Study Title: Lung Cancer Screening Eligibility Assessment

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Social and Behavioral Sciences Human Research Protocol

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PROTOCOL TITLE: Using a Simplified Tool to Predict Lung Cancer Screening (LCS) Eligibility

INTRODUCTION AND PURPOSE:
Despite growing evidence that lung cancer screening (LCS) reduces lung cancer-specific mortality, LCS across the United States and at Penn Medicine is remarkably low. This is due in part to challenges with identifying adults who meet eligibility criteria for lifetime smoking intensity (i.e., 20 pack-years or greater), which is often missing from the electronic medical record. The primary purpose of this nudge study is to test the feasibility and reliability of using three yes/no questions (i.e., the simplified eligibility tool) for predicting pack-year eligibility for LCS. If successful, we intend on using this approach in future trials as a tool to identify LCS-eligible patients and increase LCS.

OBJECTIVES:
The overarching goal of this project is to increase LCS by developing scalable and equitable strategies for identifying screening-eligible patients across Penn Medicine. We seek to achieve this goal through the following interrelated objectives:

- Objective 1. Assess feasibility of using patient-directed outreach to complete the simplified eligibility tool.
- Objective 2: Explore how recruitment messaging content and incentives impact response rates to the survey.

If successful, we intend to use this tool and the results of this study in future intervention trials designed to increase shared decision-making and uptake of LCS. We will also share this tool widely to support equitable LCS uptake across diverse patients and settings. All future trials will be submitted for separate IRB approval.

BACKGROUND:
A growing body of evidence indicates that lung cancer screening (LCS) for high-risk adults reduces lung-cancer mortality by 16-20%.[1] Despite this evidence, uptake of LCS in the United States remains suboptimal (~5% national completion rate in screening-eligible adults).[2] Additionally, there are disparities in uptake by race, sex, and other key social determinants of health, reflective of the challenges of implementing LCS equitably.[3]

LCS differs from other types of population-level cancer screening because eligibility assessment requires evaluation of lifetime smoking intensity, calculated by multiplying the average number of packs of cigarettes smoked per day by total years a person smoked (i.e., pack-years).[4] While tobacco use (i.e., current, former, never) is well captured in electronic medical records (EMR), pack-years is often missing, highlighting the need for interventions focused specifically on this component of LCS-eligibility assessment.[5] Prior approaches to assessing pack-years have used open-ended questions, which in comparison to other question formats (e.g., yes/no) is associated with increased respondent burden and lower response rates.[6] As such, we seek to develop and test the feasibility and reliability of using brief yes/no questions (“simplified eligibility tool”) for predicting 20+ pack-year eligibility for LCS. This approach has shown high positive predictive value (90.5%) in our pilot study with 303 patients, and we are now looking to test the approach in a larger and more diverse sample of adult patients at Penn Medicine. This work will also help to support future pragmatic studies aiming to test strategies to increase lung cancer screening in eligible adults.

CHARACTERISTICS OF THE STUDY POPULATION:

1. Target Population and Accrual:
The target population includes primary care patients at Penn Medicine who are potentially eligible for LCS based on age (50-80 years old) or tobacco use (currently smoked or smoked within the last 15 years) but have never been screened for nor diagnosed with lung cancer. Currently, we cannot assess full LCS-eligibility of these patients because most (70% or greater) have no information regarding pack-years in their electronic medical record (EMR); thus, limiting our ability to assess true uptake of LCS in eligible patients and missing an opportunity

to reduce lung cancer mortality in our patients. Given the population health focus, we aim to include all patients who meet study eligibility at Penn Medicine, which we estimate will be approximately 6,125 patients across the study timeline. Patients will accrue as identified in the electronic health record (EHR) throughout the study duration and contacted in batches to monitor enrollment response and address any unintended negative impacts on patients or providers that may arise.

2. Key Inclusion Criteria:
Based on available EMR data, patients will be eligible if they:

a) meet age eligibility (50-80 years old) for LCS based on 2021 USPSTF guidelines; and
b) have completed at least one primary care visit at Penn Medicine in 2020-2025

3. Key Exclusion Criteria:
Based on available EHR data, patients will be ineligible if they:

a) have a documented history of lung cancer;
b) have a documented history of completing LCS at Penn Medicine;
c) are listed as not wanting to be contacted or solicited for research; or
d) do not otherwise meet inclusion criteria.

4. Subject Recruitment and Screening:
We are requesting a waiver of HIPAA authorization to use EHR data to identify potential patient participants who meet study inclusion criteria. To ensure equity in reach, we will use a concurrent and multimodal approach to contacting and recruiting patients. Specifically, all patients with active mobile phones will be contacted first by text message with an invitation to complete the simplified eligibility tool (i.e., yes/no questions included in the protocol) using Way-to-Health. The initial text message will also include an option to “opt-out” of future text messaging or outreach related to the study. Patients who do not respond to text message outreach within one week will be sent a letter delivered via email, patient portal, and/or post (depending on availability of contact information in the EHR or patient portal activation and use). All recruitment materials are included in this application. We will contact patients no more than five times total, regardless of type of outreach (i.e., text, email, post, or portal).

5. Early Withdrawal of Subjects:
Patients can choose not to participate at any time. Participants will be given the option to “opt-out” from future study-related contact via text message or withdraw by contacting the study coordinator (phone and email information included in the recruitment letter).

6. Vulnerable Populations:
Because they are not likely to meet eligibility for LCS, children, pregnant women, fetuses, and neonates are not included in this research study. Prisoners are also not included in this study because they are unlikely to be Penn Medicine patients while incarcerated.

7. Populations vulnerable to undue influence or coercion:
Although we are not specifically targeting Penn Medicine employees, it is possible that a portion of eligible patients will also be employees. However, we will not assess nor share any information related to employer name to avoid undue influence or coercion.

STUDY DESIGN:
We will use a phased, cross-sectional approach to collect patient-reported information related to lifetime smoking history. We will assess correlation between self-reported data with smoking data (i.e., pack-years) in the subset of patients with pack-years documented in their EHR. The overall goal of this study is to develop scalable strategies for increasing identification of patients who meet 20 pack-year eligibility for LCS. The questions used in this study have been pilot tested with a smaller group of 303 patients and shown high positive predictive value (90.5%). We are now seeking to expand upon these results and apply to a larger group of patients to assess population-level reliability and eligibility assessment for LCS (Objective 1). In addition to advancing the development of a screening eligibility tool that can be applied across healthcare systems, we will use the results of the study to identify participants for future intervention trials seeking to improve LCS at Penn Medicine.

The duration of the study will be approximately 2 years, which will give sufficient time to collect patient-reported data and analyze reliability in relationship to medical record data. The research will be conducted in the Department of Family Medicine & Community Health and include all patients that meet eligibility criteria. The data collection and analysis will be conducted by trained clinical coordinators and data analysts within the PI's team that have experience with clinical trials in this context at Penn. The expected duration of active subject participation is less than 30 minutes (likely 5-10 minutes).

METHODS:

1. Study Instruments:
Participants will be asked to complete three survey questions that have been previously assessed to predict pack-year eligibility of LCS using a yes/no format. We are using a yes/no format because it reduces cognitive burden on survey respondents and therefore believe it is a more equitable approach to assessing pack-years. The survey questions are as follows and all have the same response options (Yes/No):

1. If you add up all the years when you regularly smoked cigarettes, have you smoked for 20 years or more of your life?
2. At any time in your life, did you ever regularly smoke one or more pack(s) of cigarettes per day?
3. Have you ever smoked cigarettes in the last 15 years?

2. Group Modifications:
For patients for which their primary language is listed as Spanish in the EHR, we will translate and send all study information in Spanish.

3. Method for Assigning Subjects to Groups: Randomization
The primary survey questions will not change regardless of study group. However, to enhance response, we will iteratively test how recruitment messages and offering remuneration for completing the survey impacts survey response. Specifically, we intend to randomly assign patients to one of 12 different message groups, half of which will include an incentive for completing the survey. The different groups will have slightly different introductory messaging (see recruitment materials for full messages) and we will compare survey response rates between approaches. During the study, we will review response rates and may adapt assignment to be aligned with the most effective and equitable approaches. This is meant to be exploratory and secondary to the primary aims of the study. See the include statistical analysis plan for updated information on this.

4. Administration of Surveys and/or Process:
Participants with a mobile phone listed in their medical record will be asked to complete the survey questions via text message. The questions will all be yes/no and asked in a sequence of text messages. Participants will be given the option to opt-out of participation, in addition to being provided with a phone number if they would prefer to answer the questions via telephone. Participants will be contacted via text message up to 2 times (approximately 1 week apart). Participants who do not decline further contact and do not respond to text message will be sent a recruitment letter via post, email, or portal as noted below.

Participants contacted via recruitment letter (email, patient portal, and/or post) will be asked to complete the survey using HIPAA-compliant REDCap, or by phone if preferred. The participants will be provided with a unique link to REDCap, whereby they will be asked to answer the survey questions. Patients will also be given a phone number to reach study team members if they would like to complete the survey on the phone, in addition to a mailing address if they prefer to answer the questions via mail (stamped return envelope included). Participants will be sent up to three reminders via email and given the option of opt-out of further contact by phone or email.

For recruitment letter and text message, the survey questions will be the same (described in Study Instruments).

5. Data Management:
To ensure the privacy and confidentiality of clinical data, we will only store and use identifiable data on password-protected computers connected to the UPHS server. All study materials will be tracked with a unique participant ID and the study key will remain in a password-protected REDCap data form, accessible only by the PI and approved study staff. Data files will be kept in a secure area and destroyed according to UPenn IRB timelines.

The PI and select research staff will have access to these data. Computers connected to UPHS are highly secure and are required to comply with all HIPAA requirements. These computers are more secure than other computers at UPenn and thus will be the only ones where identifiable data are kept. Access to any participant data will be limited to the PI, Co-Is, and authorized study staff. All study team members will demonstrate completion of HIPAA training and will abide by the security procedures enforced at UPHS. All output containing individual identifiable information will be treated as confidential data. This information will never be transferred electronically via email or other pathways, never be included in analytic datasets, and will not be reported outside the study team.

7. Subject Follow-up:
To explore impact of outreach, we will collect patient data in the EMR related to lung cancer screening and prevention (e.g., completed LCS, referral to tobacco cessation clinic) for up to 24 months after enrollment. All EMR data have been collected previously for non-research purposes (through clinical care) and thus, we are requesting a waiver of HIPAA authorization (see below).

STUDY PROCEDURES:

1. Detailed Description:
Potential participants will be identified using EMR data as noted above. We will first assess available contact information (i.e., email, mobile phone, and patient portal use) to identify if the patients will first be contacted via text message (if mobile phone listed in EMR), email (if email or patient portal use listed in the EMR), or post (if no mobile or email is listed in EMR). Then we will follow recruitment and administration of survey processes as noted above. All follow-up data will be collected using EMR data for up to 24 months.

2. Data Collection:
As part of our existing IRB-approved study (Protocol #830184), we have identified patients at Penn who meet age eligibility for LCS and extracted retrospective PHI and clinical data needed for this study. Thus, this study will not require retrospective extraction of data. However, we are requesting that data for prospective identification of new patients (2023-2025) and their clinical data (e.g., smoking data, LCS uptake) be collected as part of this protocol. We will use similar methods including data management and safety protocol as have been used successfully in this prior protocol. Patient-reported data (i.e., screening eligibility tool) will be collected using text message or secure survey platforms (i.e., REDCap).

3. Genetic Testing:
Not applicable

4. Use of Deception:
Not applicable

5. Statistical Analysis:
We will summarize data using descriptive statistics to assess recruitment response by age, race/ethnicity, and other key patient demographics (Objective 1). For patients who complete the screening tool and who have pack-year information documented in their medical record (anticipate ~20-30% based on prior work), we will explore the reliability of the screening tool (i.e., survey questions) to predict 20 pack-year eligibility for LCS. We will calculate the positive and negative predictive value, sensitivity, and specificity of the screening tool overall and by race, sex, and age group to assess equity. As exploratory analyses, we will use descriptive statistics and logistic regression to evaluate overall uptake of LCS in patients who complete the screening tool and assess relationships between patient characteristics (e.g., age, sex, race), smoking history, and LCS completion. For Objective 2, we have outlined our statistical analysis (see attached).

The long-term objective of this study is to increase pack-year eligibility at the population level and thus we will include all patients who meet age eligibility for LCS. Additionally, prior studies have indicated that survey response rates using are likely to be <30%, and thus including a large sample of patients will enable us adequate sample to assess reliability of the screening tool overall and within important subgroups (e.g., females and Black adults) where there are concerns regarding LCS uptake inequities.

RISK/BENEFIT ASSESSMENT:

1. Risks:
Potential risks to participating in this study are minimal and primarily include potential violation of confidentiality or privacy.

2. Benefits:
There are no direct benefits to participating in this study. If successful, this approach will be used to identify and enroll patients likely to be eligible for LCS in trials seeking to increase LCS through patient outreach. This approach will also be disseminated to other systems looking to increase uptake and equity of LCS in routine practice, adding to potential societal benefits.

3. Subject Privacy:
Being asked to disclose information about smoking history could be viewed by some patients as a violation of privacy. As such, no patient will be required or forced to answer questions to ensure subject privacy is protected.

4. Subject Confidentiality:

How will confidentiality of data be maintained? Check all that apply.

☒ Paper-based records will be kept in a secure location and only be accessible to personnel involved in the study.
☒ Computer-based files will only be made available to personnel involved in the study through the use of access privileges and passwords.
☐ Prior to access to any study-related information, personnel will be required to sign statements agreeing to protect the security and confidentiality of identifiable information.
☒ Whenever feasible, identifiers will be removed from study-related information.
☐ A Certificate of Confidentiality will be obtained because the research could place the subject at risk of criminal or civil liability or cause damage to the subject's financial standing, employability, or liability.
☒ A waiver of documentation of consent is being requested because the only link between the subject and the study would be the consent document and the primary risk is a breach of confidentiality. (This is not an option for FDA-regulated research.)
☒ Precautions are in place to ensure the data is secure by using passwords and encryption, because the research involves web-based surveys.
☐ Audio and/or video recordings will be transcribed and then destroyed to eliminate audible identification of subjects.
☐ Other (specify):

No identifying information will be shared outside of the study team, unless mandated by federal or state law. All identifying information will be removed from the analytic data set prior to analysis. Data will be securely retained and managed by the PI to support manuscripts, analysis, or future research after study completion. However, any use of data for future research outside of the scope of this study will be reviewed by IRB prior to use. Potential future research may include for example use of data for recruiting participants for studies related to LCS.

5. Protected Health Information
For recruitment purposes, the following protected health information (PHI) will be requested from the Penn EHR:

- Name, address, phone, email (for recruitment purposes)
- All elements of dates
- Medical record numbers

We are requesting dates to be able to correctly determine age and years smoked at the time of recruitment. We are also requesting medical record numbers (MRNs) to be able to track participants longitudinally to assess LCS uptake in eligible patients. Prior to analysis, the PI will transform PHI data into deidentified variables (e.g., date will be transformed into length of time from index date, and MRNs will be transformed into a unique study ID). Once deidentified, the PI will remove all PHI from the analytic dataset.

6. Compensation:

As part of our plan to test the impact of different message content on survey response, we will randomize approximately one-half of participants to be offered an incentive to complete the survey. Of these, the first 1,000 participants who complete the survey will be entered to randomly win one of 100 $50 gift cards (delivered using Clincards). All other participants will not be offered compensation for completing the survey.

7. Data and Safety Monitoring: As a minimal risk study, data and safety will be monitored on an ongoing basis by the PIs and the study team. If an adverse event or data breach is reported, the PI in collaboration with Dr. Vachani and Dr. Bekelman will evaluate the grade and relationship to the study and ensure appropriate course of action is taken and documented. The PI is ultimately responsible for reporting to the IRB and other regulatory bodies as required by Penn policies.

8. Investigator's Risk/Benefit Assessment:
The potential benefits of this study are great and include providing necessary data to understand rates of LCS in our patient population and support future studies looking to increase uptake in patients who are eligible for LCS. Given the very low rate of uptake of LCS at Penn and nationally, if proven to be successful, this study could have a significant positive impact on preventive care across healthcare systems. These potential benefits outweigh the very minimal risks, which include potential loss of privacy and confidentiality. Given the potential benefits and included protections against risk, the risks of participation do not exceed the potential benefit.

INFORMED CONSENT:

1. Consent Process:
Because this study is a nudge study that will be utilizing text message to deliver the survey, we are requesting a waiver of consent. This is justified because the recruitment involves no more than minimal risk to the subjects. The waiver will not adversely affect the rights and welfare of participants as the data are being collected as part of routine care, and care will not be directly impacted based on analysis. Lastly, given the population-level focus of the project, we aim to recruit approximately 6,125 people, and thus it would place great burden on participants to undergo a consent process for routinely collected data. All identifying information will be kept on secure UPHS servers and removed from all analytic datasets.

Waiver of HIPAA authorization:

For purposes of recruitment and linkage of survey data to EMR data, we are requesting a waiver of HIPAA authorization. This clinical trial meets the three criteria for a waiver of HIPAA authorization in accordance with the provisions for using protected health information (PHI) set forth in 45 CFR 46, § 164.512 (i) as follows: (1) the researchers require access to protected health information (PHI) in order to conduct the research, (2) The research cannot be practicably conducted without the waiver, and (3) the use or disclosure of PHI poses no more than minimal risk to participants. A request for Waiver of HIPAA form has been included in this protocol application.

RESOURCES NECESSARY FOR HUMAN RESEARCH PROTECTION:
The project is funded by an award from the National Cancer Institute. Our interdisciplinary team at the University of Pennsylvania includes investigators with distinguished records in implementation science, cancer care delivery, epidemiology, behavioral economics, pragmatic trials, EMR-based strategies, lung cancer screening, and mixed-methods research. The project will be led by Katharine Rendle, PhD, MSW, MPH, an interdisciplinary behavioral scientist specializing in cancer care delivery and implementation science research. Given the established clinical relationships with UPHS, we have access to necessary Epic data to identify patients and anticipate that research activities will be possible within the proposed timeline. Given the scope of the project and existing resources, we contend there is both sufficient time and adequate facilities to conduct the proposed research.