patients, PCPs and teams would progress through the steps of mFOCUS monthly if follow-up had not been completed (i.e., Step 2 starts 4 weeks after Step 1), so that all steps of the intervention would be delivered within 3 months. Patients with results at high risk for cancer would skip Step 1 and start mFOCUS at Step 2. The IT platform will include functionality for outreach coordinators and PNs to know when a patient should be contacted, how many contacts have been made and the outcome of those.

The figure summarizes the timing of the identification process and enrollment process by risk of the abnormal result and the timing of outreach efforts in different study arms

VI. BIOSTATISTICAL ANALYSIS

Outcomes

Table. Summary of primary and secondary outcome measures

Levels	Level Specific Measures (data source)	Example Cross Level Measures
Individual Patient	**Primary outcome:** Completion of follow-up within 120 days of mFOCUS eligibility date (EHR/ claims) **Secondary outcomes:** Completion of follow-up within 240 days of eligibility for mFOCUS (EHR/ claims)	Patient-Reported Assessment of: *Individual-PCP:* Satisfaction with care provided by PCP *Care Team:* Satisfaction with care provided by care team

	# of days to completion of diagnostic evaluation (EHR/ claims) Satisfaction with follow-up care (patient survey) Knowledge of test result and need for follow-up (patient survey)	*System:* Receipt of reminder letter, call, or email
PCP	**Secondary outcomes:** Satisfaction with ability of patients to get timely follow-up (PCP survey) Time required for management (PCP survey)	PCP-Reported Assessment of: *Individual-Patient:* Patient understanding of need for follow-up *Care Team:* Satisfaction with coordination of care *System:* Satisfaction with IT functionality to support follow-up

Covariates

Covariates will include patient characteristics available from the electronic health record **(**sex, age, primary insurance, primary language, marital status, comorbidity, # of PCP visits in prior 12 months, # of no show visits in prior 12 months), PCP characteristics (age, sex, specialty, board certification, session per week), and clinic characteristics (location, patient mix, staffing, communication and tracking protocols for abnormal cancer screening tests, screening for social determinants of health)

Analysis plan

Our primary analysis will be intention-to-treat (ITT). All eligible, enrolled patients will be part of the ITT cohort. We expect that a small number of patients may change primary care clinics within our systems. These individuals will be evaluated according to their initial intervention status. Prior to analysis, all data will be examined for accuracy, logical consistency and missing data. We expect complete data for intervention status and our outcomes. We will use multiple imputation, using the MI procedure in SAS, to account for any missing values of covariates. Through the stratified randomization we will attempt to balance patient, provider and practice characteristics between study groups. However, since randomization occurs at the practice level, we will be cautious and still compare the patient, provider and practice characteristics using Fisher exact tests, t-tests and Wilcoxon tests as appropriate to the covariate distribution. Any characteristics that show substantial clinical or statistical difference ($p<.05$) will be entered into the regression model and retained as covariates if they alter the effect estimate of the intervention by >20%.

The primary analysis model will be a random effects logistic regression, implemented through the SAS Glimmix procedure. Timely follow-up (yes/no) will be the patient-level outcome and random effects for practice and physician will allow for exchangeable correlation between patients seen within the same practice and by the same physician. The primary fixed predictors will be 3 indicator variables representing the 3 intervention arms and we will use a global likelihood ratio test to compare the 4 study arms. If the global test is significant ($p<0.05$), we will compare the intervention arms to the control group (our primary comparisons with a Bonferroni-adjusted significance level of 0.0167) and to each other (secondary comparisons). Comparisons to the control arm will capture the cumulative effects of the interventions, while comparisons between the intervention arms will capture the marginal effects of each level of intervention. We will include covariates for the type of cancer, level of initial screening abnormality, and any patient, provider or practice characteristics which are identified as confounders. Results will be presented as adjusted follow-up rates, with 95% confidence intervals, calculated using marginal standardization.

Secondary analyses will model time-to-follow-up, using a clustered proportional hazards regression to examine whether abnormal screens are followed-up as quickly as possible. Patient-level time-to-follow-up will be recorded with censoring at the end of study for patients who never received follow-up. Patients will be clustered within providers using the generalized estimating equation approach, implemented as a “frailty” analysis in the SAS Phreg procedure. An additional correlation component for patients within practices cannot be included, but we will evaluate the robustness of our findings by using an alternative model, clustering by

practice rather than provider. Predictors and covariates in this model will be identified in the same way as described above. The proportional hazards assumption for the intervention effects will be verified by entering a time-varying version of those predictors. Other secondary outcomes based on patient, provider and team surveys will use clustered linear regression models to compare satisfaction scores between study arms. Our secondary system outcome: the number of patient contacts; will be compared between arms using clustered Poisson regression. The model building will be analogous to the approach detailed above.

We will also consider several exploratory analyses. In particular, we will perform our primary and secondary analyses within each of the four types of cancer and by risk of cancer. Prior to any of these subgroup analyses, we will put the appropriate interaction terms into the primary models above. However, it was not practical to design this study to have sufficient power to pursue all of these possibilities. Instead, any "findings" in these secondary analyses will be considered as clues to be pursued in future studies and in alternative databases.

Finally, while it would be clinically important to pursue cancer detection rates, we will not do so here because we lack statistical power and because of the possibility that more cancers may be diagnosed in the intervention arms than the control arm because of higher follow-up rates with more diagnostic evaluations. We will not have long enough follow-up times to look at differences in cancer incidence related to inadequate follow-up. Instead we will perform descriptive analyses within each study arm to look at the number of incident cancers identified.

Power. Our goal to enroll 3324 patients, seen by 550 providers and randomized by 44 practices will provide 80% power to detect an 11-14% improvement in the follow-up rate for an intervention arm compared to our control arm. Although not powered for secondary subgroup analyses, we will also have 80% power for the intervention effects shown. Effects of IT interventions of this size have been seen in our past studies and are reasonable to expect,[35,37,67,78,83,101,105,106] and smaller effects would have minimal clinical importance. We have an adequate number of potential participants across our sites to achieve this sample size without including the insufficient group.

VII. RISKS AND DISCOMFORTS (Stratify by common and uncommon)

We believe that all of the risks described are uncommon. Potential risks to subjects include loss of confidentiality of healthcare data. Study staff will follow careful protocols to minimize these risks. The co-investigators will emphasize the importance of maintaining confidentiality in the training of all study staff. All study data and survey questionnaires will be coded with unique study identification numbers. Electronic data will be stored within the Partners and Dartmouth firewalls, will be password protected, and will be protected by anti-virus software. Only study staff will have access to study data on shared file areas.

Surveys may potentially cause psychological stress (topics will include barriers and facilitators to follow-up of screening abnormalities). Potential survey subjects will be informed about potential risks as part of the informational letter that they will receive before deciding whether to participate. Patients will be encouraged to discuss any concerns with their provider, prior to participating (all participants will have a PCP in this study). While unlikely, some patients may be contacted during the trial based upon inaccurate or incomplete information in her/his electronic health record. There may be psychological stress associated with such contact, but information provided by patients will be used to update the patient's record/ notify the patient's care team, thus ultimately resulting in better quality care. Study staff will specifically be trained to help patients cope with these issues. Study staff, particularly the outreach coordinators and the navigators, will be trained to specifically address any personal stressors that a patient may have that is interfering with their ability to get needed care. During the trial phase, patients are only indirectly affected through process of care modifications at the practices they attend. We do not anticipate physical risks to patients as a result of participation. Patients in the "control" arm will receive standard care as provided by their PCP and practice. Potential risks also include the time associated with survey participation for those selected. This time commitment will be minimal. Potential participants will be informed of the potential harms of participation when they decide whether to participate; participants will also be informed that they can decide to discontinue their participation at any time.

VIII. POTENTIAL BENEFITS

Participants in practices randomly assigned to the intervention arms may benefit by receiving more timely follow-up of their abnormal cancer screening test results. Patients in control practices will receive usual care under the direction of their primary care provider. If the intervention is effective, more timely follow-up of abnormal cancer screening test results could lead to earlier detection, treatment, and cure of the cancers studied in this proposal. In the future, all patients could benefit from the knowledge produced by this study through the dissemination of similar care systems.

IX. Data and Safety Monitoring (DSM) Plan

The PIs will be responsible for monitoring the safety and effectiveness of this trial, and complying with reporting requirements. The final protocol and all instruments will be reviewed by the Partners IRB, as this protocol involves patients who receive care at Partners (MGH and BWH) as well as Dartmouth. Dartmouth will be a relying site on the Partners IRB review that will be added in an amendment once the Partners protocol is approved.

Data monitoring plan

All data collection/ storage systems will be piloted before the study begins. Any patient data collected as part of the study itself will be stored electronically on secure, Partners or Dartmouth servers behind the institutional firewall with password protection and anti-virus software. Only study staff will have access to the study data on Shared File Areas. The PIs will be responsible for monitoring and assuring the validity and integrity of the data and adherence to the IRB-approved protocol.

Safety monitoring plan

The main safety risks for the study include the potential for psychological discomfort associated with the intervention. Though this should not differ among patients in intervention or control practices, those in intervention practices may receive more timely notification of an overdue abnormal test result and information about why it is important to complete recommended follow-up. The benefits of receiving timely follow-up of an abnormal cancer screening tests substantially outweigh this risk. We will monitor complaints received from patients and/or providers and notify the local IRB as required by local governance. The main risk of the study is unintended release of patient health information collected and maintained by the study investigators. As noted, we will apply rigorous data safety and monitoring standards to ensure that this does not occur.

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