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Characterizing Patient Adherence to Lung Cancer Screening Guidelines

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Characterizing Patient Adherence to Lung Cancer Screening Guidelines

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by

Yannan Lin

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ABSTRACT OF THE DISSERTATION

Characterizing Patient Adherence to Lung Cancer Screening Guidelines

by

Yannan Lin

Doctor of Philosophy in Bioengineering

University of California, Los Angeles, 2023

Professor Denise R Aberle, Co-Chair

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Lung cancer is the leading cause of cancer-related death in both sexes. Large, randomized clinical trials have demonstrated that low-dose computed tomography screening reduces mortality from lung cancer, as opposed to chest X-ray or no screening, when participants adhere to follow-up recommendations. However, low adherence rates in post-trial clinical lung cancer screening (LCS) programs have been reported across the United States (US). Low adherence to LCS in real-world clinical practice diminishes the mortality benefit of annual screening derived from clinical trials. Thus far, limited studies have examined factors affecting the patient's decision (not) to adhere to screening guidelines. This dissertation examines the factors that may predict patient non-adherence to LCS recommendations. First, we performed a systematic review and meta-analysis of 24 studies published between 2014 and 2020 that mentioned adherence to Lung-RADS recommendations, identifying factors contributing to adherence rates. Second, using the Carter-Harris conceptual

model, which enumerates psychosocial variables (e.g., smoking stigma, cancer fear, cancer fatalism) related to LCS participation and adherence, we examined these variables' availability and completeness in our medical records. Next, using a subset of variables where data were consistently available, we identified factors of non-adherence over multiple screening time points using logistic regression and mixed effects models. Lastly, we used statistical and machine learning-based methods to examine how well we could predict patient non-adherence using longitudinal data across three screening time points. This dissertation advances our understanding of factors contributing to patient non-adherence to LCS recommendations. It provides a basis for identifying patient groups that could benefit from individualized interventions to improve LCS adherence.

The dissertation of Yannan Lin is approved.

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2023

In loving memory of my grandmother, 马淑庭.

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CHAPTER 1

Introduction

1.1 Motivation

Lung cancer is the leading cause of cancer-related death in males and females in the United States (US).[1] Large, randomized clinical trials have demonstrated mortality benefits using low-dose computed tomography (LDCT) screening for lung cancer relative to chest x-rays or no screening.[2, 3] Notably, the adherence rates in the clinical trials were 90% to 95% across three rounds of screening. In 2015, the Centers for Medicare & Medicaid Services (CMS) issued a national coverage decision of screening for lung cancer with LDCT among eligible participants.[4] These actions have led to the implementation of clinical programs that utilize LDCTs for lung cancer screening (LCS) in the US.

Lung CT Screening Reporting & Data System (Lung-RADS®) is a quality assurance tool developed by the American College of Radiology to standardize reporting of LCS LDCT results and corresponding management recommendations[5]. Recommendations include an annual incidence screen for Lung-RADS 1 or 2 and a short-term interval examination for Lung-RADS 3 or 4 (e.g., chest CT, positron emission tomography (PET)/CT, tissue sampling). While the clinical trials have demonstrated mortality benefits with high patient adherence, current evidence has shown that adherence rates to Lung-RADS recommendations across clinical LCS programs varied from 25% to 59%. [6-11] To date, the literature lacks systematic evidence on factors contributing to the heterogeneous and suboptimal adherence to Lung-RADS recommendations across LCS programs in the US. Such evidence can guide the implementation of quality improvement measures with the goal of increasing rates of adherence.

Barriers to cancer screening involve factors at multiple levels.[12-16] At the patient level are psychological barriers such as denial, fear, and stigmatization; lack of education about cancer and cancer screening; lack of access to health care; and the quality of patient-provider communication. Provider-level barriers include limited knowledge about screening guidelines, ongoing skepticism about screening benefits, stigmatization of smokers, and insufficient time for shared decision-making, which is required for reimbursement by Medicare and Medicaid. Systemic barriers include lack of insurance coverage, access to care, and repeated healthcare visits. While these barriers have been examined in longstanding population-based programs such as breast cancer screening, LCS screening is in its nascent stage in the US[6, 17-19], and its barriers have not been thoroughly examined. Carter-Harris et al. proposed a conceptual model for lung cancer participation as a theoretical basis for research.[20] This conceptual model consists of five categories of screening participation and adherence antecedents, including psychological variables, demographic and health status characteristics, cognitive variables, healthcare provider recommendation, and social and environmental variables (social influence, media exposure). Although the Carter-Harris conceptual model lists variables that need to be collected to understand which factors drive non-adherence to LCS, it does not specify how to measure these variables from the data sources. Electronic medical records (EHR) are one of the common data sources to examine the predictive value of these variables. However, the level of completeness of the antecedent variables in the EHR remains unknown.

Studies from post-trial LCS programs suggest that patient demographic characteristics such as age at baseline screening exam, baseline Lung-RADS scores, and hiring an LCS program coordinator influence patient non-adherence to LCS.[7-11] However, the value of other demographic and health-related variables in predicting non-adherence has yet to be examined. These analyses are

important for understanding the factors of non-adherence that can form the basis for individualized intervention.

1.2 Contributions

This dissertation advances our understanding of patient-level factors contributing to LCS non-adherence and establishes approaches to aid in the identification of patients at high risk of non-adherence across multiple screening time points by fulfilling the following three aims:

- Aim 1: To examine the differences in patient adherence to LCS across multiple settings in the US. The hypothesis was that observed heterogeneous adherence rates across studies are associated with differences in Lung-RADS scores of the study population, patient demographics, and institutional settings. To investigate this, I conducted a systematic review and meta-analysis of the literature on adherence to LCS. First, I created descriptive qualitative summaries of study characteristics, adherence rates in specified Lung-RADS categories, and predictors of LCS non-adherence from studies that fit defined inclusion criteria. Next, I performed pooled analyses of adherence rates and subgroup analyses on demographic characteristics, including sex, race, ethnicity, and smoking status, when available. Third, I used meta-regression to determine the drivers of the heterogeneous adherence rates at the study level, such as institutional settings and baseline Lung-RADS scores.
- Aim 2: To identify data elements in the EHR that are predictors of non-adherence to LCS. Hypothesis: Predictors of non-adherence to LCS described in the Carter-Harris conceptual model are consistently captured in the EHR, controlled terminologies, or common data elements. Using the Carter-Harris conceptual model for LCS participation and adherence, I investigated whether the antecedent variables (i.e., demographics, health status characteristics,

psychological and cognitive variables, healthcare provider recommendations, and social and environmental variables) are standardized in existing vocabularies and whether these variables are readily available in the EHR.

- Aim 3: To evaluate models to predict adherence to baseline and follow-up recommendations. I hypothesized that patient non-adherence to LCS can be accurately predicted using data (e.g., demographic, socioeconomic, health status, etc.) from the EHR. To investigate whether changes in Lung-RADS scores affect adherence and, thus, should be accounted for in the prediction models, I evaluated the hypothesis that adherence increases/decreases as Lung-RADS scores upgrade/downgrade and whether adherence is stable when Lung-RADS scores remain unchanged. Using statistical and machine learning techniques, I explored three approaches to predict the likelihood of LCS non-adherence at each screen time point. This work assessed the extent of using routinely collected data in the EHR to predict non-adherence over time.

1.3 Organization

The remaining chapters of this dissertation are organized as follows:

- Chapter 2 reviews patient adherence in non-lung (e.g., breast, colorectal, etc.) cancer screening domains and discusses potential challenges in maintaining patient adherence to LCS.
- Chapter 3 presents a systematic review and meta-analysis of patient adherence to Lung-RADS recommendations in clinical LCS programs in the US, investigating the potential causes of heterogeneity in adherence rates using subgroup analysis and meta-regression.
- Chapter 4 describes the LCS cohort at UCLA and data availability of potential factors affecting LCS adherence.

- Chapter 5 identifies predictors of non-adherence to baseline Lung-RADS recommendations and evaluates their performance in identifying patients who are non-adherent to LCS recommendations.
- Chapter 6 compares three different machine learning techniques to predict patient longitudinal adherence to LCS.
- Chapter 7 summarizes the findings and contributions from this dissertation and provides future directions to build upon this work to serve the goal of improving patient adherence to LCS.

CHAPTER 2

Background

This chapter provides an overview of the adherence problem in cancer screening. We first discuss two questions in cancer screening adherence (i.e., screening participation and compliance to cancer screening guidelines), followed by a discussion on adherence to screening guidelines in breast, cervical, and colorectal cancer screening. The subsequent sections of this chapter specifically focus on LCS and some challenges in maintaining adherence to LCS. The chapter ends with a summary of barriers to cancer screening.

2.1 Cancer Screening

Due to advancing age, the growth of the world population, and the persistence of cancer-related behaviors (e.g., smoking), the global burden of cancer continues to increase.[21] Cancer screening is the process of checking for cancer or abnormal cells that may become cancer in symptom-free individuals.[22] Techniques used in cancer screening are tailored for each type of cancer, such as LDCT for LCS and mammography, breast ultrasound, or breast magnetic resonance imaging (MRI) for breast cancer screening. While screening is associated with mortality benefits, it also carries certain risks, including overdiagnosis and overtreatment.[22] Therefore, it is important that the individual make an informed decision about cancer screening participation after discussing the benefits and harms of screening with the healthcare provider (i.e., shared decision-making).

2.2 Utilization vs. Adherence

In the literature, researchers often refer to adherence to cancer screening in two ways, 1) cancer screening utilization and 2) adherence or compliance to cancer screening recommendations.

The former asks the question about screening uptake, i.e., first-time screening after becoming eligible to screen.[23] For example, the LCS participation rate in the US until 2021 was, on average, 6% across all states among high-risk individuals.[24] The second metric concentrates on whether the individual follows the cancer screening recommendations after each screening examination. For instance, the BI-RADS score is a reporting system used to describe the results and follow-up recommendations on breast cancer screening mammography, ultrasound, or MRI report. The recommendation for BI-RADS 1 is to continue routine screening.[25] The screening participant is considered adherent if she can complete the next breast screening examination within a specific time frame based on age and risk for breast cancer. Similarly, the Lung-RADS reporting system is used to standardize LDCT screening findings and management recommendations.[26] For Lung-RADS 1, the individual is adherent if he/she completes the next annual incidence LDCT within 12 months (usually including a grace period) from the current LDCT.

Screening utilization and guideline adherence are equally important in cancer prevention. With respect to screen-eligible high-risk individuals, failing to participate in cancer screening or failing to complete a recommended follow-up examination after a screen may delay cancer diagnosis, therefore, leading to worse patient outcomes such as unfavorable survival. In Chapters 3 to 6 of this dissertation, the focus is on patient adherence to cancer screening recommendations; and on improving adherence by determining factors associated with non-adherence to Lung-RADS recommendations. Although screening uptake is not studied in this dissertation, future research is necessary to identify barriers to cancer screening participation such that the benefits of screening can be maximized in the appropriate high-risk populations.

2.3 Adherence to Other Screening Programs in the US

2.2.1 Breast Cancer Screening

Breast cancer is the most common type of cancer among females globally.[27] In the 1980s and 1990s, most organizations that issued recommendations endorsed regular mammography as an essential part of preventive care because screen-detected breast cancers were associated with reduced morbidity and mortality.[28, 29] In 1996, the United States Preventive Services Task Force (USPSTF) issued a Grade A recommendation that women aged 50 to 69 receive screening for breast cancer every 1 to 2 years using mammography alone or mammography and annual clinical breast examination.[30] The most recent guideline in 2016 recommended biennial screening mammography for women 50 to 74 years of age (Grade B). Data from the National Health Survey shows that breast cancer screening rates in the United States increased between 1987 and 1998. During this period, women aged 50-74 years who received a mammogram within two years increased from 36% in 1987 to 72% in 1998 (see **Fig. 2.1**). Beginning in 1998, breast cancer screening rates stabilized. In 2019, the rate rose to 76.4%, with a targeted increase to 77.1% in 11 years by the Healthy People 2030 Target, where the Healthy People Objectives are science-based, 10-year national objectives created to improve the health of all Americans.[31]

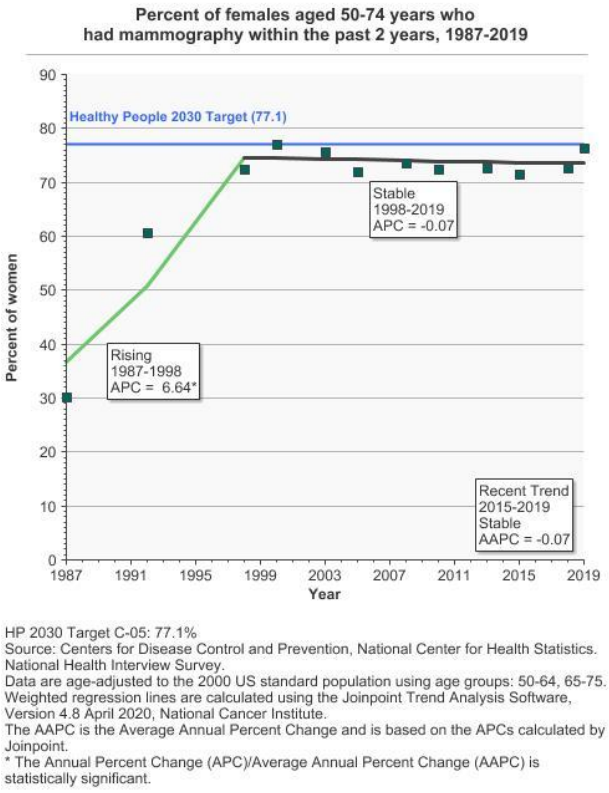

Fig. 2.1 Percent of females aged 50-74 who had mammography within the past two years, 1987-2019. HP: Health People. Source: https://progressreport.cancer.gov/detection/breast_cancer

Over the years, efforts have been undertaken to attain high mammography use. Interventions in the 80s and 90s contributed considerably to today's high breast cancer screening rate (i.e., the rising phase in **Fig. 2.1**). Earlier national-wise efforts included 1) expanded media coverage, national and local information efforts and screening programs to promote mammography[32], 2) increased physician referral[33], 3) informing females that the radiation from a mammogram is negligible, and thus, should not deter them from receiving regular mammograms[32], and 4) reducing the cost of mammograms by local efforts and by legislation in an increasing number of states[34]. Be-

sides 29 states requiring insurance companies to provide some level of coverage for mammography by July 1990[32], Medicare Part B first covered mammography in 1991.[35] Later on, CDC launched the National Breast and Cervical Cancer Early Detection Program (NBCCEDP) in 1991 to develop comprehensive programs for the early detection of breast and cervical cancers, directed toward women aged 40 years or greater and to women who have low incomes, are underinsured or uninsured, or are from racial/ethnic minority groups.[36] In 1992 and 1993, this act resulted in 1) substantial increases in the number of screening sites in 12 states (1305 screening sites during 1992 vs. 575 in 1991), 2) the implementation of 2900 public education programs to motivate women to seek screening services, 3) ~300 training programs for health-care providers, and 4) collaborations to plan, implement, and evaluate these programs as well as to establish or modify of cancer-control plans to address breast and cervical cancers.[36] NBCCEDP has funded 70 programs as of 2021, providing breast and cervical cancer screening services to approximately 6.1 million women.[37]

An earlier study by Clark et al.[38] reported the average weighted rates of repeating mammography between was 46.1% (confidence interval: 39.4%, 52.8%) from 1990 to 2001. From 1998 to 2008, studies have reported that adherence to baseline mammography (i.e., one on-schedule repeat screen after the initial mammogram) was between 24% and 81.5% in some NBCCEDP programs.[39-42] In non-NBCCEDP-funded programs, the longitudinal adherence rates to mammography (i.e., long-term on-schedule repeat mammograms) were 42%-85%.[43-46] Previous studies have found the following interventions effective in improving repeat mammography adherence, timely telephone communication to schedule diagnostic follow-up examinations[47], providing in-

person education about breast cancer and the benefits of screening mammography[48], sending mammogram-specific reminder letters[49], and using tailored telephone counseling and print[50] or automated telephone reminders[51], etc.

2.2.2 Cervical Cancer Screening

Aside from breast cancer, cervical cancer is one of the most commonly diagnosed cancers among females.[27] Screening for cervical cancer was part of the regular checkup before the 1980s without specification of age as recommended by the American Cancer Society (ACS).[29] Between 1980 and 1987, the ACS recommended 1) a yearly Papanicolaou (Pap) test for women 20 and over (under 20 if sexually active) but after two negative examinations one year apart, at least every three years; 2) a pelvic exam for 20 to 39 every three years and yearly pelvic exam for 40 and over.[29] The recommendation has been updated over years of evaluation on the benefits of screening. The most recent USPSTF recommendation for cervical cancer screening is every three years with cervical cytology alone in women aged 21 to 29 years, every three years with cervical cytology alone, every five years with high-risk human papillomavirus (hrHPV) testing alone, or every five years with hrHPV testing in combination with cytology in women aged 30 to 65 years.[52] The percentage of females aged 21-65 years who were up-to-date with cervical cancer screening was relatively stable and high between 1987 and 2019.[52] Although there was a small decline from 2000 to 2019, the rate was consistently over 70% and even surpassed the Healthy People 2030 Target of 84% between 1998 and 2003. Besides, over 70% rates of participant adherence to cervical cancer screening guidelines were reported in previous studies. [53, 54]

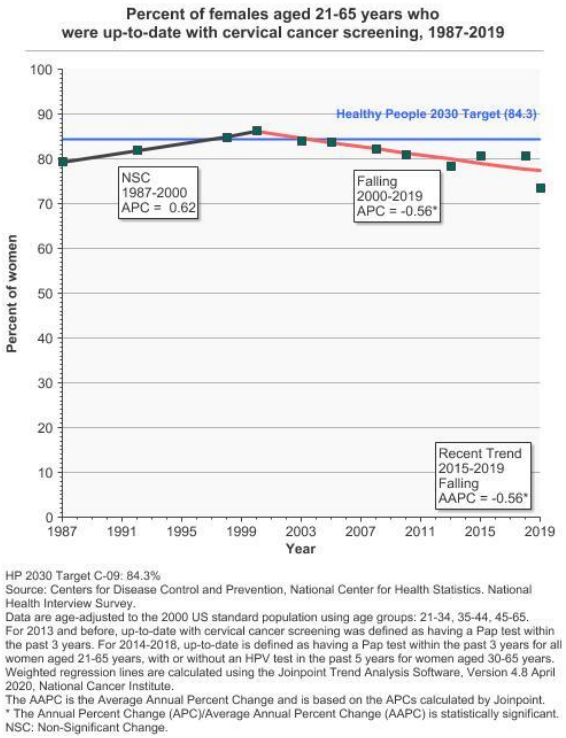

Fig. 2.2 Percent of females aged 21-65 who were up-to-date with cervical cancer screening, 1987-2019. HP: Health People. Source: https://progressreport.cancer.gov/detection/cervical_cancer

To encourage more eligible women to participate in cervical cancer screening, Pap smears were first covered by Medicare (Plan B) coverage in 1989, and the copay was waived beginning January 1, 2011, as a result of the Affordable Care Act.[35] Furthermore, government-funded cancer control programs helped secure the high cervical cancer screening rate, such as the NBCCEDP (see Section 2.2.1 for details). In an NBCCEDP-funded program, the adherence rates to follow-up recommendations after an abnormal Pap smear test ranged from 62% to 95% depending on the defined time interval of adherence (e.g., adhered in 60 days or 365 days).[55] Another NBCCEDP-funded program reported that the adherence rate to follow-up recommendations after two abnormal Pap results was 72.3% (44% colposcopy and 28.3% repeat Pap) among 10,004 women.[56] In a

larger NBCCEDP-funded program involving 45,049 abnormal Pap results, 62.8 % were followed with an HPV test, 8.6 % with a repeat Pap test within 15 months, and 14.6 % with a colposcopy.[57] A number of strategies have been successful in improving follow-up to abnormal pap smears, including telephone counseling, personalized follow-up reminders, physician reminders, educational programs such as a slide-tape program on pap smears, and economic incentives such as transportation incentives. [58-61]

2.2.3 Colorectal Cancer Screening

Colorectal cancer is one of the most common cancers in both sexes.[27] Before the 1980s, the screening recommendation for colorectal cancer was a regular checkup for adults aged 40 years and over.[29] Between 1980 and 1989, the ACS recommended yearly digital rectal exam (DRE) for individuals aged 40 and over, yearly fecal occult blood test (FOBT) for 50 and over, and proctosigmoidoscopy for 50 and over (frequency: after two normal exams one year apart, every 3 to 5 years).[29] Also, in 1996, the USPSTF issued the first recommendation for colorectal cancer screening for all persons aged 50 or over.[62] The recommendation was then updated in 2002, 2008, 2016, and 2021. The 2021 version recommends colorectal cancer screening for adults 50 to 75 years, Grade A, and for adults aged 45 to 49 years, Grade B.[63] The percentage of adults aged 50-75 years who were up-to-date with colorectal cancer screening has been rising since 2000, increasing from 38% in 2000 to 67% in 2019.[64] However, there is still room for improvement to reach the Healthy People 2030 Target of 74%.

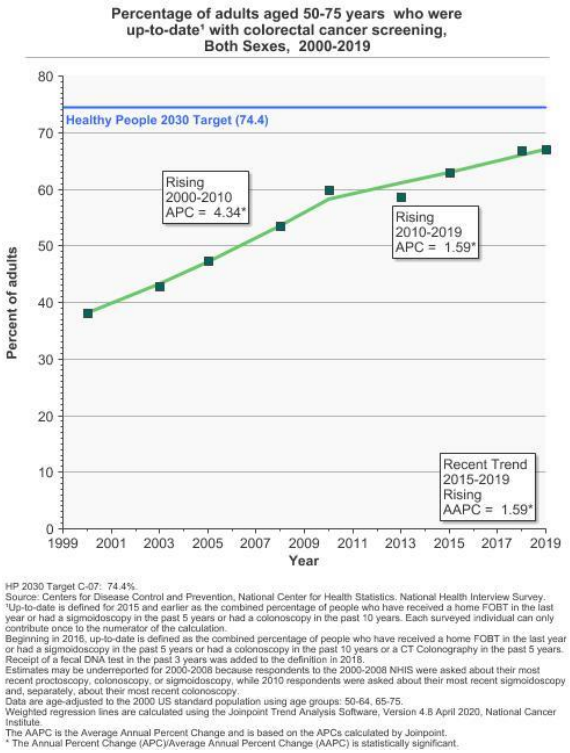

Fig. 2.3 Percentage of adults aged 50-75 who were up-to-date with colorectal cancer screening in both sexes, 2000-2019. HP: Health People. Source: https://progressreport.cancer.gov/detection/colorectal_cancer

Medicare began reimbursement for guaiac FOBT, barium enema, and sigmoidoscopy as of January 1, 1998, but at the time, screening colonoscopy was only covered in individuals with an increased risk of colorectal cancer, such as a family history.[65] In 2001, the Consolidated Appropriations Act extended colonoscopy coverage to all individuals regardless of risk for colorectal cancer.[66] An interventional study reported adherence rates to colorectal cancer screening recommendations were 38%-69%, 41%-100%, and 52%-100% at one-, two-, or three-year follow-ups for different subgroups, respectively.[67] Two community-based observational studies reported 25–44% adherence to a second round of FOBT among previously adherent individuals.[68, 69] Multi-level tailored interventions on outreach (e.g., sending test results to patients), navigation (e.g.,

trained personnel to assist individuals through the screening process), patient education, provider education, reminders to both patients and providers, and financial incentives were effective in improving patient adherence to colorectal screening recommendations. [70-73]

2.4 Adherence to Lung Cancer Screening in the US

2.4.1 Randomized Clinical Trials Demonstrating Benefits of LCS

Two large randomized clinical trials have demonstrated at least a 20% mortality reduction from lung cancer using LDCT screening compared with chest radiography or no screening. In particular, participant adherence rates in these trials were high, over 90%.

2.4.1.1 The National Lung Screening Trial (NLST)

The NLST[2], sponsored by the National Cancer Institute and conducted by the American College of Radiology Imaging Network and the Lung Screening Study group, compared two ways of detecting lung cancer: LDCT and standard chest X-ray.[74] The eligibility criteria were adults between 55 and 74 years of age, had a history of smoking of at least 30 pack-years and had quit within the past 15 years if former smokers. In total, 53,454 participants were randomly assigned to undergo three annual screenings with either LDCT (n=26,722) or chest radiography (n=26,732). The trial demonstrated a 20% (95% CI, 6.8 to 26.7; p=0.004) mortality reduction from lung cancer using LDCT screening as opposed to chest radiography in 2011. The rate of adherence to the screening protocol across the three rounds was 95% and 93% in the LDCT and radiography groups, respectively.

2.4.1.2 The Nederlands–Leuvens Longkanker Screenings Onderzoek (NELSON) Trial

Initiated in 2000, the NELSON trial[3] aimed to show a 25% reduction in lung cancer mortality or more with LDCT screening in high-risk male participants at ten years of follow-up. The trial enrolled former and current smokers between the ages of 50 and 74. The 15,789 participants (13,195 males for primary analysis and 2,594 females for sensitivity analysis) were randomly assigned to undergo three rounds of screenings annually with LDCT or no screening. At ten years of follow-up, the cumulative rate ratio for death from lung cancer at ten years was 0.76 (95% confidence interval [CI], 0.61 to 0.94; P=0.01) in the LCCT group as compared with the control group in males; in females, the rate ratio was 0.67 (95% CI, 0.38 to 1.14) at ten years of follow-up. The average adherence to CT screening was 90.0% among males.

2.4.2 Eligibility and Coverage for LCS

Prior to the 80s, the ACS supported the use of chest X-ray for those in whom lung cancer is most often found (e.g., heavy smokers, asbestos workers, etc.).[29] No specific recommendations were made by either the ACS or the USPSTF until 2013, two years after the publication of the NLST[2] results, where screening with LDCT was found to be associated with reduced mortality as opposed to a chest x-ray. The USPSTF 2013 eligibility criteria for LCS were current or former smokers aged 55 to 80 years with a minimum 30 pack-year (number of packs per day x number of years smoked) smoking history and within 15 years since quit.[75] In 2021, the age and smoking history criteria of the USPSTF guidelines were lowered to 50 and 20 pack-years, respectively.[76] Besides the USPSTF guideline, other societies and associations in the US have also proposed similar LCS recommendations (see **Table 2.1**). The cost of LDCT scans is covered for eligible individuals by the CMS for Medicare beneficiaries and state Medicaid fee-for-service programs or by

private insurers under the Affordable Care Act for all preventative services grades "B" or higher, including LDCT for LCS.[77]

Table 2.1 Lung cancer screening guidelines and recommendations in the United States.

Organization	Eligible Individuals	Year
American Association for Thoracic Surgery[78]	1. Age 55 to 79 years with ≥30 pack-year smoking history. 2. Long-term lung cancer survivors who have completed four years of surveillance without recurrence and who can tolerate lung cancer treatment in order to detect second primary lung cancer until the age of 79. 3. Age 50 to 79 years with a 20 pack-year smoking history and additional comorbidity that produces a cumulative risk of developing lung cancer ≥5% in 5 years.	2012
American Cancer Society[18]	Age 55 to 74 years with ≥30 pack-year smoking history, either currently smoking or have quit within the past 15 years, and who are in relatively good health.	2019
American College of Chest Physicians[79]	Age 55 to 77 years with ≥30 pack-year smoking history and either continue to smoke or have quit within the past 15 years.	2021
Centers for Medicare & Medicaid Services[80]	Age 50 to 77 years with ≥20 pack-year smoking history and smoking cessation <15 years.	2022
National Comprehensive Cancer Network[81]	Group 1: Age 55 to 77 years with ≥30 pack-year smoking history and smoking cessation <15 years.	2022
	Group 2: Age ≥50 years and ≥20 pack-year smoking history and additional risk factors such as occupational exposure to lung carcinogens.	

Table 2.1 Lung cancer screening guidelines and recommendations in the United States.

Organization	Eligible Individuals	Year
United States Preventive Services Task Force[76]	Age 50 to 80 years with ≥20 pack-year smoking history and smoking cessation <15 years	2021

2.4.3 Potential Challenges in Maintaining Patient Adherence to LCS

Relative to breast, colorectal, and cervical cancer screenings, clinical LCS programs are still nascent. Even though the USPSTF has relaxed the eligibility criteria on age and smoking history to allow more smokers to be eligible for LCS, the overall participation rate remains low. According to the American Lung Association, less than 6% of screen-eligible Americans have undergone LDCT screening by 2021.[24] While Massachusetts had the highest LCS adoption rate (i.e., 16%), some states, such as California, had a screening rate as low as 1.0%, significantly lower than the national rate of 6%.[24] Besides low adoption, adherence to LCS recommendations can also be challenging in the following aspects.

1. The nascence of clinical LCS programs. Unlike breast, cervical, and colorectal cancer screenings, where the first USPSTF recommendations were published in 1996, the earliest USPSTF recommendation for LCS was issued in 2013, after which LCS was widely adopted clinically. In breast cancer screening, the most significant rate of adoption occurred between 1987 and 1998. It is likely that LCS is still in its nascent stage because, so far, clinical LCS programs have been developing for only ten years. Therefore, much remains unknown pertaining to what affects the individual's decision (not) to participate in LCS and (not) to adhere to screening recommendations.

2. Radiation exposure concerns. Exposure to ionizing radiation from repeated mammograms may increase the risk of developing breast cancer[82]. However, the benefits of screening outweigh the risk.[83] In LCS, there is a concern about the increased risk of cancers due to exposure to ionizing radiation from repeated LDCT scans.[84] Although radiation exposure and cancer risk from LCS LDCT are non-negligible, they can be considered acceptable in terms of the considerable mortality reduction associated with screening.[85] Assuming an average estimated effective dose of 1.5 mSv and annual lifetime screening from 50 to 75 years old based on the NLST settings, Brenner et al.[86] estimated lung cancer excess risk due to LDCT radiation of 0.23% and 0.85% for males and females, respectively, while Frank et al.[87] estimated an excess risk of 0.07% for males and 0.14% for females. Fear of developing radiation-induced cancers may be a major factor contributing to non-adherence to repeated LDCT screens.
3. Short follow-up intervals. Once an individual has completed the first or baseline cancer screening examination, a follow-up recommendation is provided to ensure a subsequent assessment within an appropriate time interval. For example, the screening frequency among eligible women is every three or five years for cervical cancer screening[88] and biennial for breast cancer screening[89]. Unlike other types of cancer screenings where the recommended follow-up interval is at least one year from the current screen, the LCS recommendations, as defined by the Lung-RADS[5], are characterized by shorter follow-up intervals. Per Lung-RADS, annual screening with LDCT in 12 months is recommended for negative screens (i.e., Lung-RADS 1 or 2 category), whereas LDCT in 6 months, 3 months, or diagnostic testing with chest CT, positron emission tomography-computed tomography (PET-CT), or tissue biopsy are recommended for positive screens (i.e., Lung-RADS 3, 4A, and 4B/X). For positive screens, the

potential for faster growth rates of some lung cancers justifies shorter times to follow-up (e.g., LDCT in 6 or 3 months or diagnostic workups as early as possible).[90] The potential downsides of short follow-up intervals include anxiety and scheduling inflexibility, which may result in a late follow-up or no-show for the recommended follow-up examination.

4. Smoking stigma. For most cancers, the individual's risk increases from low to high, mainly due to female sex or aging. For example, by the USPSTF guidelines, breast and colorectal cancer screenings are recommended beginning at age 50 for women and all adults, respectively. But for LCS, apart from aging, smoking history is also one important qualification criterion. Smoking is considered a risk factor for several malignancies, including the mouth and throat, larynx, esophagus, stomach, kidney, pancreas, liver, bladder, cervix, colon, and rectum, and a type of leukemia[91], which encourages smoking to be viewed as aberrant behavior.[92] People who smoke, especially heavy smokers, may feel stigmatized about this unhealthy behavior and become increasingly marginalized and isolated (e.g., social withdrawal from nonsmokers).[93] This may prevent them from undergoing a baseline LCS LDCT scan or coming back for annual or short-term interval examinations once they have initiated LCS.
5. Lack of patient education. Before the beneficiary's first LDCT screening examination, the Centers for Medicare and Medicaid Services requires a shared decision-making visit (CPT code: G0296) that is appropriately documented in the beneficiary's medical records.[80] During the shared decision-making visit, the physician, nurse practitioner, or physician assistant will discuss the following with the patient 1) determination of their eligibility, 2) shared decision-making, 3) counseling on the importance of adherence to annual LDCT screens, 4) the impact

of comorbidities and ability or willingness to undergo diagnosis and treatment, and 5) counseling on the importance of maintaining cigarette smoking abstinence (former smoker) or the importance and of smoking cessation and information about tobacco cessation interventions (current smoker). However, sometimes the clinician may have limited time for shared decision-making and does not have an opportunity to evaluate the patient's knowledge about lung cancer screening either immediately after the discussion or in the long run.

6. Lack of customized patient reminders. After an LDCT screen, reminding a patient about their follow-up examination is not solely the patient's responsibility. The members of an LCS program need to build a robust reminder system that sends out personalized reminders to patients based on their Lung-RADS score and risk of non-adherence at the following examination. This requires an understanding of the factors causing patients to be non-adherent at their institution, such that these risk factors can be incorporated into prediction models to generate the probability of non-adherence for the next follow-up. For those predicted to be non-adherent, multiple reminders may be sent to this patient through a combination of reminder letters, telephone reminders, and primary care physician involvement. For those at lower risk of non-adherence, single reminders may be sufficient.

2.5 Potential Factors Influencing Adherence to Cancer Screening

Anticipating patient behavior and providing specific interventions are important components of successful cancer screening programs. If the benefits of cancer screening are to be achieved (i.e., improved early detection rates and reduced cancer-specific mortality), participation in and adherence to recommended actions are surely critical. Given the relative nascence of LCS,

little is known about why screen-eligible smokers decide (not) to undergo screening. The following sections of this chapter discuss potential factors affecting cancer screening adherence.

2.5.1 Social Determinants of Health (SDH)

Another set of variables associated with breast, cervical, and colorectal cancer screening participation is SDH[94], which is "conditions in the places where people live, learn, work, and play that affect a wide range of health and quality of life risks and outcomes."[95] Seven out of the 18 antecedent variables mentioned in the Carter-Harris conceptual model (see Section 2.5.2) are broadly considered SDH variables, including gender, race/ethnicity, income, education, smoking-related stigma, social influence, and media exposure.[96] We will assess the associations between these variables and non-adherence to Lung-RADS recommendations in Chapters 4 to 6. With respect to the SDH variables not included in the Carter-Harris conceptual model, more research is needed to understand their roles in patient adherence to LCS. For instance, in a recent study on the impact of SDH on LCS adherence, the authors found housing insecurity was associated with non-adherent to the baseline Lung-RADS recommendations.[97]

2.5.2 The Carter-Harris Conceptual Model

To identify factors associated with screening behavior in lung cancer, Carter-Harris et al. developed a conceptual model for LCS participation and adherence.[20] This model proposes that multiple factors can influence LCS participation and adherence, including psychological variables; demographic and health status characteristics; cognitive variables; receiving a healthcare provider recommendation; social and environmental variables; LCS health beliefs; and the shared decision-making process between an individual and their health care provider (**Fig. 2.4**). Chapter 4 examines the representation and availability of these variables in our medical records and existing medical

vocabularies. Chapters 5 and 6 investigate the value of the variables available in our medical records in predicting LCS adherence.

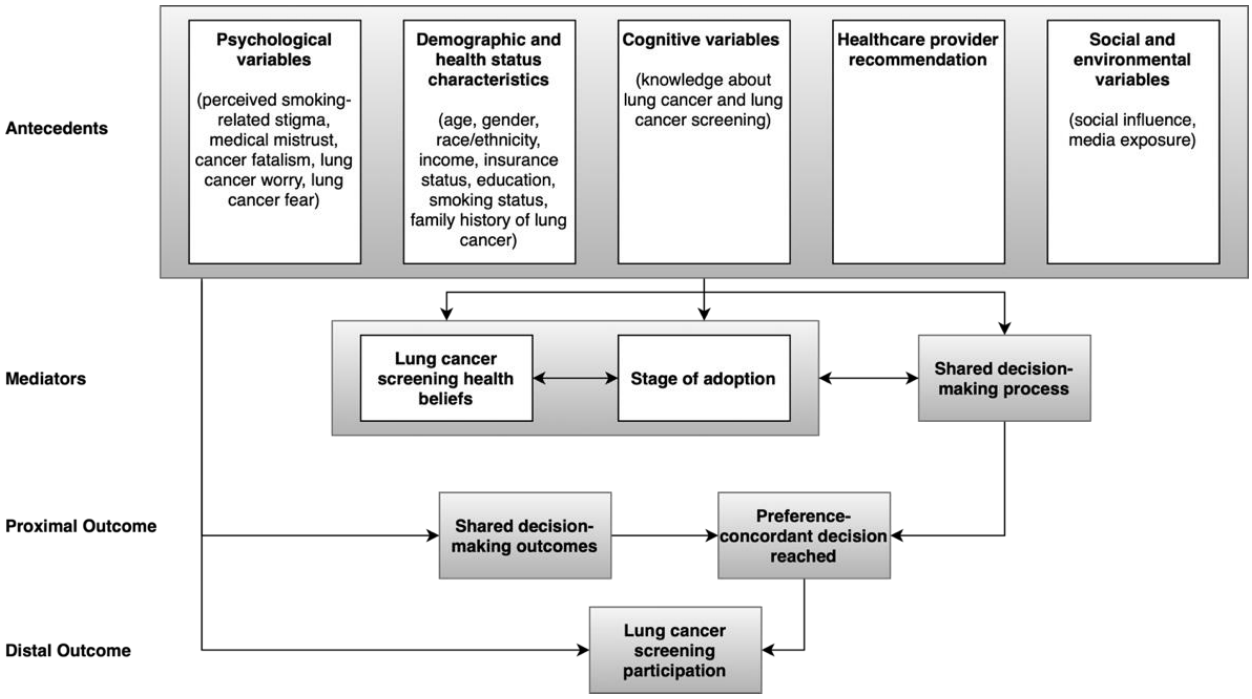

Fig. 2.4 The Carter-Harris conceptual model for lung cancer screening participation.

2.5.3 Additional Barriers to Cancer Screening

Barriers to cancer screening involve factors at several levels. Womeodu and Bailey[98] summarize patient, provider, and institutional barriers to cancer screening (see **Table 2.2**). This dissertation focuses on individual/patient-level barriers, investigating factors associated with non-adherence to LCS recommendations. Healthcare provider and system-level barriers are outside the scope of this work.

Table 2.2 Barriers to cancer screening by Womeodu & Bailey.

Level	Item
Individual/Patient	Knowledge, attitudes, and beliefs about cancer
	Noncompliance with screening recommendations
	Perceived cancer susceptibility
	Perceived benefits and discomfort of screening
	Perceived benefits and discomfort of potential treatment
	Fear of positive results
	Personal characteristics: ethnicity, age, socioeconomic status, educational attainment
	Employer requirements
	Arranging care for dependents
	Insurance status
	Transportation
Health Care Provider	Knowledge of cancer risk and causation
	Knowledge and comfort with screening guidelines
	Knowledge of cultural determinants of health behavior
	Personal characteristics: education, age, gender
	Practice priorities and beliefs
	Delivery of appropriate screening advice
	Addressing other pressing health issues

Table 2.2 Barriers to cancer screening by Womeodu & Bailey.

Level	Item
	Time constraints
Medical System	Accessibility and acceptability of healthcare services
	Accessibility and acceptability of screening test
	Accessibility of screening test site
	Lack of tracking and follow-up care
	Lack of third-party reimbursement, deductibles
	Cost Of screening test

CHAPTER 3

Current Status of Patient Adherence to Lung-RADS Recommendations in the US

This chapter is adapted from "Patient Adherence to Lung CT Screening Reporting & Data System–Recommended Screening Intervals in the United States: A Systematic Review and Meta-Analysis," published in the Journal of Thoracic Oncology in 2022.[99]*, "Lin Y, Fu M, Inoue K, Jeon CY, Hsu W. Response to Letter to the Editor. J Thorac Oncol. 2022;17(3):e27-e28. doi:10.1016/j.jtho.2021.12.013"*[100]*, and "Lin Y, Fu M, Inoue K, Jeon CY, Prosper AE. Response to Letter to the Editor. J Thorac Oncol. 2022;17(4):e47-e48. doi:10.1016/j.jtho.2022.01.014."* [101]

Chapter 2 provides an overview of the adherence problem in cancer screening alongside a description of adherence in non-LCS domains and some challenges in maintaining LCS adherence. Because LCS has only been adopted in clinical practices for a decade in the US, there lacks a systematic review of patient adherence to LCS recommendations. In this chapter, we report the current evidence of patient adherence to LCS in the United States, identifying subgroups across which substantial differences in adherence rates are observed. The overall adherence rate identified in the meta-analysis is far below that seen in the National Lung Screening Trial (NLST), potentially diminishing the survival benefits conferred by LCS in clinical practice. By calling attention to the heterogeneity in screening adherence, this work provides a foundation for future interventions to optimize adherence, in turn maximizing the survival benefit of LCS.

3.1 Overview

Despite the potential of annual screening to reduce mortality from lung cancer, studies from post-NLST community clinical LCS programs revealed that the adherence rate was less than 50%[6,

[7], far lower than the over 90% adherence rate found across the three rounds of screening in the NLST.[2] Adherence to screening recommendations is essential to realizing mortality benefits because incidence lung cancers (i.e., screen-detected cancers at incidence screen) revealed shortened survivals, approximating interval lung cancers (i.e., cancers diagnosed after a negative screen and before another screen).[102] Three recent systematic reviews and meta-analyses reported patient adherence to LCS. Lam et al.[103] focused on non-adherence to returning for another annual low-dose computed tomography (LDCT) screening. Their review included publications from clinical studies worldwide and reported a pooled non-adherence rate of 28% (95% confidence interval [CI]: 20%-37%) at the first annual screen using 12 studies. Lopez-Olivo et al.[104] then reported a pooled adherence rate of 55% (95% CI: 44%[104]-66%) over all follow-up periods across 15 studies that used any screen-reporting guideline in the US. Kunitomo et al.[105] specifically examined the racial differences in adherence to LCS between Black and White participants and found lower adherence in Black on average across seven studies. Studies that used both Lung-RADS and other reporting guidelines were included.

The Lung-RADS is a quality assurance to standardize LCS LDCT reporting and management recommendations.[26] Nodule size, characteristics, and location are considered when assigning Lung-RADS scores. Nodule management guidelines vary based on Lung-RADS categories, with LDCT in 12 and 6 months for Lung-RADS 1 to 2 and 3, respectively, as well as LDCT in 3 months or positron emission tomography (PET)-CT for Lung-RADS 4A and chest CT, PET-CT, or tissue sampling for Lung-RADS 4B/X.[5] Given that none of the three systematic reviews and meta-analyses reported adherence to Lung-RADS recommendations, the literature lacks systematic evidence on adherence to LCS based on Lung-RADS guidelines. As a preliminary analysis[106], we conducted

a literature review that included seven studies and found that adherence rates varied across all studies (baseline Lung-RADS 1&2: 16% to 66%; baseline Lung-RADS 3&4: 61% to 87%), of which the majority (6/7) had a relatively small sample size (300~500 participants). Additional studies are necessary to determine the sources of heterogeneity in adherence rates among these LCS programs. To bridge the gap, we conducted a systematic review and meta-analysis on patient adherence to Lung-RADS recommended screening intervals across clinical LCS programs in the US. Our focus lies in identifying sources of heterogeneity in adherence rates using subgroup analyses and meta-regression. Additionally, we propose a standardized approach to reporting LCS adherence rates according to the gaps in data identified through our work.

3.2 Methods

This systematic review and meta-analysis were reported in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses statement.[107] The Covidence software (Melbourne, Australia) was used for the title and abstract screening, full-text review, data extraction, and quality assessment. The systematic review and meta-analysis were registered in PROSPERO (CRD42020189326).

3.2.1 Eligibility Criteria

Studies that reported patient adherence to Lung-RADS recommendations in the US were included. The clinical LCS programs where the study was conducted needed to be affiliated with a US hospital. We restricted the screening modality to LDCT and the LDCT reporting guidelines to Lung-RADS recommendations. There was no limitation on the type of study design for inclusion. Any study that was published prior to the release date of Lung-RADS (April 28, 2014) was excluded. We limited publication language to English.

3.2.2 Search Strategy and Study Selection

We searched eligible original studies in the following electronic databases from January 1, 2014, to December 17, 2020: MEDLINE (accessed through PubMed), EMBASE, Web of Science, and the Cochrane Central Register of Controlled Trials (CENTRAL). In addition, we searched Google Scholar between January 1, 2014 and December 17, 2020. Moreover, conference abstract databases from influential conferences in cancer research and radiology were also searched. Databases of the American Association for Cancer Research, American Society of Clinical Oncology, American Thoracic Society, Radiological Society of North America, and Society of Thoracic Radiology were searched from 2014 to 2020, whereas the American Roentgen Ray Society database was searched from 2019 to 2020. We manually searched the reference list of the included studies. Lung cancer, cancer screening, and adherence were three categories of keywords. **Table 3.1** summarizes keywords used in PubMed. Synonyms such as lung neoplasms, early detection of cancer, and patient adherence were identified for each category. After that, the three keyword categories were combined into a comprehensive search strategy, which was tailored for each database and conference achieve. **Appendix Table S3.1** demonstrates the literature search conducted in PubMed. Both journal articles and conference abstracts were included in this review. Two reviewers performed literature screening independently, and discrepancies were resolved through a group discussion involving a third reviewer.

Table 3.1 Keywords used in MEDLINE.

Keyword	Similar meaning or category
Lung neoplasms [MeSH]	Pulmonary neoplasms, lung neoplasm, pulmonary neoplasm, lung cancer, lung cancers, pulmonary cancer, pulmonary cancers, cancer of the lung, cancer of lung
Early detection of cancer [MeSH]	Cancer early detection, cancer screening, cancer screening test, cancer screening tests, cancer early detection, early diagnosis of cancer, cancer early diagnosis, early cancer diagnosis
Guideline adherence [MeSH]	Patient compliance [MeSH], Patient dropouts [MeSH], patient dropout, protocol compliance, patient adherence, patient non-compliance, patient non compliance, patient noncompliance, patient non-adherence, patient non adherence, patient nonadherence, loss to follow up

3.2.3 Data Items and Data Extraction

Data elements were extracted by two independent reviewers, and discrepancies were resolved through a discussion. Extracted data items are summarized in **Table 3.2**.

Table 3.2 Summary of extracted data elements.

Category	Variables
Identification	Title, first author, publication year, type of publication (journal article or conference abstract), and institutional setting (e.g., academic, community, etc.)
Methods	Study design, the start and end dates of patient recruitment, the end date of follow-up, LCS guideline for patient enrollment, additional patient inclusion and exclusion criteria, patient referral to the LCS program, program resources such as program

Table 3.2 Summary of extracted data elements.

Category	Variables
	coordinators/navigators, shared decision-making services, smoking cessation services, use of a clinical LCS database, and interventions for adherence
LCS adherence	The total number of patients, patient baseline characteristics, baseline Lung-RADS scores, the definition of adherence, overall adherence rate, and adherence rate stratified by Lung-RADS scores and other factors (e.g., demographics), factors associated with non-adherence, and reasons for non-adherence.

LCS: lung cancer screening; Lung-RADS: Lung CT Screening Reporting & Data System.

3.2.4 Risk of Bias Assessment

The quality of the included studies was evaluated by two reviewers independently, using relevant items from the Newcastle-Ottawa Scale for cohort studies.[108] Disagreements were resolved through consensus between the two reviewers or by a group discussion involving a third reviewer. We considered five relevant items (**Appendix Table S3.2**): (1) representativeness of the exposed cohort, (2) ascertainment of exposure, (3) demonstration that outcome of interest was not present at the start of study, (4) assessment of outcome, and (5) whether follow-up was long enough for outcomes to occur. The remaining three items were irrelevant in this context. The selection of the unexposed group and the comparison between the two cohorts were irrelevant because the adherence rate is similar to the prevalence rate in cross-sectional studies. Besides, lost to follow-up participants were accounted for in the analysis by counting towards the non-adherent group. Thus, attrition bias is not a concern for this specific systematic review and meta-analysis,

3.2.5 Summary Measures

The follow-up examination of Lung-RADS 1 and 2 was defined as an annual incidence screen (i.e., LDCT in 12 months) and that for Lung-RADS 3 and 4 as an interval short term follow-up examination (i.e., LDCT in 3 to 6 months, chest CT, PET-CT, or tissue sampling). Annual screening time points were labeled T0, T1, T2, etc. for baseline, incidence screens at 1, 2 years, etc., respectively. Adherence was defined as the completion of an annual incidence screen or early follow-up examination within the time period stated in each study. The primary outcome was adherence rate, calculated as the number of adherent patients divided by the total number of enrolled patients. When available, adherence rates in subgroups were extracted from each study as a secondary outcome, such as adherence rates stratified by Lung-RADS score and demographics. Due to inconsistencies in defining adherence across the included studies, adherence rates were grouped into defined adherence and anytime adherence. The former had a clear definition of adherence (e.g., annual incidence screen within 15 months from the baseline screen), whereas the latter considered patients as adherent as long as they received a follow-up examination during the study period.

3.2.6 Statistical Analysis

In the systematic review, we extracted and summarized study-level characteristics, adherence rates (both overall and stratified), and potential factors that were associated with non-adherence. In the meta-analysis, our focus was on the rate of adherence to the baseline Lung-RADS recommendations. Four studies did not mention whether the calculated adherence rate was to the baseline Lung-RADS recommendations.[109-112] We contacted the authors for clarification and received responses from all authors. We used random effects models to perform meta-analyses of

adherence rates (proportions) with the inverse-variance weighting method and the Freeman-Tukey double arcsine transformation to better approximate the normal distribution while stabilizing the variances.[113] We used the I-squared index (>75% as large heterogeneity) [114] and Cochran's Q test [115] ($p<0.05$ indicates significant heterogeneity) to identify and measure heterogeneity in adherence rates across included studies. Sensitivity analyses were conducted to evaluate the influence of adherence rates from conference abstracts on pooled adherence rates by excluding them from the meta-analyses. To further identify the causes of heterogeneity in adherence rates, we performed subgroup analyses and used bivariate and multivariable mixed effects meta-regression models with the restricted maximum-likelihood estimator[116] and Freeman-Tukey double arcsine-transformed adherence rates. We did not perform robust cluster meta-regression because our sample size was too small to yield accurate results ($N<20$).[117] The following study-level characteristics were included in the meta-regression models, Lung-RADS, institutional setting, a program with coordinators/navigators, shared decision-making, smoking cessation services, interventions for adherence, and publication type. Publication bias was assessed using funnel plots and Egger's test.[118] All analyses were performed in R version 3.6.3 (R packages: "meta" and "metafor"). [119-121]

3.3 Results

3.3.1 Search Results

A total of 655 studies were identified through searching the citation databases, and 84 studies were identified through other sources, including a non-citation database, conference proceeding archives, and the reference list of included studies. After removing 697 duplicates and irrelevant records, 47 full-text articles were evaluated for eligibility. Among the 47 publications, 23 were further excluded due to wrong outcomes, duplication, or non-original investigation. Twenty-four

studies[6-8, 109-112, 122-138] were eligible for qualitative synthesis (systematic review), and 21 studies[6-8, 109-112, 123, 124, 126-136, 138] were eligible for quantitative synthesis (meta-analysis) (**Fig. 3.1**).

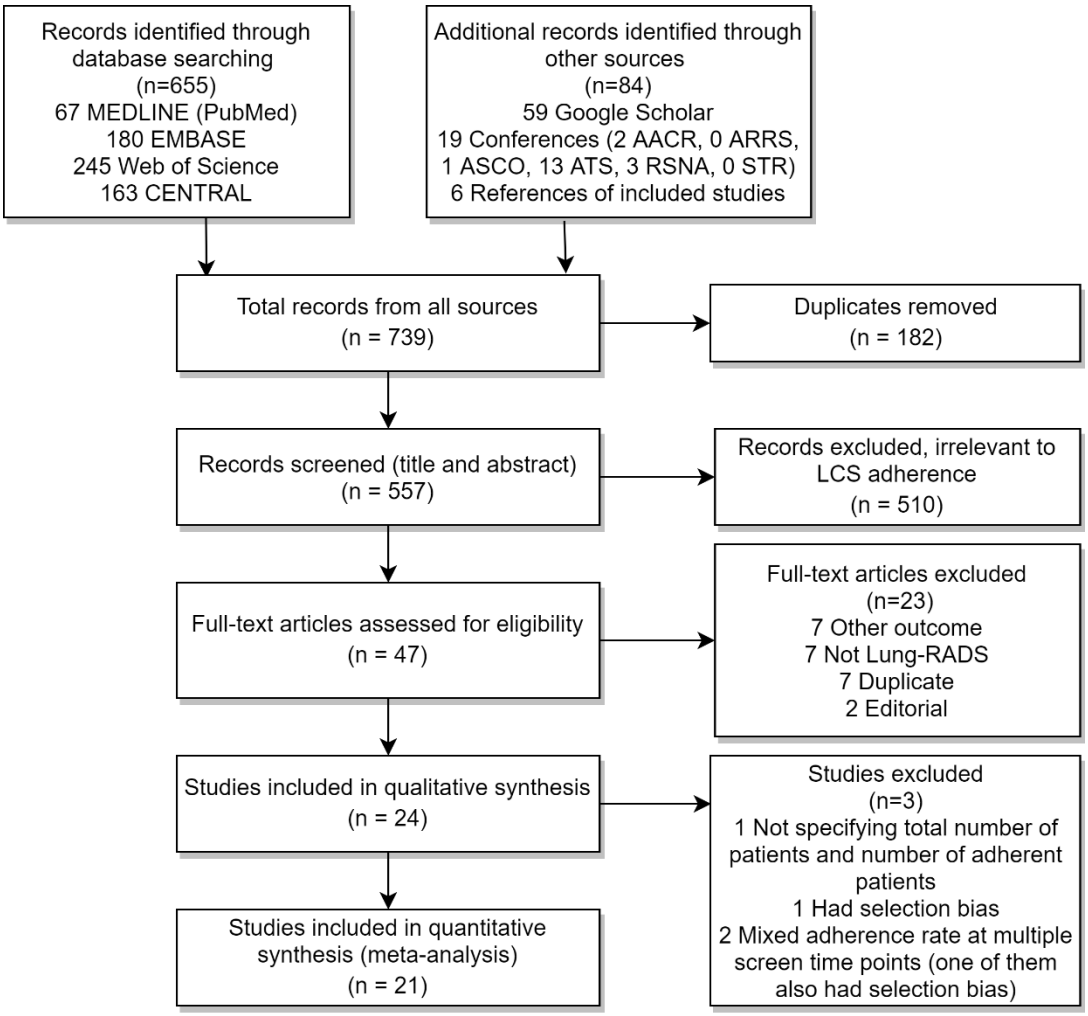

Fig. 3.1 The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow diagram for adherence to Lung-RADS recommended screening intervals. CENTRAL: Cochrane Central Register of Controlled Trials; AACR: American Association for Cancer Research; ARRS: American Roentgen Ray Society; ASCO: American Society of Clinical Oncology; ATS: American Thoracic Society; RSNA: Radiological Society of North America; STR: Society of Thoracic Radiology; LCS: lung cancer screening; Lung-RADS: Lung CT Screening Reporting & Data System.

3.3.2 Quality (Risk of Bias) Assessment

Table 3.3 summarizes the risk of bias assessment at the study level. We excluded one study[122] from the meta-analyses because it excluded non-adherent patients who did not come back after the baseline examination. In three studies[123-125], we assumed that exposure (LCS examination and Lung-RADS information) and outcomes (adherence statuses) data were obtained from patient medical records, although this was not stated explicitly. In two studies[109, 126], patients with a pending follow-up examination were excluded from the adherence rate calculation because their adherence statuses were yet to be determined. Adherence outcomes were unknown at the start of all included studies, as patients undergoing LDCT needed to be followed up to determine adherence.

Table 3.3 Risk of bias in individual studies assessed with the Newcastle-Ottawa Scale for cohort studies.

Study	Selection				Comparability[a]	Outcome		
	Exposed cohort	Unexposed cohort[a]	Ascertainment of exposure	Outcome not present at start of study		Assessment of outcome	Follow-up long enough for outcomes to occur	Adequacy of follow up[a]
Alshora 2018[127]	*		*	*		*	*	
Angotti 2020[110]	*		*	*		*	*	

Table 3.3 Risk of bias in individual studies assessed with the Newcastle-Ottawa Scale for cohort studies.

Study	Selection				Comparability[a]	Outcome		
	Exposed cohort	Unexposed cohort[a]	Ascertainment of exposure	Outcome not present at start of study		Assessment of outcome	Follow-up long enough for outcomes to occur	Adequacy of follow up[a]
Barbosa 2020[122]			*	*		*	*	
Bellinger 2020[128]	*		*	*		*	*	
Bernstein 2019[123]	*			*			*	
Bhandari 2019[6]	*		*	*		*	*	
Brillante 2019[129]	*		*	*		*	*	
Cattaneo 2018[7]	*		*	*		*	*	
Deepak 2020[109]	*		*	*		*		
Guichet 2018[130]	*		*	*		*	*	

Table 3.3 Risk of bias in individual studies assessed with the Newcastle-Ottawa Scale for cohort studies.

Study	Selection				Comparability[a]	Outcome		
	Exposed cohort	Unexposed cohort[a]	Ascertainment of exposure	Outcome not present at start of study		Assessment of outcome	Follow-up long enough for outcomes to occur	Adequacy of follow up[a]
Hirsch 2019[131]	*		*	*		*	*	
Jacobs 2017[126]	*		*	*		*		
Kaminetzky 2019[132]	*		*	*		*	*	
Lake 2020[133]	*		*	*		*	*	
Li 2018[134]	*		*	*		*	*	
Muñoz-Largacha 2018[124]	*			*			*	
Plank 2018[111]	*		*	*		*	*	
Rodriguez 2020[135]	*		*	*		*	*	
Sakoda 2018[136]	*		*	*		*	*	

Table 3.3 Risk of bias in individual studies assessed with the Newcastle-Ottawa Scale for cohort studies.

Study	Selection				Comparability[a]	Outcome		
	Exposed cohort	Unexposed cohort[a]	Ascertainment of exposure	Outcome not present at start of study		Assessment of outcome	Follow-up long enough for outcomes to occur	Adequacy of follow up[a]
Seastedt 2020[112]	*		*	*		*	*	
Spalluto 2020[8]	*		*	*		*	*	
Stowell 2020[137]	*		*	*		*	*	
Triplette 2020[138]	*		*	*		*	*	
Wernli 2020[125]	*			*			*	

[a] Irrelevant items in the context of lung cancer screening adherence.

3.3.3 Study Characteristics

The characteristics of the 24 included studies[6-8, 109-112, 122-138] are summarized in **Table 3.4**. Among the 24 studies, the distribution of institutional settings was 17 academic,[8, 109-111, 122, 124, 127-135, 137, 138] four community,[6, 7, 123, 126] two Kaiser Permanente,[125, 136] and one Veterans Affairs,[112]

with most being retrospective studies.[6-8, 109-112, 122-127, 129-131, 133-138] The study period varied for each individual study. Eligibility criteria for LCS mentioned in the studies included guidelines from the American Association for Thoracic Surgery,[109] American Cancer Society,[109] Centers for Medicare and Medicaid Services,[126, 128, 131] National Comprehensive Cancer Network,[109, 111, 127, 128, 130, 134] National Cancer Institute,[109] NLST,[7, 132, 135] and the United States Preventive Services Task Force.[109, 112, 124, 128, 130, 137] There were 20 studies[7, 8, 109, 111, 112, 122-124, 126-128, 130-138] that described LCS program resources, which included program coordinators/navigators, shared decision-making services, smoking cessation services, and use of a dedicated clinical LCS database. Additional details are reported in **Appendix Table S3.3**, such as publication type, additional inclusion criteria, exclusion criteria, referral types, retrospective assignment of Lung-RADS scores, adherence determination for certain subgroups (e.g., died or became ineligible during follow-up), and reasons for non-adherence.

Table 3.4 Characteristics of included studies on patient adherence to Lung-RADS recommended screening intervals (N=24).

Study	Institutional setting	Study design	Study period	LCS eligibility criteria	Program resources	Cohort size (patients)	Patient characteristics
Alshora 2018[127]	Academic	Retrospective cohort	Baseline LDCT 2012-01-12 to 2013-06-12, followed through 2014-09-12	NCCN	Program coordinators/navigators; SDM; smoking cessation; management system; database; standardized patient discharge protocol	901	Female: 44.2%; White>95%; current smokers: 45.9%, former smokers: 54.1%
Angotti 2020[110]	Academic	Retrospective cohort	Baseline LDCT 2016 to 2018	Not reported	Not reported	1444	Not reported
Barbosa 2020[122]	Academic	Retrospective cohort	LDCT 2014-05-01 to 2019-07-11	Age >50 and <80, ≥30 pack-years, current smoker or former smoker quit within 15 years	Data maintained in Excel and REDCap	260	Mean age 65.5, median age 66; female: 51.9%; current smokers 55.0%, former smokers 45.0%; mean pack-years: 51.1, median pack-years: 45

Table 3.4 Characteristics of included studies on patient adherence to Lung-RADS recommended screening intervals (N=24).

Study	Institutional setting	Study design	Study period	LCS eligibility criteria	Program resources	Cohort size (patients)	Patient characteristics
Bellinger 2020[128]	Academic	Prospective cohort	Baseline LDCT 2014-11 to 2016-03	USPSTF, CMS, NCCN	Program coordinators/navigators	268	Female: 49.6%; White: 76.1%, Black: 22.4%, not reported: 1.5%; current smokers: 62.7%, former smokers: 37.3%
Bernstein 2019[123]	Community	Retrospective cohort	Baseline LDCT 2015-05-01 to 2018-05-01	Not reported	Program coordinators/navigators	631	Female: 48.7%
Bhandari 2019[6]	Community	Retrospective cohort	LDCT 2016-2017	Not reported	Not reported	3428	Not reported
Brillante 2019[129]	Academic	Retrospective cohort	Not reported	Not reported	Not reported	32	Mean age: 64.8; Black: 75.0%; Medicare/Medicaid: 75.0%

Table 3.4 Characteristics of included studies on patient adherence to Lung-RADS recommended screening intervals (N=24).

Study	Institutional setting	Study design	Study period	LCS eligibility criteria	Program resources	Cohort size (patients)	Patient characteristics
Cattaneo 2018[7]	Community	Retrospective cohort	Baseline LDCT 2012-01 to 2015-09-30, followed through 2016-12-31	NLST	Program coordinators/navigators; SDM; smoking cessation; database; multidisciplinary program for management	1241	Median age: 66; female 52.5%; White: 87.3%, Black: 10.2%, other race: 1.5%, not reported: 1.0%; current smokers 49.1%, former smokers 48.2%, not reported: 2.7%; median pack-years: 40; Medicare: 45.5%, private insurance: 49.7%, Medicaid: 1.4%, not reported: 3.4%
Deepak 2020[109]	Academic	Retrospective cohort	Not reported	USPSTF, AATS, ACS, NCI, NCCN	Data maintained in Excel	166	Female: 47.0%; White: 15.7%, Black: 81.9%, Asian: 1.2%, not reported: 1.2%

Table 3.4 Characteristics of included studies on patient adherence to Lung-RADS recommended screening intervals (N=24).

Study	Institutional setting	Study design	Study period	LCS eligibility criteria	Program resources	Cohort size (patients)	Patient characteristics
Guichet 2018*[130]	Academic	Retrospective cohort	Baseline LDCT 2015-07-21 to 2017-04-03, followed through 2017-08-01	NCCN	Program coordinators/navigators; database	275	Mean age: 59; female: 47.6%; White: 5.1%, Black: 83.6%, Asian: 0.7%, Hispanic/Latino: 10.5%; current smokers: 81.1%; median pack-years: 40
Hirsch 2019[131]	Academic	Retrospective cohort	Baseline LDCT 2014-07-01 to 2016-12-31	CMS	Program coordinators/navigators; SDM; database	259	Mean age: 64.1; female: 42.9%; White: 82.6%; current smokers: 54.8%, former smokers: 45.2%; mean pack-years: 48.6; government insurance: 73.7%, private insurance: 23.2%, other: 3.1%
Jacobs 2017[126]	Community	Retrospective cohort	Baseline LDCT 2014-06-01 to 2015-12-31	CMS	SDM; smoking cessation	680	Median age: 64; female: 44.7%; current smokers: 45.1%; former smokers: 48.4%, not reported: 6.5%; median pack-years: 44.5

Table 3.4 Characteristics of included studies on patient adherence to Lung-RADS recommended screening intervals (N=24).

Study	Institutional setting	Study design	Study period	LCS eligibility criteria	Program resources	Cohort size (patients)	Patient characteristics
Kaminetzky 2019[132]	Academic	Prospective cohort	Baseline LDCT 2012-12 to 2016-12	NLST	Program coordinators/navigators; data maintained in Excel	1181	Mean age: 64; female: 51.8%; White: 22.9%, Black: 31.4%; Hispanic/Latino: 30.9%; Asian: 0.7%, not reported: 14.1%; current smokers: 71.4%, former smokers: 28.6%; median pack-years: 45; Medicare: 55.7%, Medicaid: 21.0%
Lake 2020[133]	Academic	Retrospective cohort	Baseline LDCT 2015-05 to 2017-07, followed through 2019-09-06	Not reported	Program coordinators/navigators; SDM; database	477	Mean age: 64.3, female: 53.0%; White: 57.9%, Black: 42.1%; current smokers: 57.2%, former smokers: 41.1%, not reported: 1.6%; mean pack-years: 48.5
Li 2018*[134]	Academic	Retrospective cohort	Baseline LDCT 2015-07-21 to 2018-03-20	USPSTF, NCCN	Program coordinators/navigators	370	Mean age: 60; female: 45.1%; White: 9.0%, Black: 77.0%, Asian: 5.0%, Hispanic/Latino: 8.0%; current smokers: 81.0%; median pack-years: 42

Table 3.4 Characteristics of included studies on patient adherence to Lung-RADS recommended screening intervals (N=24).

Study	Institutional setting	Study design	Study period	LCS eligibility criteria	Program resources	Cohort size (patients)	Patient characteristics
Muñoz-Largacha 2018[124]	Academic	Retrospective cohort	Baseline LDCT 2015-03 to 2016-07	USPSTF	Program coordinators/navigators	554	Mean age: 63; female: 39.9%; White: 47.8%, Black: 31.4%, Asian/Native American: 5.1%, Hispanic/Latino: 10.1%, not reported: 5.6%; current smokers: 51.6%, former smokers: 24.5%, not reported: 23.8%; Medicare/Medicaid: 64.0%, private insurance: 36.0%
Plank 2018[111]	Academic	Retrospective cohort	Not reported	NCCN	Smoking cessation; REDCap	825	Mean age: 60; female: 40.0%; current smokers: 42.0%; mean pack-years: 46
Rodriguez 2020[135]	Academic	Retrospective cohort	Baseline LDCT 2016 to 2019	NLST	SDM	421	Black: 15.0%, Hispanic/Latino: 47.3%
Sakoda 2018[9]	Kaiser Permanente	Retrospective cohort	Baseline LDCT 2014-07 to 2015-06	Not reported	Database	145	Median age: 66; female: 39.0%; White: 71.0%, current smokers: 76.0%

Table 3.4 Characteristics of included studies on patient adherence to Lung-RADS recommended screening intervals (N=24).

Study	Institutional setting	Study design	Study period	LCS eligibility criteria	Program resources	Cohort size (patients)	Patient characteristics
Seastedt 2020[112]	VA	Retrospective cohort	Baseline LDCT 2013 to 2019-06	USPSTF	Smoking cessation; database	242	Median age 67; female: 30.6%; White: 57.9%, Black: 20.2%, other: 21.9%; current smokers: 43.4%, former smoker: 56.6%; mean pack-years: 41
Spalluto 2020[8]	Academic	Retrospective cohort	Baseline LDCT 2014-01-01 to 2016-09-30, followed through 2018-03-31	Not reported	Program coordinators/navigators; SDM; smoking cessation; database	319	Mean age: 64.1; female: 49.2%; White: 86.8%, Black: 7.2%, other or not reported: 6.0%; Hispanic/Latino: 1.3%
Stowell 2020[137]	Academic	Retrospective cohort	LDCT 2016-01-01 to 2018-10-17	USPSTF	Program coordinators/navigators; SDM; data warehouse	1954	Female: 48.1%; White: 90.9%, non-White: 9.1%; current smokers: 56.0%; Medicaid: 25.8%

Table 3.4 Characteristics of included studies on patient adherence to Lung-RADS recommended screening intervals (N=24).

Study	Institutional setting	Study design	Study period	LCS eligibility criteria	Program resources	Cohort size (patients)	Patient characteristics
Triplette 2020[138]	Academic	Retrospective cohort	Baseline LDCT 2012 to 2017-09, followed through 2018-12	Not reported	Database	668	Median age: 63; female: 32.8%; White: 76.8%, Black: 10.5%, Asian: 4.2%, other: 1.9%, not reported: 6.6%; Hispanic/Latino: 1.8%, non-Hispanic/Latino: 84.7%, not reported: 13.5%; current smokers: 54.5%, former smokers: 45.5%; median pack-years: 47; Medicaid: 15.7%, Medicare: 46.0%, private insurance: 26.8% , Medicare plus private: 7.5%, self-pay: 1.0%, not reported: 3.0%
Wernli 2020[125]	Kaiser Permanente	Retrospective cohort	Baseline LDCT 2015 to 2019-07	Not reported	Not reported	2274	Not reported

Table 3.4 Characteristics of included studies on patient adherence to Lung-RADS recommended screening intervals (N=24).

Study	Institutional setting	Study design	Study period	LCS eligibility criteria	Program resources	Cohort size (patients)	Patient characteristics

Lung-RADS: Lung CT Screening Reporting & Data System; LCS: lung cancer screening; LDCT: low-dose computed tomography; NCCN: National Comprehensive Cancer Network; SDM: shared decision-making; USPSTF: United States Preventive Services Task Force; CMS: Centers for Medicare & Medicaid Services; NLST: National Lung Screening Trail; AATS: American Association for Thoracic Surgery; ACS: American Cancer Society; NCI: National Cancer Institute; VA: Veterans Affairs.

* The two studies were essentially the same cohort that only differed in the end date of the study. They were both included because adherence was assessed for different Lung-RADS categories with Lung-RADS 1-2 for Li et al.[134] and Lung-RADS 3-4 for Guichet et al. [130]

3.3.4 Adherence Rates in Specific Lung-RADS Categories

Given that adherence rates were not evaluated for all Lung-RADS categories among all studies, we extracted adherence rates and relevant information in specific Lung-RADS categories for the 24 studies.[6-8, 109-112, 122-138] There were ten studies[7, 8, 110-112, 127, 128, 131, 133, 138] that reported interventions for adherence, such as reminder letters and phone calls. In addition, there were 14 studies[7, 109, 112, 122, 124, 127-131, 133, 136-138] that reported Lung-RADS distributions. Heterogeneous definitions of adherence were used for the same Lung-RADS categories across different studies, among which completion of an annual screen or early follow-up within three months (or 90 days) of recommended date was the most frequently used criterion.[7, 8, 111, 112, 123, 125, 127, 135, 137, 138] Both overall and Lung-RADS–stratified defined and anytime adherence rates are summarized in **Table 3.5**.

Table 3.5 Adherence rates in specified Lung-RADS categories.

Study	Cohort size (patients)	Interventions for adherence	Lung-RADS distribution	Patient characteristics	Definition of adherence	Defined adherence rate	Anytime adherence rate
Alshora 2018[127]	901	Reminder letters, phone calls, PCP involvement	Lung-RADS 1-2: 69.1% Lung-RADS 3: 27.4% Lung-RADS 4: 3.4%	Lung-RADS 1-4: Female: 44.2%; White: >95.0%; current smokers: 45.9%, former smokers: 54.1%	Completion of an annual incidence screen or early follow-up exam within 3 months of recommended date	Time point: T1 Lung-RADS 1-4: 85.7% Lung-RADS 1-2: 85.6% Lung-RADS 3: 85.0% Lung-RADS 4: 93.5%	Not reported
Angotti 2020[110]	1444	Centralized component: Phone calls, certified letters; Decentralized component:	Not reported	Not reported	Completion of an annual incidence screen in 12 months ± 60 days for Lung-RADS 1-2; Completion of an early follow-up exam in 6 months ± 45 days for Lung-RADS 3; Completion of an early	Time point: T1* Lung-RADS 1-4: 62.1%	Not reported

Table 3.5 Adherence rates in specified Lung-RADS categories.

Study	Cohort size (patients)	Interventions for adherence	Lung-RADS distribution	Patient characteristics	Definition of adherence	Defined adherence rate	Anytime adherence rate
		PCP involvement, EMR notifications			follow-up exam in 3 months ± 30 days for Lung-RADS 4		
Barbosa 2020[122]	570 (number of LDCT scans from 260 patients)	Not reported	Lung-RADS 1: 36.0% Lung-RADS 2: 56.5% Lung-RADS 3: 4.6% Lung-RADS 4A: 1.6% Lung-RADS 4B: 1.1% Lung-RADS 4X: 0.4%	Not reported	Completion of an annual incidence screen or follow up CT within ± 1 month of recommended date; Completion of a PET/CT exam or biopsy within 3 months of the radiology report date	Time point: multiple Lung-RADS 1-4: 43.0% Lung-RADS 1: 33.2% Lung-RADS 2: 46.3% Lung-RADS 3: 53.9% Lung-RADS 4A: 77.8% Lung-RADS 4B: 83.3%	Not reported

Table 3.5 Adherence rates in specified Lung-RADS categories.

Study	Cohort size (patients)	Interventions for adherence	Lung-RADS distribution	Patient characteristics	Definition of adherence	Defined adherence rate	Anytime adherence rate
						Lung-RADS 4X: 100.0%	
Bellinger 2020[128]	268	Reminder letters	Lung-RADS 1: 31.7% Lung-RADS 2: 52.6% Lung-RADS 3: 11.2% Lung-RADS 4: 4.5%	Lung-RADS 1-4: Female: 49.6%; White: 76.1%, Black: 22.4%, not reported: 1.5%; current smokers: 62.7%, former smokers: 37.3%	Completion of an annual incidence screen or early follow-up exam within 2 months of recommended date	Time point: T1 Lung-RADS 1-4: 48.1% Lung-RADS 1-2: 43.8% Lung-RADS 3-4: 71.4%	Not reported
Bernstein 2019[123]	631	Not reported	Not reported	Lung-RADS 1-4: Female: 48.7%	Completion of an annual incidence screen or early follow-up exam within 3	Time point: T1 Lung-RADS 1-4: 55.8% Lung-RADS 1: 35.1% Lung-RADS 2: 56.8%	Not reported

Table 3.5 Adherence rates in specified Lung-RADS categories.

Study	Cohort size (patients)	Interventions for adherence	Lung-RADS distribution	Patient characteristics	Definition of adherence	Defined adherence rate	Anytime adherence rate
					months of recommended date	Lung-RADS 3: 75.5% Lung-RADS 4: 94.0%	
Bhandari 2019[6]	1546	Not reported	Not reported	Not reported	Not reported	Not reported	Time point: T1 Lung-RADS 1-2: 49.9%
Brillante 2019[129]	32	Not reported	Lung-RADS 3: 65.6% Lung-RADS 4: 34.4%	Lung-RADS 3-4: Mean age: 64.8; Black: 75.0%; Medicare/Medicaid: 75.0%	Not reported	Not reported	Time point: T1 Lung-RADS 3-4: 65.6% Lung-RADS 3: 52.4% Lung-RADS 4: 90.9%
Cattaneo 2018[7]	776	Reminder cards, phone calls, PCP involvement	Lung-RADS 1-2: 65.9% Lung-RADS 3-4: 34.1%	Lung-RADS 1-2: Female: 54.8%; White: 89.0%, Black: 8.6%, other: 2.3%; current smokers: 44.8%, former	Completion of an annual incidence screen or early follow-up exam within 3	Time point: T1 Lung-RADS 1-2: 37.4%	Time point: T1 Lung-RADS 1-4: 63.8% Lung-RADS 1-2:

Table 3.5 Adherence rates in specified Lung-RADS categories.

Study	Cohort size (patients)	Interventions for adherence	Lung-RADS distribution	Patient characteristics	Definition of adherence	Defined adherence rate	Anytime adherence rate
				smokers: 48.3%. not reported: 6.8%; Medicare: 44.0%, private insurance: 49.5%, Medicaid: 2.0%, not reported: 4.5%	months of recommended date		51.1% Lung-RADS 3-4: 88.2%
Deepak 2020[109]	146****	Not reported	Lung-RADS 1: 46.6% Lung-RADS 2: 42.5% Lung-RADS 3: 5.5% Lung-RADS 4A: 2.7% Lung-RADS 4B: 2.1% Lung-RADS 4X: 0.7%	Not reported	Not reported	Not reported	Time point: T1* Lung-RADS: 49.3% Lung-RADS 1: 58.8% Lung-RADS 2: 43.5% Lung-RADS 3: 37.5% Lung-RADS 4A: 0 Lung-RADS 4B: 66.7% Lung-RADS 4X: 0

Table 3.5 Adherence rates in specified Lung-RADS categories.

Study	Cohort size (patients)	Interventions for adherence	Lung-RADS distribution	Patient characteristics	Definition of adherence	Defined adherence rate	Anytime adherence rate
Guichet 2018***[130]	32	Not reported	Lung-RADS 3: 53.1% Lung-RADS 4: 46.9%	Not reported	Not reported	Not reported	Time point: T1 Lung-RADS 3-4: 75.0%
Hirsch 2019[131]	259	Reminders by a nurse navigator or PCP	Lung-RADS 1: 62.9% Lung-RADS 2: 37.1%	Lung-RADS 1-2: Mean age: 64.1; female: 42.9%; White: 82.6%; current smokers: 54.8%, former smokers: 45.2%; mean pack-years: 48.6; government insurance: 73.7%, private insurance: 23.2%, other: 3.1%	Completion of an annual incidence screen within 6 months of recommended date	Time point: T1 Lung-RADS 1-2: 50.6%	Not reported
Jacobs 2017[126]	113****	Not reported	Not reported	Not reported	Not reported	Not reported	Time point: T1 Lung-RADS 3-4: 83.2%

Table 3.5 Adherence rates in specified Lung-RADS categories.

Study	Cohort size (patients)	Interventions for adherence	Lung-RADS distribution	Patient characteristics	Definition of adherence	Defined adherence rate	Anytime adherence rate
Kaminetzky 2019[132]	663	Not reported	Not reported	Not reported	Not reported	Not reported	Time point: T1, T2, T3 T1 Lung-RADS 1-2: 46.5% T2 Lung-RADS 1-2: 37.8% T3 Lung-RADS 1-2: 27.8%
Lake 2020[133]	477	Reminder letters, phone calls, PCP involvement	Lung-RADS 1: 38.2% Lung-RADS 2: 47.2% Lung-RADS 3: 9.0% Lung-RADS 4: 5.7%	Lung-RADS 1-4: Mean age: 64.3, female: 53.0%; White: 57.9%, Black: 42.1%; current smokers: 57.2%, former smokers: 41.1%, not reported: 1.6%; mean pack-years: 48.5	Completion of an annual incidence screen or early follow-up exam within ± 1 month of recommended date	Time point: T1 Lung-RADS 1-4: 16.6% Lung-RADS 1: 8.8% Lung-RADS 2: 6.7% Lung-RADS 3: 65.1% Lung-RADS 4: 74.1%	Time point: T1 Lung-RADS 1-4: 30.8% Lung-RADS 1: 18.7% Lung-RADS 2: 20.9% Lung-RADS 3: 90.7% Lung-RADS 4: 100.0%

Table 3.5 Adherence rates in specified Lung-RADS categories.

Study	Cohort size (patients)	Interventions for adherence	Lung-RADS distribution	Patient characteristics	Definition of adherence	Defined adherence rate	Anytime adherence rate
Li 2018***[134]	271	Not reported	Not reported	Not reported	Not reported	Not reported	Time point: T1 Lung-RADS 1-2: 54.2%
Muñoz-Largacha 2018[124]	42	Not reported	Lung-RADS 4: 100.0%	Lung-RADS 4: Mean age: 64; female: 35.7%; White: 57.0%, Black: 24.0%, Hispanic/Latino: 7.0%, Asian: 10.0%, not reported: 2.4%; current smokers: 57.0%, former smokers: 26.0%, not reported: 17.0%; Medicare/Medicaid: 69.0%, private insurance: 31.0%	Not reported	Not reported	Time point: T1 Lung-RADS 4: 97.6%

Table 3.5 Adherence rates in specified Lung-RADS categories.

Study	Cohort size (patients)	Interventions for adherence	Lung-RADS distribution	Patient characteristics	Definition of adherence	Defined adherence rate	Anytime adherence rate
Plank 2018[111]	629**	Reminder letters, phone calls, certified letters*	Not reported	Not reported	Completion of an annual incidence screen or early follow-up exam within 3 months of recommended date	Time point: T1* Lung-RADS 1-4: 86.0%	Not reported
Rodriguez 2020[135]	258	Not reported	Not reported	Not reported	Completion of an annual incidence screen within 3 months of recommended date	Time point: T1 Lung-RADS 1-2: 31.4%	Not reported

Table 3.5 Adherence rates in specified Lung-RADS categories.

Study	Cohort size (patients)	Interventions for adherence	Lung-RADS distribution	Patient characteristics	Definition of adherence	Defined adherence rate	Anytime adherence rate
Sakoda 2018[136]	145	Not reported	Lung-RADS 1-2: 84.1% Lung-RADS 3-4: 15.9%	Lung-RADS 1-4: Median age: 66; female: 39.0%; White: 71.0%; current smokers: 76.0%	Completion of an annual incidence screen within10 to 14 months for Lung-RADS 1-2; Completion of an early follow-up exam within ±30 days of the recommended date for Lung-RADS 3-4	Time point: T1 Lung-RADS 1-4: 29.0% Lung-RADS 1-2: 23.0% Lung-RADS 3-4: 61.0%	Not reported
Seastedt 2020[112]	179	Reminder letters, phone calls	Lung-RADS 1: 18.4% Lung-RADS 2: 73.2% Lung-RADS 3: 4.5% Lung-RADS 4: 3.9%	Not reported	Completion of an annual incidence screen or early follow-up exam within 3 months of recommended date	Time point: T1* Lung-RADS 1-4: 77.1% Lung-RADS 1: 81.8% Lung-RADS 2: 77.1%	Not reported

Table 3.5 Adherence rates in specified Lung-RADS categories.

Study	Cohort size (patients)	Interventions for adherence	Lung-RADS distribution	Patient characteristics	Definition of adherence	Defined adherence rate	Anytime adherence rate
						Lung-RADS 3: 75.0% Lung-RADS 4: 57.1%	
Spalluto 2020[8]	319	Reminder letters, phone calls	Not reported	Lung-RADS 1-2: Mean age: 64.1; female: 49.2%; White: 86.8%, Black: 7.2%, other or not reported: 6.0%; Hispanic/Latino: 1.3%	Completion of an annual incidence screen within 3 months and 6 months of recommended date	Time point: T1 Within 3 months Lung-RADS 1-2: 59.2% Within 6 months Lung-RADS 1-2: 63.9%	Time point: T1 Lung-RADS 1-2: 73.0%
Stowell 2020[137]	1954	Not reported	Lung-RADS 1: 20.2% Lung-RADS 2: 64.9% Lung-RADS 3: 14.9%	Lung-RADS 1-3: Female: 48.1%; White: 90.9%, non-White: 9.1%; current smokers: 56.0%; Medicaid: 25.8%	Completion of an annual incidence screen or early follow-up exam within 1 month or 3 months of recommended date	Time point: multiple Within 1 month Lung-RADS 1-3: 39.8% Within 3 months Lung-RADS 1-3: 55.5%	Not reported

Table 3.5 Adherence rates in specified Lung-RADS categories.

Study	Cohort size (patients)	Interventions for adherence	Lung-RADS distribution	Patient characteristics	Definition of adherence	Defined adherence rate	Anytime adherence rate
Triplette 2020[138]	668	Reminder letters	Lung-RADS 1: 23.4% Lung-RADS 2: 57.3% Lung-RADS 3: 9.0% Lung-RADS 4A: 6.1% Lung-RADS 4B: 2.8% Lung-RADS 4X: 1.3%	Lung-RADS 1-4: Median age: 63; female: 32.8%; White: 76.8%, Black: 10.5%, Asian: 4.2%, other: 1.9%, not reported: 6.6%; Hispanic/Latino: 1.8%, non-Hispanic/Latino: 84.7%, not reported: 13.5%; current smokers: 54.5%, former smokers: 45.5%; median pack-years: 47; Medicaid: 15.7%, Medicare: 46.0%, private insurance: 26.8% , Medicare plus private: 7.5%, self-pay: 1.0%, not reported: 3.0%	Completion of an annual incidence screen or early follow-up exam within 3 months of recommended date	Time point: T1 Lung-RADS 1-4: 46.6% Lung-RADS 1: 34.0% Lung-RADS 2: 41.8% Lung-RADS 3: 61.7% Lung-RADS 4A: 85.4% Lung-RADS 4B: 89.5% Lung-RADS 4X: 100.0%	Time point: T1 Lung-RADS 1-4: 70.5%

Table 3.5 Adherence rates in specified Lung-RADS categories.

Study	Cohort size (patients)	Interventions for adherence	Lung-RADS distribution	Patient characteristics	Definition of adherence	Defined adherence rate	Anytime adherence rate
Wernli 2020[125]	2274	Not reported	Not reported	Not reported	Completion of an annual incidence screen or early follow-up exam within 3 months of recommended date	Time point: T1 Lung-RADS 1-2: 31.5% Lung-RADS 3: 51.1%	Not reported

Lung-RADS: Lung CT Screening Reporting & Data System; PCP: primary care provider; T1, T2, T3: annual incidence screens at one, two, three years; EMR: electronic medical record; LDCT: low-dose computed tomography; CT: computed tomography; Defined adherence: Adherence was defined as completion of annual incidence screen or early follow-up exam within a specified time interval from recommended date. Anytime adherence: Patients are considered adherent as long as they received a follow-up exam anytime during the course of the study period.

* Information/Confirmation provided by the authors of the study. **The authors confirmed that the 86% adherence rate was based on 629 (out of 825) patients who were due for their follow-up imaging exam. ***The two studies were essentially the same cohort that only differed in the end date of the study. They were both included because adherence was assessed for different Lung-RADS categories with Lung-RADS 1-2 for Li et al.[134] and Lung-RADS 3-4 for Guichet et al.[130] ****Patients with pending/waiting follow-up imaging exams were excluded (Deepak et al.[109] excluded N=20; Jacobs et al.[126] excluded N=20).

3.3.5 Meta-Analysis of Adherence Rates at T1

We performed a pooled analysis of adherence rates at T1 among the eligible studies (N=21).[6-8, 109-112, 123, 124, 126-136, 138] Three studies were excluded from the meta-analysis because (1) Wernli et al.[125] only reported adherence rates without specifying the total numbers of included and adherent patients, and (2) adherence rates at T1 could not be extracted from studies by Barbosa et al.[122] and Stowell et al.[137] In addition, Spalluto et al.[8] reported adherence rates at both 90-day and 180-day windows. To minimize variations in the definition of adherence and be consistent with definitions used by most studies, only 90-day (3-month) adherence rates were included in the meta-analyses for this study. As found in **Fig. 3.2 a and b**, the pooled adherence rate was 57% (95% CI: 46%–69%) for defined adherence among 6689 patients and 65% (95% CI: 55%–75%) for anytime adherence among 5085 patients. Significant heterogeneity between studies was observed (I^2=99%, $p < 0.05$ for defined adherence; I^2=98%, $p < 0.05$ for anytime adherence). Sensitivity analyses on adherence rates from journal articles revealed similar results (Appendix **Fig. S3.1 a and b**).

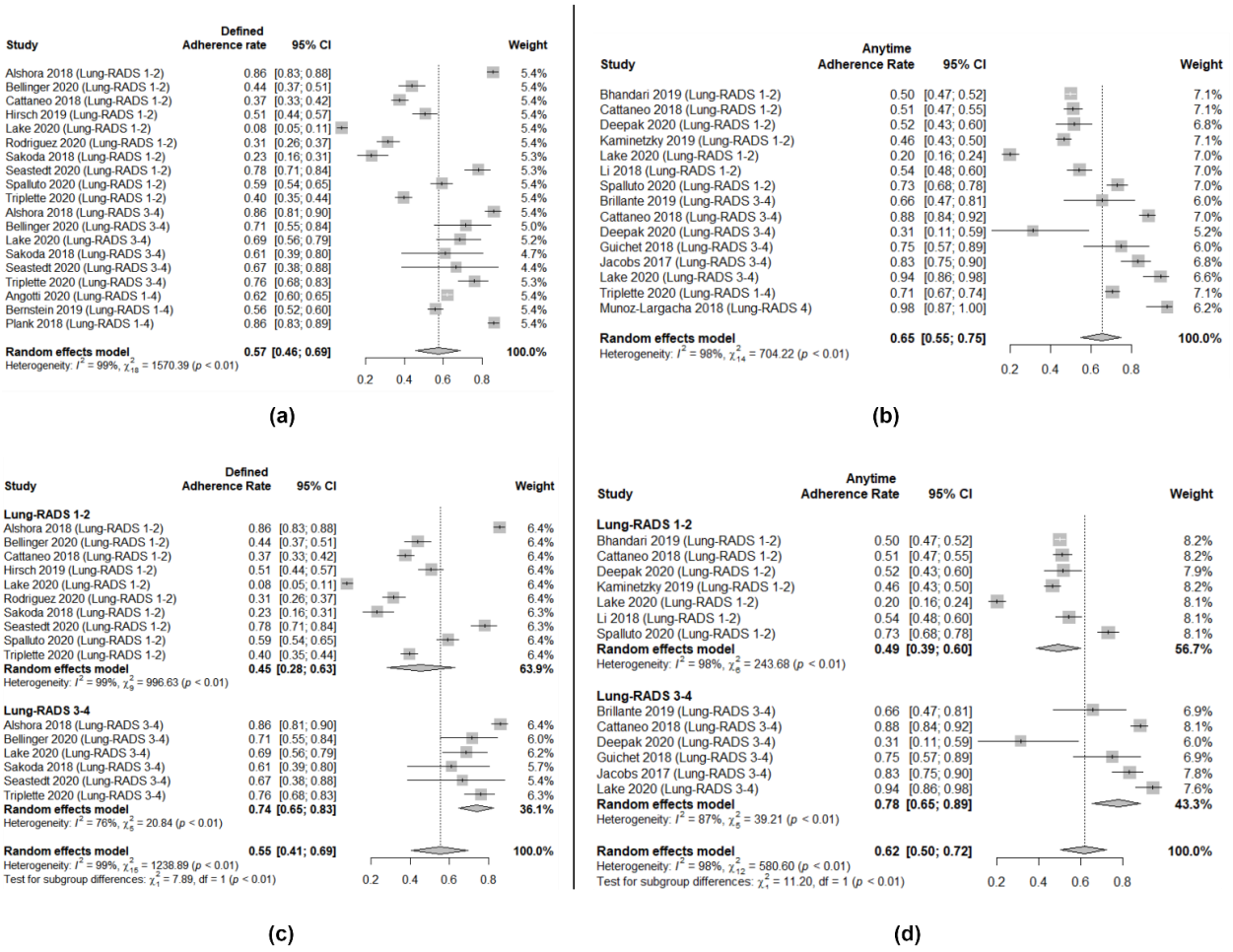

Fig. 3.2 The pooled adherence rates to Lung-RADS recommended screening intervals at T1. (a) Forest plot of defined adherence rates (total n=6689). (b) Forest plot of anytime adherence rates (total n=5085). (c) Forest plot of defined adherence rates stratified by Lung-RADS categories (total n=3985, Lung-RADS 1-2 n=3428, Lung-RADS 3-4 n=557). (d) Forest plot of anytime adherence rates stratified by Lung-RADS categories (total n=4375, Lung-RADS 1-2 n=3847, Lung-RADS 3-4 n=528). Defined adherence: Adherence was defined as the completion of an annual incidence screen or early follow-up exam within a specified time interval from the recommended date. Anytime adherence: Patients are considered adherent as long as they receive a follow-up exam anytime during the course of the study period. Lung-RADS: Lung CT Screening Reporting & Data System; T1: annual incidence screen at one year; CI: confidence interval.

3.3.6 Subgroup Analyses on Adherence Rates at T1

In the subgroup analysis for Lung-RADS categories, studies that did not report adherence rates in Lung-RADS 1 to 2 or Lung-RADS 3 to 4 were excluded.[110, 111, 123, 124] For defined adherence, the pooled adherence rate was 45% (95% CI: 28%–63%) in Lung-RADS 1 to 2 among 3428 patients and 74% (95% CI: 65%–83%) in Lung-RADS 3 to 4 among 557 patients (test for subgroup differences $p < 0.05$); however, for anytime adherence, the pooled adherence rate was 49% (95% CI: 39%–60%) in Lung-RADS 1 to 2 among 3847 patients and 78% (95% CI: 65%–89%) in Lung-RADS 3 to 4 among 528 patients (test for subgroup differences $p < 0.05$) (**Fig. 3.2 c and d**). Furthermore, we performed a meta-analysis of defined adherence rates among a subset of the studies in which adherence was defined as completion of the annual screen or early follow-up examination within three months (90 days) of the recommended date (**Appendix Fig. S3.2**) and observed significant subgroup differences between Lung-RADS 1 to 2 and Lung-RADS 3 to 4 ($p < 0.05$). In addition, sensitivity analyses removing adherence rates from conference abstracts also revealed significant subgroup differences between Lung-RADS 1 to 2 and Lung-RADS 3 to 4 (**Appendix Fig. S3.1 c and d; $p < 0.05$**). Because of limited data, additional subgroup analyses by sex, race, and smoking status did not reveal significant subgroup differences in adherence rates (**Appendix Fig. S3.3; $p > 0.05$**).

3.3.7 Potential for Publication Bias

Funnel plots of meta-analyses are found in **Appendix Fig. S3.4 to S3.7**. In Egger's regression tests for funnel plot asymmetry, we found no evidence of the potential publication bias (i.e., $p > 0.05$) except for the pooled anytime adherence rates from journal articles (**Appendix Fig. S3.5B; $p < 0.05$**).

3.3.8 Meta-regression

Because substantial differences were identified between Lung-RADS 1 to 2 and Lung-RADS 3 to 4 for both defined and anytime adherence, studies that reported adherence rate only in Lung-RADS 1 to 4[110, 111, 123] or a specific Lung-RADS category[124] were excluded from meta-regression analyses (**Table 3.6**). Detailed information on outcome and independent variables across 17 studies included in this meta-regression analysis is found in **Appendix Table S3.4**. In bivariate meta-regression analyses, Lung-RADS categories (1–2 versus 3–4) were found to be associated with adherence rates for both defined and anytime adherence ($p < 0.05$ for both). In addition, the mention of smoking cessation services (yes versus not reported) was associated with defined adherence ($p < 0.05$). After adjusting for institutional setting, programs with coordinators/navigators, shared decision-making services, interventions for adherence, and publication type, Lung-RADS categories (1–2 versus 3–4) and mentioning of smoking cessation services (yes versus not reported) were associated with defined adherence rates ($p < 0.05$). Further subgroup analysis revealed a higher adherence rate among studies that reported smoking cessation services as opposed to those that did not (70%, 95% CI: 50%–87% versus 46%, 95% CI: 31%–61%); however, the difference was not significant ($p > 0.05$).

Table 3.6 Meta-regression on LCS adherence at T1.

Adherence type	Variable	Bivariate			Multivariable		
		Coefficient	95% CI	p-value	Coefficient	95% CI	p-value
Defined (N=16)	Lung-RADS						
	1-2 (referent: 3-4)	0.2776	(0.0440, 0.5112)	0.0199	0.2696	(0.0722, 0.4670)	0.0074
	Institutional setting						
	Academic (referent: non-academic)	-0.0392	(-0.3240, 0.2455)	0.7871	-0.2647	(-0.5645, 0.0352)	0.0836
	Program coordinators/navigators						
	Not reported (referent: yes)	0.0341	(-0.2300, 0.2982)	0.8002	-0.0034	(-0.3032, 0.2963)	0.9821
	Shared decision-making						
	Not reported (referent: yes)	-0.0391	(-0.3006, 0.2223)	0.7691	-0.1761	(-0.4715, 0.1192)	0.2425
	Smoking cessation						
	Not reported (referent: yes)	0.2456	(0.0077, 0.4835)	0.0431	0.4145	(0.1380, 0.6910)	0.0033
	Interventions for adherence						
	Not reported (referent: yes)	0.2241	(-0.0934, 0.5416)	0.1665	-0.0549	(-0.4253, 0.3155)	0.7715
	Publication type						

Table 3.6 Meta-regression on LCS adherence at T1.

Adherence type	Variable	Bivariate			Multivariable		
		Coefficient	95% CI	p-value	Coefficient	95% CI	p-value
	Abstract (referent: article)	0.2241	(-0.0934, 0.5416)	0.1665	*	*	*
Anytime (N=13)	Lung-RADS						
	1-2 (referent: 3-4)	0.2890	(0.0766, 0.5014)	0.0077	0.2880	(-0.0092, 0.5852)	0.0575
	Institutional setting						
	Academic (referent: non-academic)	0.1212	(-0.1668, 0.4091)	0.4095	-0.0178	(-0.5010, 0.4655)	0.9426
	Program coordinators/navigators						
	Not reported (referent: yes)	0.0638	(-0.2200, 0.3475)	0.6595	0.0919	(-0.3820, 0.5659)	0.7038
	Shared decision-making						
	Not reported (referent: yes)	0.1683	(-0.0907, 0.4273)	0.2027	-0.0236	(-0.8425, 0.7953)	0.9550
	Smoking cessation						
	Not reported (referent: yes)	0.2101	(-0.0584, 0.4785)	0.1251	0.1895	(-0.3623, 0.7412)	0.5010
	Interventions for adherence						

Table 3.6 Meta-regression on LCS adherence at T1.

Adherence type	Variable	Bivariate			Multivariable		
		Coefficient	95% CI	p-value	Coefficient	95% CI	p-value
	Not reported (referent: yes)	0.0968	(-0.1805, 0.3740)	0.4939	-0.0373	(-0.7601, 0.6856)	0.9195
	Publication type						
	Abstract (referent: article)	0.1454	(-0.1471, 0.4379)	0.3299	0.0679	(-0.4179, 0.5537)	0.7841

* Publication type was dropped from the multivariable model due to high correlation with the interventions for adherence variable in defined adherence.

LCS: lung cancer screening; Lung-RADS: Lung CT Screening Reporting & Data System; T1: annual incidence screen at one year; CI: confidence interval; Defined adherence: Adherence was defined as completion of an annual screen or early follow-up exam within a specified time interval from recommended date; Anytime adherence: Patients are considered adherent as long as they received a follow-up exam anytime during the course of the study period.

3.3.9 Predictors of Non-adherence

Table 3.7 summarizes potential predictors of LCS adherence with p values derived from Pearson's chi-square test and ORs derived from bivariate or multivariable logistic regression. Bellinger et al.[128] found that patients with Lung-RADS 3 to 4 were more adherent compared with those with Lung-RADS 1 to 2 ($p < 0.05$). Similar findings were found by Triplette et al.[138] (referent: Lung-RADS 1, Lung-RADS 3: OR=3.8, 95% CI: 1.9–7.7; Lung-RADS 4: OR=14, 95% CI: 6.0–32) and Bernstein et al.[123] (referent: Lung-RADS 1, Lung-RADS 2: OR=2.43, 95% CI: 1.66–3.56; Lung-RADS 3: OR=5.39, 95% CI: 2.71–10.72; Lung-RADS 4: OR=28.86, 95% CI: 8.60–96.87). Alshora et al.[127] reported that female patients were more adherent ($p < 0.05$), whereas Seastedt et al.[112] concluded that male patients were more adherent (OR=2.57, 95% CI: 1.36–4.87). Three studies[112, 123, 127] revealed that older patients were more adherent than younger patients ($p < 0.05$ for Alshora et al.[127] and Bernstein et al.[123] and OR=1.43, 95% CI: 1.03–2.01 for Seastedt et al.[112]). Higher adherence rates were also associated with referral to LCS by pulmonary medicine and thoracic surgery[123] ($p < 0.05$), having a reminder from either a nurse navigator or primary care provider[131] ($p < 0.05$), having a dedicated program coordinator[8] ($p< 0.05$), or being a former smoker[138] (OR=1.7, 95% CI: 1.2–2.5). On the basis of these findings, when data were available, we further attempted to investigate whether incorporating predictors of non-adherence as fixed effects terms in the random effects meta-analysis models reduced the heterogeneity score, I^2. Nevertheless, we were not able to perform this analysis owing to the small number of studies reporting mean age, percent of females, percentage of whites, and percentage of former smokers (**Appendix Table S3.5**).

Table 3.7 Summary of predictors of LCS adherence at T1.

Study	Adherence type	Lung-RADS categories	Main findings
Alshora 2018[127]	Defined	Lung-RADS 1-4	(1) Female patients were more adherent compared to male patients (p=0.035). (2) Patients 65 to 73 years old were more adherent compared to patients 50 to 64 years old (p=0.040).
Bellinger 2020[128]	Defined	Lung-RADS 1-4	(1) Patients with Lung-RADS 3 and 4 were more adherent compared to those with Lung-RADS 1 and 2 (p<0.01).
Bernstein 2019[123]	Defined	Lung-RADS 1-4	(1) Compared to patients with Lung-RADS 1, those with Lung-RADS 2, 3, and 4 were more adherent (Lung-RADS 2: OR=2.43, 95% CI: 1.66-3.56; Lung-RADS 3: OR=5.39, 95% CI: 2.71-10.72; Lung-RADS 4: OR=28.86, 95% CI: 8.60-96.87). (2) Age greater than 65 was associated with increased adherence (p=0.002). (3) Adherence was higher in patients referred by pulmonary medicine and thoracic surgery than for others (p=0.016).
Hirsch 2019[131]	Defined	Lung-RADS 1-2	(1) Having a reminder from either a nurse navigator or PCP was associated with increased adherence (p<0.001).

Table 3.7 Summary of predictors of LCS adherence at T1.

Study	Adherence type	Lung-RADS categories	Main findings
Seastedt 2020[112]	Defined	Lung-RADS 1-4	Adjusting for race, negative screens, smoking status, and rank, (1) older patients were more adherent than younger patients (OR=1.43, 95% CI: 1.03-2.01); (2) male patients were more adherent than female patients (OR=2.57, 95% CI: 1.36-4.87).
Spalluto 2020[8]	Defined	Lung-RADS 1-2	(1) Hiring a dedicated program coordinator was associated with increased adherence (p<0.005).
Triplette 2020[138]	Defined	Lung-RADS 1-4	Adjusting for age, race, ethnicity, insurance status, origin of referral, CCI, S category, location, year of enrollment, and presence of tracking intervention, (1) patients with Lung-RADS 3 (OR=3.8, 95% CI: 1.9-7.7) and Lung-RADS 4 (OR=14, 95% CI: 6.0-32) were more adherent compared to those with Lung-RADS 1; (2) former smokers were adherent than current smokers (OR=1.7, 95% CI: 1.2-2.5).

p: Pearson's chi-square test p value; OR: odds ratio from logistic regression.

LCS: lung cancer screening; T1: annual incidence screen at one year; Lung-RADS: Lung CT Screening Reporting & Data System; Defined adherence: Adherence was defined as completion of an annual incidence screen or early follow-up exam within a specified time interval from recommended date; OR: odds ratio.; CI: confidence interval;

Table 3.7 Summary of predictors of LCS adherence at T1.

Study	Adherence type	Lung-RADS categories	Main findings

PCP: primary care provider; CCI: Charlson Comorbidity Index; S category: a significant non-lung cancer related finding.

3.4 Discussion

This systematic review and meta-analysis focused on LCS adherence to Lung-RADS recommendations. Lung-RADS guidelines were developed on the basis of findings from the NLST and other screening studies; among the goals was lowering false-positive and false discovery rates[126] while providing standardized management algorithms for clinical practice. Before the release of Lung-RADS, the NLST protocol recommended early follow-up imaging for nodules 4 mm in diameter or larger[139] and the Fleischner 2005 guidelines recommended follow-up for solid nodules greater than 4 mm in diameter.[140] The Lung-RADS threshold for early follow-up is nodules greater than or equal to 6 mm, resulting in fewer positive screens and the number of recommended early follow-up examinations. This decline was not due to a change in adherence patterns but rather the impact of changing the minimum size threshold for early follow-up examinations. As a result, we purposely excluded studies that reported LCS adherence rates on the basis of other follow-up recommendations.

Highly heterogeneous adherence rates were observed across studies. We found significantly higher adherence rates in patients with Lung-RADS 3 (risk for lung cancer at 1%–2%) and 4 (risk > 5%) than Lung-RADS 1 and 2 (risk < 1%). It is likely that patients and referrers are more concerned about nodules at a higher risk for lung cancer, prompting greater adherence to recommended screening intervals in Lung-RADS 3 to 4. Reporting of smoking cessation services contributed to the heterogeneity in defined adherence rates (bivariate and multivariable meta-regression: $p < 0.05$), but the test for subgroup differences was insignificant ($p > 0.05$). Regardless, it is crucial that patients and referrers alike understand that screening is most effective when performed

regularly, including for those with negative baseline screens, as de novo nodules, those detected after a negative screen, are more aggressive than those detected at baseline screen.[102]

Although adherence rates varied widely across studies, none of them approximated the 95% adherence observed in the LDCT arm in the NLST, which could adversely affect the mortality benefits of LCS. Beyond the more tightly controlled environment of a clinical trial, differences in demographic distributions between the included studies and the NLST could be one of the causes for the differences in adherence rates. Participants in the NLST were greater than 90% white, 59% male, and 52% former smokers at baseline.[2] Only one study[127] had demographic distributions at baseline screen similar to the NLST. Insurance coverage could be another barrier to returning for additional screening examinations because only screen-eligible patients aged 65 years or older qualify for Medicare insurance. Moreover, when retrospectively applying the Lung-RADS criteria to the NLST, the Lung-RADS distribution at baseline screen for Lung-RADS 1 to 2 is 86%, and for Lung-RADS 3 to 4 is 14%.[141] Similar distributions were observed in only five studies.[109, 128, 133, 136, 138] Perhaps most importantly, the NLST used an active process for patient follow-up by issuing an annual or biannual questionnaire and a study update form; if forms were not completed, participants were contacted by a staff member.[139] In post-NLST clinical practices, despite some sites reporting comparable interventions to ensure adherence that included reminders by means of mail, telephone calls, and involving the patient's primary care provider, the overall adherence rates remain low. This implies that the low adherence rates found in clinical practices could be caused by multiple factors, including but not limited to patient characteristics, insurance coverage, Lung-RADS category, and interventions for adherence.

Furthermore, several studies investigated reasons for non-adherence, including (1) the patient declining the annual incidence screen or early follow-up examination,[126, 127] (2) the screening center's inability to contact the patient,[127] (3) failure of the provider to order the annual incidence screen or early follow-up examination,[127] (4) patient completed screening elsewhere,[112, 128] (5) patient not contacted to schedule an examination,[142] and (6) LCS was not a priority as opposed to other medical issues.[112] Spalluto et al.[8] reported patient-identified barriers to LCS, such as lack of transportation, lack of communication by physicians, lack of current symptoms (hence the need for screening), and financial costs. Similar barriers to LCS have been reported by Wang et al.[143]

Significant heterogeneity in adherence rates was detected and measured using Cochran's Q test and I2 statistic. We can further quantify the magnitude of heterogeneity using tau-squared (τ^2), which is the between-study variance.[144] As stated in the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 Expanded Checklist[107], it is helpful to report tau-squared. Reporting tau-squared neither changes our original finding of significant heterogeneity in adherence rates nor the results of the downstream analysis to identify the sources of heterogeneity. Additionally, we have performed additional tests for publication bias for the models in **Fig. 3.2**, and the test results are similar to Egger's test used in the article. It is worth noting that all tests for publication bias have limitations.[145] For example, there was substantial between-study heterogeneity detected in the meta-analysis, and the trim and fill method may perform poorly when considerable between-study heterogeneity exists.[146] Egger's test, Begg's test, and funnel plots assume studies with positive findings are more often published than those with negative results.[147] However, the assumption of positive results being more frequently published is not necessarily

true for studies focusing on proportional outcomes (e.g., the rate of adherence in our case).[147] Although publication bias can be evaluated using these methods, the interpretation of their results should be contextualized given stated limitations.

This analysis would not be affected by the version of the Lung-RADS used in each study. The focus of this systematic review and meta-analysis is on patient adherence to Lung-RADS recommended screening intervals. Although we acknowledge that the change in Lung-RADS reporting of perifissural nodules and ground-glass nodules would affect the assignment of Lung-RADS score, it would not affect the recommended screening intervals associated with each Lung-RADS category. From Lung-RADS version 1.0 to version 1.1, the Lung-RADS-recommended screening intervals remain unchanged for each Lung-RADS category.[148, 149] In addition, the between-study heterogeneity in the rates of adherence is attributable to the varying lengths of follow-up in each individual study. In our analysis, we have attempted to account for the varying study periods of the included studies. We grouped adherence rates based on their definitions. For a defined adherence, the patients need to complete an annual incidence screen or early follow-up examination within a specified time interval from the recommended date. For example, if the specified time interval was three months for Lung-RADS 2, then the patient would be defined as adherent if the first annual incidence screen was completed within 15 months from the baseline screen (**Fig. 3.3** Patient 1 and 2); otherwise, the patient would be defined as non-adherent. In the non-adherent case, the patient should be followed for at least 15 months to be classified as non-adherent (**Fig. 3.3** Patient 3); if not, then they should be removed from the analysis (**Fig. 3.3** Patient 4). This was assessed using the 'whether follow-up was long enough for outcomes to occur' item in the quality assessment section. If the follow-up period was not long enough, the authors would note

the number of 'pending/waiting' follow-up examinations in the text. For example, 20 patients from Deepak et al.[109] and 20 patients from Jacobs et al.[126] had pending follow-up examinations at the end of the study periods. Since these patients were not followed long enough to determine defined adherence, they were excluded from the adherence rate calculation. For anytime adherence, the length of the follow-up period would not become a concern because patients would be defined as adherent if they received a follow-up examination anytime during the course of the study period. The study by Muñoz-Largacha et al.[124] mentioned by the authors, is one of the examples where only anytime adherence was reported. Last, it is important to assess the heterogeneity in adherence rates using data from the general population. However, due to the limited reporting of such data, future research is needed to conduct the proposed analysis. Currently, data from institutional settings remains the primary source for evaluating patient adherence to LCS recommendations.

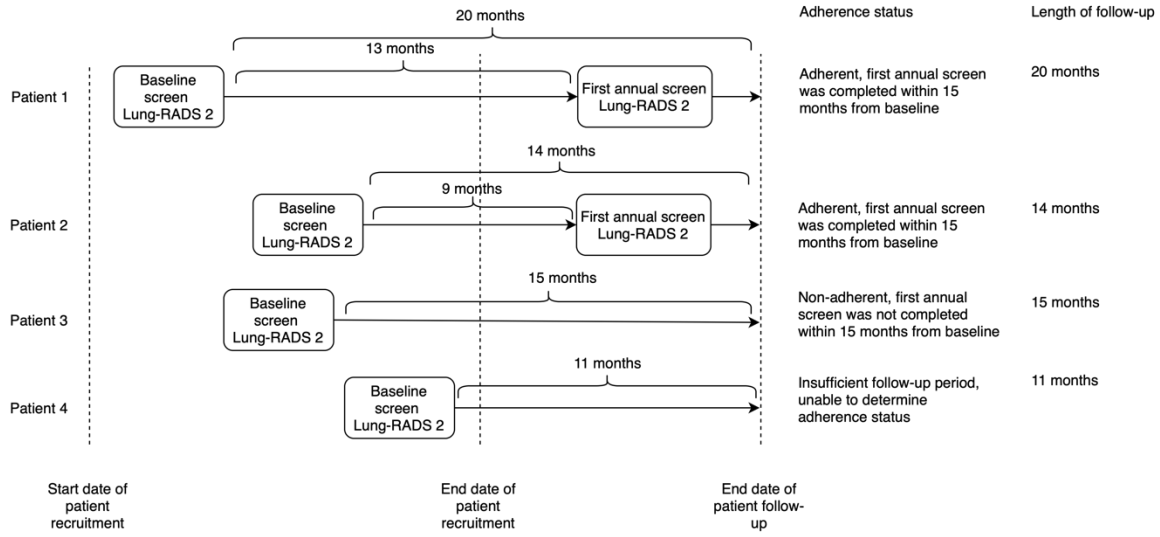

Fig. 3.3 Illustration of how patient adherence to baseline Lung-RADS recommendations is defined. All patients were assumed to have had a baseline Lung-RADS 2 screen. Adherence was defined as the completion of the first annual screen within 15 months from the baseline screen. Lung-RADS: Lung CT Screening Reporting & Data System.

This systematic review and meta-analysis have several limitations. First, we included both conference abstracts and journal articles in the review. Abstracts are more susceptible to missing details that can be used to evaluate potential sources of heterogeneity in adherence rates, such as interventions for adherence, LCS program resources, and adherence rates in subgroups. Second, we were unable to perform a meta-analysis on adherence rates beyond the first annual incidence screen owing to the scarcity of data. Capturing adherence rates beyond T1 can provide richer information in that adherence rates at different screen time points may vary. As suggested by Kaminetzky et al.,[132] adherence rates among Lung-RADS 1 to 2 were 46%, 38%, and 28% at T1, T2, and T3, respectively. Third, there were insufficient data on adherence rates among subgroups for sex, race, and smoking status to reveal the true differences in adherence rates between subgroups. Last but not least, we provided a summary of predictors of non-adherence identified in individual studies (**Table 3.7**). Still, we did not perform a meta-analysis on these predictors owing to concerns about their degree of heterogeneity and lack of published data. Such meta-analysis might better inform modifiable factors and effective interventions that can improve adherence rates.

Given the heterogeneity we observed in reporting adherence to LCS, we have developed a checklist to guide future research and publications (**Table 3.8**). These data elements span several categories, such as the following: study period, eligibility criteria, LCS program resources, screening characteristics, and outcome reporting. These data elements provide necessary information to evaluate screening and enable comparisons across programs while also providing data across sex, race/ethnicity, smoking status, and insurance status which may influence adherence. These additional data elements would inform directions for future research, including the following: (1) eval-

uating patient adherence longitudinally, (2) identifying barriers to LCS and patterns of non-adherence, (3) evaluating tailored interventions to optimize adherence, and (4) applying machine learning based approaches to realize the individualized intervention.

Table 3.8 A checklist for reporting LCS adherence.

Adherence reporting variable	No.	Item
Study period	1	State the start date of patient recruitment
	2	State the end date of patient recruitment
	3	State the end date of patient follow-up
Eligibility criteria	4	Specify LCS guidelines for patient eligibility (e.g., USPSTF)
	5	Describe any additional inclusion/exclusion criteria
LCS program resources	6	Indicate if a program coordinator/navigator is part of the LCS program and their responsibilities
	7	Report whether shared decision-making is offered by the LCS program
	8	Indicate whether smoking cessation services are provided, including counseling and treatment
	9	Describe any interventions used by the LCS program to increase adherence (e.g., phone calls, reminder letters, clinician communications)
Screening characteristics	10	Present patient characteristics at each screen (e.g., demographics, smoking status, pack-years, insurance status, etc.)
	11	Specify Lung-RADS distribution at each screen
Outcome reporting	12	Provide an objective definition of adherence

Table 3.8 A checklist for reporting LCS adherence.

Adherence reporting variable	No.	Item
	13	State whether patients who died or became ineligible for additional screens during follow-up were labeled as adherent or non-adherent, or excluded from the analysis
	14	Specify screen time point for assessing adherence (e.g., T1: first annual incidence screen after initial screen; early 3 month follow-up scan)
	15	For each adherence rate, give number of adherent patients (numerator) and total number of patients (denominator)
	16	Provide adherence rates for each individual Lung-RADS category
Additional data elements	17	Report adherence rates in other subgroups (e.g., males vs females, current vs former smokers)
	18	List any identified predictors of non-adherence
	19	Summarize reasons for non-adherence

LCS: lung cancer screening; USPSTF: United States Preventive Services Task Force; Lung-RADS: Lung CT Screening Reporting & Data System.

3.5 Conclusion

This study reveals that the overall rates of adherence to Lung-RADS–recommended screening intervals in clinical practices are low as compared with the more than 90% adherence found in the NLST: 57% for defined adherence and 65% for anytime adherence. Meta-analysis of adherence rates reveals significant between-study heterogeneity. Through meta-regression, Lung-RADS categories and reporting of smoking cessation services contribute to this heterogeneity. In subgroup analysis, patients with baseline Lung-RADS 3 to 4 are more adherent than those with baseline Lung-RADS 1 to 2, suggesting tailored interventions on the basis of Lung-RADS categories may be beneficial. Furthermore, inconsistent reporting of adherence rates and supporting details are observed. Standardized reporting of adherence rates to LCS is necessary for the guidance of research and identification of interventions for improving adherence.

In summary, this systematic review and meta-analysis identifies the Lung-RADS score as a consistent factor that causes the adherence rates to vary in clinical LCS programs in the US. In the following chapters, the Lung-RADS score will be included as one of the potential predictors of patient adherence to LCS.

CHAPTER 4

The Lung Cancer Screening Cohort at UCLA

Chapter 3 is a comprehensive overview of patient adherence to Lung-RADS recommendations in clinical practices across the United States. While the Lung-RADS score is a significant predictor of non-adherence, other patient-level predictors exist, such as socioeconomic and health status variables, but their predictive value remains largely unstudied. The purpose of this chapter is to introduce the UCLA LCS cohort as the basis for studying these patient-level predictors. We examined the availability of relevant social determinants of health (SDH) variables using the Carter-Harris conceptual model as a basis. We also describe nuances associated with using patient-level data, including the fact that LCS was not offered during the start of the COVID-19 pandemic. This chapter begins with an introduction to the LCS cohort at our institution, followed by a discussion on the impact of the COVID-19 pandemic on LCS participation and adherence at our institution. We then describe the independent and dependent variables used in Chapters 5 and 6. Last, we investigate the availability and degree of standardization of the antecedent variables from the Carter-Harris conceptual model in our medical records and published ontologies and controlled vocabularies.

4.1 Study Population

4.1.1 The UCLA Multidisciplinary Lung Cancer Screening Program

UCLA Health launched the UCLA Multidisciplinary Lung Cancer Screening Program (MLSP) in 2015[150] with a commitment to the prevention and early detection of lung cancer, screening nearly 1,000 patients each year. The program has grown since its 2015 inception, now staffed

by dedicated thoracic radiologists, a dedicated nurse practitioner, and two administrative staff. Together, the MLSP team ensures compliance with federal requirements and provides eligibility determination and shared decision-making (a requirement for CMS coverage). Prior to Mar 2021, the MLSP followed the USPSTF recommendation; individuals who met the following criteria were encouraged to participate in LCS: current and former smokers between 55-80 years of age, minimum 30 pack-year smoking history, and within 15 years since quit if a former smoker. The program has also regularly collected other risk factors, such as exposure to radon or asbestos, respiratory or other cancers, or a family history of lung cancer. The team updated their eligibility criteria following the 2021 USPSTF revision of the LCS guidelines, by lowering the age at screening onset and smoking intensity to 50 years and 20 pack-years, respectively. The greatest effect of these revisions is on LCS utilization because a broader cohort of smokers become eligible for LCS. The focus of this dissertation, patient adherence to Lung-RADS recommendations, is unaffected because the recommended follow-up intervals remain unchanged for each Lung-RADS category. Having built a robust screening team, the MLSP is now poised to implement quality improvement measures with the goal of increasing the rate of enrollment into the MLSP as well as rates of adherence by patients who have already entered the program. Specifically, the remaining chapters of this dissertation will focus on the investigation of patient adherence to LCS at UCLA, identifying patient-level risk factors, revealing patterns of adherence over multiple screening time points, and building machine learning-based models to predict longitudinal adherence.

4.1.2 Cohort Definition

Although the MSLP launched in 2015, UCLA Health began offering LDCT screens as early as 2013. The first version of Lung-RADS (Lung-RADS v 1.0)[148] was released on April 28,

2014. Lung-RADS scores were manually assigned to LDCT examinations that were performed prior to the release date of Lung-RADS v 1.0 by a board-certified thoracic radiologist. Our dataset captures 3727 patients who have completed at least one LDCT examination at UCLA between July 31, 2013 and November 11, 2021 (last date of follow-up prior to December 8, 2021) across ten geographically distributed UCLA Health sites where LCS is offered. We excluded 809 patients who did not have sufficient follow-up time to determine adherence status by the end date of follow-up (see **Fig 4.1**), leaving 2860 eligible patients (see **Fig. 4.2**). Among 2860 patients with at least one LDCT screen during the enrollment period, 364 were excluded (see **Fig. 4.2** for exclusion criteria). **Table 4.1** provides a summary of the patient demographics of the remaining 2496 patients. Chapters 5 and 6 used subsets of the 2496 patients to determine factors associated with non-adherence to LCS. In Chapter 6, where adherence across multiple time points was assessed, annual screens or interval short-term interval LDCT screens were excluded if patients were greater than 80 years of age at the time of screen (n=69), the screen was a Lung-RADS 0, signifying an incomplete exam, presumed inflammatory process, or awaiting historical comparison exams (n=8), or the screening examination was incorrectly ordered for non-screening purposes such as surveillance imaging in a patient with known lung cancer or for short term reassessment of a positive screening result (n=25).

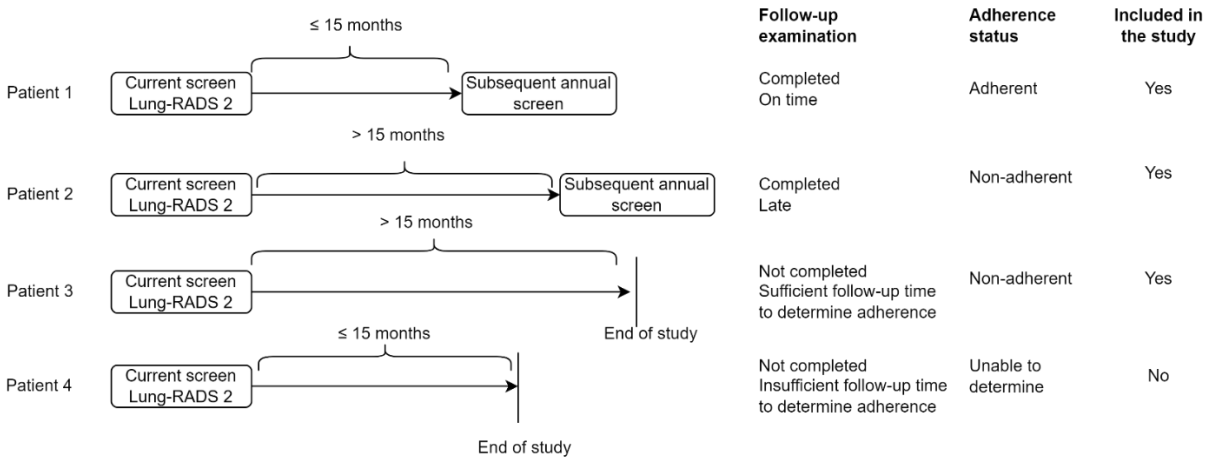

Fig. 4.1 Examples of determining patient adherence statuses to Lung-RADS recommendations. All patients were assumed to have had a current Lung-RADS 2 screen. Adherence was defined as completion of the subsequent annual screen within 15 months from the current screen. Lung-RADS: Lung CT Screening Reporting & Data System.

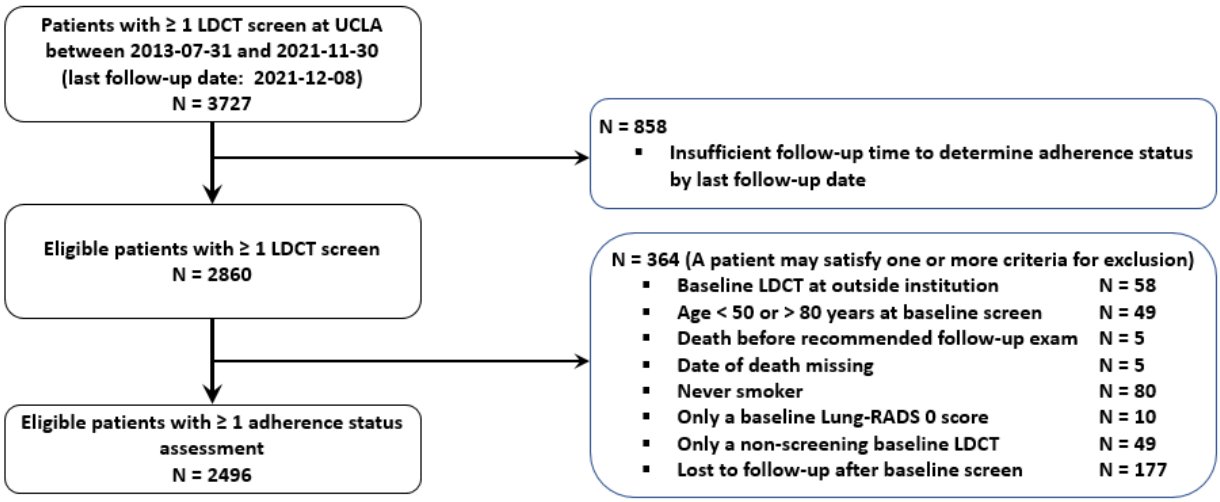

Fig. 4.2 The flow diagram of patient enrollment.

Table 4.1 Patient characteristics (N=2496).

Variable	n (%)
Age in years	
<65	1075 (43.1)
≥65	1421 (56.9)
Sex	
Female	1010 (40.5)
Male	1486 (59.5)
Race/ethnicity	
Asian	203 (8.1)
Black	168 (6.7)
Hispanic/Latino	134 (5.4)
White	1887 (75.6)
Other [a]	52 (2.1)
Missing	52 (2.1)
Education level	
Less than college	1091 (43.7)
College Graduate	673 (27.0)
Postgraduate	474 (19.0)
Missing	258 (10.3)
Smoking status	

Table 4.1 Patient characteristics (N=2496).

Variable	n (%)
Current	977 (39.1)
Former	1487 (59.6)
Missing	32 (1.3)
Family history of lung cancer	
Yes	558 (22.4)
No	1938 (77.6)
Primary insurance	
Medicare/Medicaid	1060 (42.5)
Private or commercial	1380 (55.3)
VA	1 (0.0)
Self-pay	37 (1.5)
Other	1 (0.0)
Missing	17 (0.7)

[a] Subcategories in other race: American Indian or Alaska Native, Native Hawaiian or Pacific Islander, more than one race, or other racial and ethnic groups not otherwise stated.

4.1.3 Data Sources

Data from the UCLA LCS cohort was obtained from two sources through data requests, the Integrated Diagnostics (IDx) Lung Database and UCLA Clinical and Translational Science Institute (CTSI). These are briefly described below.

4.1.3.1 IDx Lung Database

The IDx Lung Database is part of the IDx Shared Resource, a joint initiative within the Departments of Radiological Sciences and Pathology and Laboratory Medicine within the David Geffen School of Medicine at UCLA. In particular, the IDx Lung database supports research in the early detection and diagnosis of lung cancer using machine learning-based methods. The goals of establishing this database are to support researchers and clinicians in training and testing machine and deep learning-based approaches for characterizing pulmonary nodules and characterizing early lung cancers.

This longitudinal lung database captures patients undergoing LCS at UCLA Health and hosts structured and highly curated data. Data from the electronic medical records (EMR) are entered into the database using structured data forms with pre-defined data fields and are validated by at least a second data entry staff member to ensure high data quality. The database captures patients' demographic, clinical, imaging, pathologic, and treatment data, linking this information with semantic and quantitative features extracted from diagnostic images. We extracted relevant data elements from this database for the analyses in the following chapters, including demographics, socioeconomic status, health status, Lung-RADS score, and follow-up information to determine adherence.

4.1.3.2 UCLA Clinical & Translational Science Institute (CTSI)

The UCLA CTSI is a research partnership across four institutions, including UCLA, Cedars-Sinai Medical Center, Charles R. Drew University of Medicine and Science, and Harbor-UCLA Medical Center/Lundquist Institute for Biomedical Innovation. Since its inception in 2011, the CTSI has produced and implemented innovations that impact the greatest health needs of people.

Because the IDx Lung Database does not capture zip code and state area deprivation index (ADI) information, we requested these data elements from the UCLA CTSI. Zip code is used to estimate the patient's family median annual income and calculate the distance between the patient's home and the screening center where their LDCT scans were performed.

4.2 Variables Related to LCS

Table 4.2 summarizes the independent and dependent variables to model adherence in the UCLA LCS cohort in Chapters 5 and 6.

Table 4.2 The independent and dependent variables used in the models mentioned in Chapters 5 and 6.

Variable		Category	Note
Independent	Lung-RADS	1-2, 3, 4A, 4B/X or 1-2 (negative), 3-4 (positive)	
	Age in years		The difference between the date of an LDCT and the date of birth
	Sex	Female, male	

Table 4.2 The independent and dependent variables used in the models mentioned in Chapters 5 and 6.

Variable		Category	Note
	Race/ethnicity	White, Black, Hispanic/Latino, Asian, other	
	Education level	Less than college, college graduate, postgraduate	
	Family history of lung cancer	Yes, no	
	Smoking status	Current, former	
	Primary insurance	Medicaid/Medicare, private or commercial, other	
	Age-adjusted CCI	Low (0-1), intermediate (2-3), high (≥4)	Calculation according to Suidan et al.[151]
	Distance to screening center	Short (≤median), long (>median)	The distance between the patient's home zip code and screening center in miles
	Median household income	Low (≤median), high (>median)	Median family income mapped with the 2010 Census database using home zip code
	ADI state rank	Low (≤median), high (>median)	

Table 4.2 The independent and dependent variables used in the models mentioned in Chapters 5 and 6.

Variable		Category	Note
	Type of referring physician	Pulmonology, Thoracic Oncology/Radiology/Surgery Other	The clinical specialty of the referring physician
	Expected follow-up exam	Pre-COVID-19, during COVID-19 pause, post-COVID-19 pause	
Dependent	Adherence status	Adherent, non-adherent	On-time adherence

On-time adherence: defined as completion of a recommended or more aggressive follow-up examination with 15 (Lung-RADS 1-2), 9 (Lung-RADS 3), 5 (Lung-RADS 4A), and 3 (Lung-RADS 4b/x) months from the current LDCT.

Lung-RADS: Lung CT Screening Reporting & Data System; CCI: Charlson Comorbidity Index; ADI: Area Deprivation Index; LDCT: low-dose computed tomography.

4.2.1 The Independent Variables

Baseline factors of interest included Lung-RADS score, age, sex, race/ethnicity, education level, family history of lung cancer, smoking status, primary insurance status, age-adjusted Charlson Comorbidity Index (CCI)[151], distance to screening center, median family income, area deprivation index (ADI) state rank[152], and type of referring physician. Race and ethnicity data were obtained from a self-reported questionnaire administered prior to the LDCT screening examination that was stored as a discrete series of the screening exam in our picture archiving and communication system. When such data were missing from the questionnaire, data in the electronic medical

record were extracted. The 'Other' race/ethnicity category included American Indian or Alaska Native, Native Hawaiian or Pacific Islander, more than one race, or other racial and ethnic groups not otherwise stated. Age-adjusted CCI was grouped into three categories: low (0-1), intermediate (2-3), and high (≥4)11. Median family income was mapped with the 2010 Census data using the home zip code. Distance to the screening center was estimated between the home zip code and the zip code of the screening center. We dichotomized the following variables: ADI state rank, median family income, and distance to the screening center: low/short (≤median) and high/long (>median).

In July 2017, the MSLP recruited a nurse practitioner to function as the co-director of the program and to assist patient enrollment and eligibility assessment (e.g., performing shared decision-making with patients), as well as to remind patients about their follow-up examination after an LDCT screen. Prior to July 2017, the ordering provider (primary care or pulmonology) was responsible for reminding their patient to come back in. We assessed if there was a difference between adherence rates to baseline Lung-RADS recommendations before and after July 2017 and found non-significant results. A logistic regression model was used, adjusting for Lung-RADS score, patient demographics, socioeconomic status, and health-related variables. As such, we did not include the presence of a study coordinator as a variable in our models discussed in Chapters 5 and 6.

The analysis in Section 4.4 showed that there was a significant decrease in adherence in the post-COVID-19 period as opposed to the pre-COVID-19 period ($p<0.05$). Thus, we included a variable that denotes whether the expected follow-up examination was pre, during, or post COVID-19 shutdown period. **Fig. 4.3** plots the number of LDCTs by month from 2018 to 2021. The overall trend across the four years is similar, except for a sharp drop from March to May 2020.

This finding aligns with our definition of the COVID-19 shutdown period (see Section 4.4), which extended from March 19 to May 19, 2020.

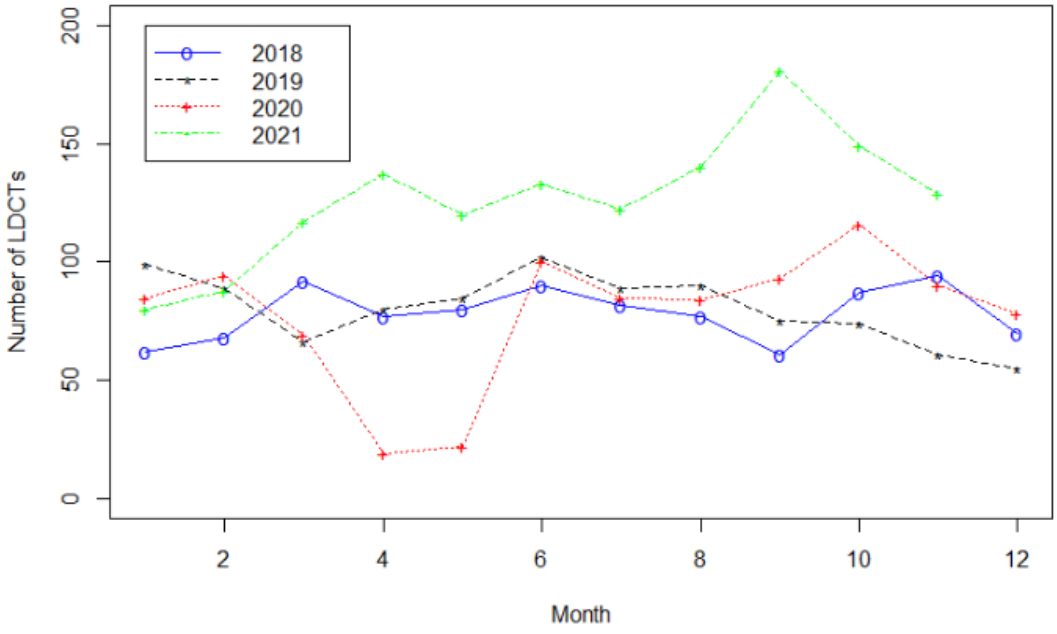

Fig. 4.3 Plots of numbers of monthly LCS LDCTs from 2018 to 2022 at UCLA Health. LCS: lung cancer screening; LDCT: low dose computed tomography.

4.2.2 The Dependent Variable

The patient outcome of the study was non-adherence, defined as failing to comply with follow-up recommendations based on the Lung-RADS category, factoring in some time allowance from the recommended period. Adherence was defined for Lung-RADS 1-2 as completing the next annual screen within 12 months + 3 months; for Lung-RADS 3, completing a recommended interval repeat LDCT within 6 months + 3 months; for Lung-RADS 4A, completing an interval LDCT within 3 months + 2 months; and for Lung-RADS 4B/X, completing more definitive diagnostic workup (i.e., diagnostic CT chest, PET-CT, or tissue sampling) within 3 months of the abnormal

screen (see **Fig. 4.1**). Patients were considered adherent if they completed a more invasive (i.e., diagnostic CT chest, PET-CT, or tissue sampling as opposed to LDCT) follow-up examination within the defined time intervals.

4.3 Availability of the Antecedent Variables from the Carter-Harris Conceptual Model

This section is part of the paper "Capturing Demographic, Health-Related, and Psychosocial Variables in a Standardized Manner: Towards Improving Cancer Screening Adherence," presented at the 2022 American Medical Informatics Association Annual Symposium.[153]

4.3.1 Overview

Although the Carter-Harris conceptual model[20] provides a blueprint of what variables should be considered, it does not specify how to measure and encode these variables to facilitate data sharing and semantic interoperability. Markedly, the current state of data capture for the enumerated variables (e.g., cancer fatalism, smoking-related stigma, lung cancer worry, fear, etc.) is not well characterized, and it is not clear how to best collect this information and from what data sources. In this work, we focus on capturing the antecedents from the Carter-Harris conceptual model in a consistent and standardized manner. Antecedents are the circumstances that exist before a behavior related to cancer screening. In the Carter-Harris model, antecedents, a combination of SDH and psychological and cognitive variables, are precursors to the stage of adoption for LCS, the shared decision-making process, and the subsequent outcomes concerning LCS behavior (**Fig. 2.4**). In prior studies, such antecedents have been shown to correlate with patient participation in lung, breast, cervical, or colorectal cancer screening programs.[20] Our goal is to examine the current state and gaps in the standardized collection of SDH data, using cancer screening as a driving

application. We investigate whether data standards exist for demographic, health-related, and psychosocial variables and their level of completeness in the EHR. To our knowledge, no analysis has characterized the current representations of variables affecting LCS participation – or, more generally – and adherence across the EHR and existing medical ontologies.

4.3.2 Methods

4.3.2.1 Defining and Mapping Variables

Carter-Harris et al. grouped antecedents into five categories (**Fig. 2.4**): 1) psychological variables, 2) demographic and health status characteristics, 3) cognitive variables, 4) healthcare provider recommendation, and 5) social and environmental variables. Each category consists of a set of variables, such as social influence and media exposure. Among the 18 antecedents, seven are broadly considered SDH, including gender, race/ethnicity, income, education, smoking-related stigma, social influence, and media exposure.[96] For each variable, we defined a data element with permissible values, mapping it to EHR data relevant to the specific antecedent, published ontologies, controlled vocabularies (see Section 4.3.2.2), and/or survey instruments whenever possible. Next, we identified potential data sources for each data element. Information sources were represented in various formats, including the EHR and questions in a survey instrument, such as Shen's scale for measuring fatalism[154]. When more than one source of representation was available for a specific variable, we listed the most used representation(s) reported in systematic reviews on measures/survey instruments of these variables (e.g., a systematic review on measuring medical mistrust[155]). Considering data elements that are not currently collected in a standardized manner, we identified existing techniques in literature that have been used to collect this information (e.g., survey instruments).

4.3.2.2 Identifying Relevant Data Elements in the EHR, Existing Ontologies, and Literature

1. Search strategy. The search terms were the exact expression of antecedents from the Carter-Harris conceptual model. Specifically, we independently searched representations for each antecedent variable across potential data sources. For example, 'medical mistrust' was used as the search term (or keyword) for the medical mistrust variable mentioned in the antecedents. We did not add synonyms of the antecedents in the search terms. However, we also used a more general term that was not specific to LCS for certain variables. For example, we searched cancer "worry" and cancer "fear" in addition to more specific lung cancer worries and fears.
2. Searching the EHR. Using our institution's EHR (Epic Systems, Verona, WI) as a representative example, we investigated which variables were presently captured, whether captured data were collected in a consistent and standardized format; and if the variables were not available, alternative sources that could be used. This process was conducted in three ways: 1) examining data elements that are displayed in the EHR user interface, 2) using the 'Search' bar with keywords, and 3) consulting with clinicians on unstructured fields that may contain relevant information. In addition to examining data elements that are explicitly captured in the EHR, we also examined data elements collected as part of a questionnaire administered to the patient before his/her LDCT screening exam; a digitized copy of the questionnaire is retained as a series within the LDCT screening exam in our picture archiving and communications system. This questionnaire collects data variables required by the PLCOM2012 6-year lung cancer risk model[156] in a standardized manner (i.e., all multiple-choice questions, no free-text questions).

The EHR search was conducted by one author, who has two years of experience in extracting patient information from our institution's EHR.

3. Searching other catalogs and resources. Alongside searching the EHR, we queried BioPortal[157], a comprehensive repository of biomedical ontologies and terminologies, and used 'Class Search' to examine existing medical ontologies for the antecedents. In addition to BioPortal, search results from three vocabulary systems/toolkits were summarized, NIH Common Data Elements (provides access to structured data elements that have been recommended or required to use in research sponsored by the NIH or other organizations)[158], NIH RADx-UP Common Data Elements (captures a variety of variables such as sociodemographic, housing, insurance, medical history, health status, tobacco use, medical trust, etc.)[159], and PhenX Toolkit (covers SDH variables, tobacco use, etc.)[160]. Finally, PubMed and Google Scholar were used to identify measures not captured in the EHR. Two authors searched BioPortal, the NIH Common Data Elements, NIH RADx-UP Common Data Elements, and PhenX Toolkit for relevant concepts (end date of search: Mar 8, 2022). Discrepancies in search results were resolved through a consensus discussion.

4.3.2.3 Data Quality Assessment

We focused on one dimension in data quality assessment – data completeness – where we characterized the current level of coverage for antecedents by reporting what percentage of variables could be represented using existing standardized data elements. Specifically, we identified what percentage of data elements can be populated using information that is readily collected in the EHR, NIH Common Data Elements, NIH RADx-UP Common Data Elements, and PhenX

Toolkit because these ontologies were likely to capture representations for a large number of antecedent variables given their broad coverage of data elements in demographics, health-related, and psychosocial variables. We also assessed the percent of antecedents captured in survey instruments from literature (unstandardized data).

4.3.3 Results

Table 4.3 (a simplified version provided below, see https://github.com/allyn1982/AMIA_2022_Student_Paper for the full version) summarizes possible data sources for antecedents from the Carter-Harris conceptual model.

Table 4.3 (Simplified Version) Potential data sources of antecedents in the Carter-Harris conceptual model for lung cancer screening participation.

Variable	Definition	Common data sources	Dimensions	No. Items	Scales/Values
Perceived smoking-related stigma	A social process by which exclusion, rejection, blame or devaluation occurs[161]	Proxy: stigma. BioPortal: two original ontologies in psychology and nursing practice. Proxy: 'covid_iso_chal' in NIH RADx-UP CDE.			
		Stuber et al.[93] 2009	Devaluation	2	Four-point Likert scale
			The respondents' perceptions that they are the subject of differential treatment due to smoking	3	Dichotomous
		Internalized Stigma of Smoking Inventory[92] (α=0.80, 0.81, and 0.70 for self stigma, felt stigma, and discrimination experiences, respectively) 2015	Self stigma	3	Four-point Likert scale
			Felt stigma	3	
			Discrimination experiences	2	
Medical mistrust	Distrust of medical personnel and organizations[162]	Proxy: 'trust_doc_2' in NIH RADx-UP CDE. BioPortal: none exists.			
		Medical Mistrust Index[163] (α=0.76) 2009	NA	7	Four-point Likert scale
			Suspicion	6	Five-point Likert scale

Table 4.3 (Simplified Version) Potential data sources of antecedents in the Carter-Harris conceptual model for lung cancer screening participation.

Variable	Definition	Common data sources	Dimensions	No. Items	Scales/Values
Cancer fatalism	The belief that death is inevitable when cancer is present[165]	Group-Based Medical Mistrust Scale[164] (α=0.83) 2004	Group disparity	3	Five-point Likert scale
			Lack of support	3	
		Other instruments mentioned in a systematic review[155]			
		Proxy: fatalism. BioPortal: two original ontologies in psychology and consumer health.			
		Shen et al.[154] (applicable across a wider range of health conditions and with a broader set of culture) (overall α=0.88, α=0.86, 0.80, 0.82 for predetermination, luck, and pessimism, respectively) 2009	Predetermination	10	
			Luck	4	
			Pessimism	6	
		Other instruments mentioned in a systematic review[166]			

Table 4.3 (Simplified Version) Potential data sources of antecedents in the Carter-Harris conceptual model for lung cancer screening participation.

Variable	Definition	Common data sources	Dimensions	No. Items	Scales/Values
Lung cancer worry	Concerns about developing cancer or cancer recurrence, and the impact of these concerns on daily functioning, among individuals at risk for hereditary cancer[167]	NIH CDE, BioPortal: one original ontology in LOINC.			
		Proxy: cancer worry. BioPortal: one original ontology. Cancer Worry Scale[168] (α=0.87) 2014	NA	8	Four-point Likert scale
		Proxy instrument: breast cancer worry[169] (α=0.85) 2012	NA	2	Categorical
Lung cancer fear	The threat of what a lung cancer diagnosis may mean to the individual[170, 171]	Proxy: cancer fear. BioPortal: three original ontologies in primary care and clinical terms.			
		Psychological Consequences Questionnaire[171] 2008	NA	3	Five-point scale
Age	Age	EHR, NIH CDE, NIH RADx-UP CDE, PhenX Toolkit, BioPortal: >10 original ontologies.	NA	NA	Continuous or categorical
Gender	Gender	EHR, NIH CDE, NIH RADx-UP CDE, PhenX Toolkit, BioPortal: >10 original ontologies.	NA	NA	Dichotomous

Table 4.3 (Simplified Version) Potential data sources of antecedents in the Carter-Harris conceptual model for lung cancer screening participation.

Variable	Definition	Common data sources	Dimensions	No. Items	Scales/Values
	Proxy: sex	EHR, NIH CDE, NIH RADx-UP CDE, PhenX Toolkit, BioPortal: >10 original ontologies.	NA	NA	Dichotomous
Race/ethnicity	Race/ethnicity	EHR, NIH CDE, NIH RADx-UP CDE, PhenX Toolkit, BioPortal: >10 original ontologies.	NA	NA	Categorical
Income	Income: ontology-specific definitions	EHR, NIH CDE, NIH RADx-UP CDE, PhenX Toolkit, BioPortal: >10 original ontologies.	NA	NA	Continuous or categorical
	Proxy: zip code (map family income)	EHR, NIH CDE, NIH RADx-UP CDE, PhenX Toolkit, BioPortal: >10 original ontologies.	NA	NA	Continuous or categorical
Insurance status	Insurance status	EHR, NIH CDE, NIH RADx-UP CDE, PhenX Toolkit, BioPortal: >10 original ontologies.	NA	NA	Categorical
Education	The highest level of education	EHR (source: UCLA-specific questionnaire), NIH CDE, NIH RADx-UP CDE, PhenX Toolkit, BioPortal: >10 original ontologies.	NA	NA	Categorical

Table 4.3 (Simplified Version) Potential data sources of antecedents in the Carter-Harris conceptual model for lung cancer screening participation.

Variable	Definition	Common data sources	Dimensions	No. Items	Scales/Values
Smoking status	Smoking status	EHR, NIH CDE, NIH RADx-UP CDE, PhenX Toolkit, BioPortal: >10 original ontologies.	NA	NA	Categorical
Family history of lung cancer	A reported family history of lung cancer in one or more family members	EHR, BioPortal: one original ontology.	NA	NA	Dichotomous
		BioPortal: none exists.			
Knowledge about lung cancer	Awareness of symptoms and risk factors of lung cancer[172]	Lung Cancer Awareness Measure[172] (overall α=0.88, α=0.91 and 0.74 for the warning signs and risk factors subscales) 2012	Socio-demographical characteristics	6	Dichotomous or categorical
			Knowledge of warning signs for lung cancer	14	Continuous
			Knowledge of risk factors of lung cancer	9	
		BioPortal: none exists.			

Table 4.3 (Simplified Version) Potential data sources of antecedents in the Carter-Harris conceptual model for lung cancer screening participation.

Variable	Definition	Common data sources	Dimensions	No. Items	Scales/Values
Knowledge about lung cancer screening	Knowledge about lung cancer screening guidelines and frequency	Proxy: adapted from colorectal cancer screening[173]	Screening participation	1 (2 follow-up questions)	Dichotomous (follow-up questions: free text)
			Screening frequency	1	Free text
Healthcare provider recommendation	Documented recommendations of getting a screening LDCT from healthcare providers	BioPortal: none exists.			
		EHR (free text)	NA	NA	Free text
Social influence	The influence of family and friends on an individual's behavior[174]	BioPortal: one original ontology.			
		Proxy: adapted from breast cancer screening[175] (α=0.93)	NA	7	Five-point scale

Media exposure	The potential influence of commercial, print, and social media on cancer screening participation[176, 177]	BioPortal: one original ontology in psychology.			
		Proxy: 'Media Use During COVID-19' in PhenX Toolkit.			
		Proxy: media exposure[44] (α=0.74 and 0.65 for general and health-specific media exposure, respectively) 2014	General media exposure	2	Continuous
			Health-specific media exposure	3	Categorical

α: Cronbach's alpha, a measure of internal consistency or reliability for a survey/questionnaire.

EHR: electronic health record, NIH: National Institutes of Health, CDE: common data elements, LOINC: Logical Observation Identifier Names and Codes.

Demographic and health status characteristics (age, gender, race/ethnicity, income, insurance status, education, smoking status, and family history of lung cancer) were well-standardized in current medical vocabularies. All variables were captured in the EHR system at our institution in a normalized manner (i.e., each stored as a variable with standardized values in the EHR database). Seven of eight variables could be obtained from all three medical ontologies (the NIH Common Data Elements, NIH RADx-UP Common Data Elements, and PhenX Toolkit). Our institution's EHR implementation lacks a structured field that indicates whether a screen-eligible patient received a recommendation for LCS from a healthcare provider. Still, healthcare provider recommendations for LCS among high-risk individuals were documented in physicians' notes or the "Indication" section of a screening CT interpretation.

The remaining three categories of antecedents were largely unstandardized: we found standardized mappings for a few psychological, cognitive, social, and environmental antecedents from our EHR system, BioPortal searches, or the three medical ontologies (the NIH Common Data Elements, NIH RADx-UP Common Data Elements, and PhenX Toolkit), and most of these mappings were proxies. For example, there existed ontologies for stigma (as a proxy for smoking-related stigma) and fatalism (as a proxy for cancer fatalism) in BioPortal. Therefore, we attempted to map the measurements of these variables with survey instruments developed in the literature. For the five psychological variables (i.e., perceived smoking-related stigma, medical mistrust, cancer fatalism, lung cancer worries, and lung cancer fear), we found at least one instrument that had been used to measure these variables. The instruments were either a direct mapping of the antecedent developed from a screening or non-screening cohort or a proxy instrument used in other

domains (such as cancer screening and COVID-19) that could potentially be used in cancer screening. For cognitive variables, the Lung Cancer Awareness Measure[172] could be used to assess patients' knowledge about lung cancer. Given that no instruments had been developed to measure patients' knowledge about LCS, we listed a proxy instrument, a modified version of an instrument developed to assess patients' knowledge about colorectal cancer screening[173]. Similarly, no instruments existed for measuring social influence among participants in LCS. We adapted instruments originating from breast cancer screening.[175] A proxy instrument[178] for measuring general and health-specific media exposure was included for media exposure because no studies had investigated the effect of media exposure on LCS behavior.

In total, among 18 antecedents, nine (50%) variables were captured in the EHR system at our institution (**Table 4.4**). Two standardized medical vocabulary repositories captured up to half of the antecedents: eight (44%) variables were found in the NIH Common Data Elements repository, and nine (50%) variables were indexed in the NIH RADx-UP Common Data Elements repository. The PhenX Toolkit had representations for eight (44%) antecedents. Although the EHR and three medical vocabularies captured 44-50% of the antecedents, most variables were from the demographic and health status characteristics category. Survey instruments from the literature provided measures for the nine (50%) psychological, cognitive, social, and environmental variables, six of which (including proxies) were indexed in BioPortal. Using a combination of EHR and survey instruments from the literature, all 18 antecedents were captured. Yet 22% of these antecedents (including three survey instruments that were not included in BioPortal and the healthcare

provider recommendation variable, which was documented in free text in the EHR) lacked a standardized data format and varied in semantics and permissible values, depending on survey instrument of EHR implementation.

Table 4.4 Summary of representations of antecedents in the Carter-Harris conceptual model.

No	Variable	EHR	NIH Common Data Elements	NIH RADx-UP Common Data Elements	Phenx Toolkit	Instruments from literature
1	Perceived smoking-related stigma			✓*		✓
2	Medical mistrust			✓*		✓
3	Cancer fatalism					✓
4	Lung cancer worry		✓			✓
5	Lung cancer fear					✓
6	Age	✓	✓	✓	✓	
7	Gender (or sex)	✓	✓	✓	✓	
8	Race/ethnicity	✓	✓	✓	✓	
9	Income [a]	✓	✓	✓	✓	
10	Insurance status	✓	✓	✓	✓	
11	Education	✓	✓	✓	✓	

Table 4.4 Summary of representations of antecedents in the Carter-Harris conceptual model.

No	Variable	EHR	NIH Common Data Elements	NIH RADx-UP Common Data Elements	Phenx Toolkit	Instruments from literature
12	Smoking status	✓	✓	✓	✓	
13	Family history of lung cancer	✓				
14	Knowledge about lung cancer					✓
15	Knowledge about lung cancer screening					✓*
16	Healthcare provider recommendation	✓**				
17	Social influence					✓*
18	Media exposure				✓*	✓*
Percent captured (%)		50 (9/18)	44 (8/18)	50 (9/18)	44 (8/18)	50 (9/18)

[a] Include family income mapped by zip code.

* Need to adapt from other domains, such as COVID-19, breast and colorectal cancer screening.

** Unstandardized. E.g., free text.

EHR: electronic health record, NIH: National Institutes of Health.

4.3.4 Discussion

Using LCS as an example, our study highlights the lack of consistent and standardized representations for variables that are needed to understand the drivers of patient participation in and adherence to cancer screening. In this exploratory analysis, we mapped antecedents from the Carter-Harris conceptual model to existing standardized medical vocabularies and EHR data, identifying gaps in data elements that needed to be collected from additional sources (i.e., survey instruments). Our analysis suggests that many common antecedents, including psychological, cognitive, social, and environmental variables, have yet to be standardized and consistently represented. While a previous study revealed more than 1,000 clinical codes in common medical vocabularies (i.e., LOINC, SNOMED CT, ICD-10-CM, and CPT) that could potentially be used to document SDH-related clinical activities,[179] our study showed that a number of antecedents are missing from these codes.

In the absence of standardized representations from either the EHR or common data vocabularies, researchers face the challenge of selecting the most appropriate survey instrument to address a specific antecedent. For example, a systematic review of medical mistrust measures revealed at least 12 measures or scales for assessing medical mistrust across a wide variety of health topics, including cancer screening, and observed varied conceptualizations of the term 'medical mistrust'.[155] We must understand how medical mistrust and other antecedents should be conceptualized in the context of cancer screening before suggesting standardized representations.

Facilitating clinical research in cancer screening by capture of psychological, cognitive, social, and environmental variables is critical to ensuring the completeness and consistency of collected data. Improving the systematic collection of these antecedents in a standardized manner will aid

in the identification of factors that predict whether a patient will adhere to screening follow-up recommendations; this information can be used to tailor interventions to patients to encourage their adherence. While a number of toolkits and resources that include SDH data elements exist, these disparate efforts, combined with a lack of awareness among investigators, result in poor adoption and inconsistent use of standards. One promising initiative, the Gravity Project, has been developing consensus-driven standards to promote the interoperability of available SDH data in EHRs.[180] A centralized clearinghouse for SDH resources and data collection instruments could aid in the standardization of SDH variables. While several groups have proposed various ontologies to represent different aspects of SDH[181, 182], much work needs to be done to broaden the coverage of existing ontologies to cover antecedents in the Carter-Harris conceptual model. As demonstrated in our work, common data elements need to be developed around specific use cases, such as cancer screening. Societies and professional organizations should promote the development of these common data elements and serve as resources for their respective communities on how to utilize these resources. For example, societies that run national registries (e.g., National Lung Screening Registry) could promote the use of standardized SDH specific to screening to ensure interoperability of collected data across sites. When these standardized variables are readily available for use in clinical research, researchers can verify them, allowing more opportunities to refine and improve our knowledge in predicting patient participation in and adherence to cancer screening.

This work has a number of limitations. A single investigator conducted the searches in our institution's EHR. Additional raters for this task could minimize errors in the searches and increase the reliability of findings. This study is limited to determining the completeness of obtaining antecedent information from EHR and other data sources. We did not assess data quality in other

dimensions, such as data consistency, accuracy, timelessness, and validity. We limited the variables to the 18 antecedents from the Carter-Harris conceptual model. However, additional barriers to cancer screening are unaddressed by this model, including the patient's lack of access to health care, ongoing skepticism about screening benefits, insufficient time for providers to discuss cancer screening, and a provider's knowledge deficits about screening guidelines.[13, 16] We did not perform a comprehensive analysis of mapping quality between antecedents and possible data sources. Although this study examined antecedents specific to LCS, our approach could generalize to any domain, i.e., mapping standardized representations to data elements in a conceptual model that can later be incorporated into analyses to inform clinical decisions.

A deep understanding of disparities in cancer screening can facilitate interventions to improve patient participation in and adherence to cancer screening programs. Current EHR systems and standardized medical vocabularies (i.e., NIH Common Data Elements and NIH RADx-UP Common Data Elements, etc.) cannot comprehensively represent variables that capture patients' beliefs about smoking, psychological influences, cancer and cancer screening, social and environmental factors in a standardized manner. Systematic collection of this information could help researchers understand why screen-eligible patients decide (not) to undergo screening and why screening patients (do not) adhere to screening guidelines. While there exist survey instruments in the literature for measuring psychological, cognitive, social, and environmental variables, a lack of consistent representations of these variables impedes reliable and reproducible research. To systematically collect psychological, mental, social, and environmental variables that influence participation in and adherence to cancer screening recommendations, we need to be attuned to how

these variables are conceptualized, determine standardized representations through systematic reviews, make the variables available in common clinical data sources (such as EHR), and encourage researchers to verify and improve their standardization in clinical research.

4.4 The Impact of COVID-19 Shutdown on LCS at UCLA

This section is adapted from the conference abstract, "The short-term impact of COVID-19 on lung cancer screening participation and adherence.", presented at the 2022 American Association for Cancer Research Annual Meeting.[183]

4.4.1 Overview

Elective imaging procedures, including LCS LDCT exams, were paused during the height of the COVID-19 pandemic at our institution to conserve healthcare resources and minimize risk as we learned how to mitigate the spread of COVID-19. We aimed to investigate the short-term impact of this COVID-19-related screening pause on patient participation and adherence to LCS.

4.4.2 Methods

We analyzed data from 5,133 LDCT screening exams performed at our institution from 2,961 patients who were aged 50-80 at each screen between July 31, 2013 and Dec 30, 2020. Independent t-test, Pearson's chi-square, and Fisher's exact tests were used to compare the monthly average number of LDCTs, on-time adherence rates (i.e., completion of recommended or more invasive follow-up within 15, 9, 5, and 3 months for Lung-RADS 1/2, 3, 4A, and 4B/4X, respectively), percentages of positive screens (Lung-RADS 3 and 4), and lung cancer diagnoses across pre- (July 31, 2013 ~ Mar 18, 2020), during (Mar 19, 2020 ~ May 19, 2020), and post-COVID-19 screening pause (May 20, 2020 and after) periods.

4.4.3 Results

Compared with the pre-COVID-19 screening pause, there was a significant decrease in the monthly average number of LDCTs during the COVID-19 screening pause period (total monthly mean ± standard deviation (sd): pre 55±28 vs during 17±1, $p<0.05$; new patient monthly mean ± sd: pre 34±16 vs during 6±2, $p<0.05$). However, a surge in LCS activities was observed after the COVID-19 screening pause period (total: during 17±1 vs post 89±10, $p<0.05$; new: during 6±2 vs post 42±8, $p<0.05$), surpassing monthly means in the pre-COVID-19 period (total: pre 55±28 vs post 89±10, $p<0.05$; new: pre 34±16 vs. post 42±8, $p<0.05$). Overall on-time adherence decreased in the post-COVID-19 period as opposed to the pre-COVID-19 period ($p<0.05$). There were no significant changes in the percentage of positive screens across the three periods ($p>0.05$). Among the 88 patients diagnosed with lung cancers, 76 diagnoses were made before the COVID-19 pandemic, 12 diagnoses were made after the COVID-19 pause, and no lung cancer diagnoses were made during the COVID-19 screening pause period. There were no significant differences in terms of the rate of lung cancer (pre 2.9% vs post 1.9%, $p>0.05$) and the percent of advanced lung cancers (pre 20% vs post 0%, $p>0.05$) during the two periods.

4.4.4 Discussion

The rate of LCS exams performed at our institution declined during the early days of the COVID-19 pandemic as elective exams were paused. Once screening resumed, we experienced a surge in the rate of LCS that surpassed pre-COVID-19 rates. Although there were no significant changes in the percentages of positive screens and lung cancer diagnoses shortly after the COVID-19 screening pause period, long-term follow-up is needed to monitor these trends. Additionally,

interventions may be needed to improve rates of patients' timely adherence to LCS follow-up recommendations, which decreased in the post-COVID-19 period.

4.5 Conclusion

This chapter discusses available data elements needed to model adherence in the medical records at UCLA. Although the Carter-Harris conceptual model for LCS participation and adherence specifies 18 antecedent variables for consideration, not all psychosocial variables are captured by our institution's EHR system, and therefore, they are missing from the analyses in Chapters 5 and 6. In addition, our LCS screening program was paused for two months during the COVID-19 pandemic in 2020; we investigated the impact of the shutdown on LCS participation and adherence and accounted for its effect by including a variable in the models. Using available data elements as mentioned in **Table 4.2**, Chapters 5 and 6 explore the identification of patient-level predictors of non-adherence to LCS and the development of prediction models that aim to identify non-adherent patients to Lung-RADS recommendations.

CHAPTER 5

Prediction of Patient Non-adherence to Baseline Lung-RADS recommendations

Previous work has demonstrated that demographic and health status variables are predictive of non-adherence to LCS guidelines across diverse settings in the US. However, whether these factors are applicable to the UCLA LCS cohort remains unknown. In the last chapter, we thoroughly examined which antecedent variables from the Carter-Harris conceptual model are readily available in our medical records. In this chapter, we identify risk factors of non-adherence and evaluate machine learning models, including these variables as features to help identify patients at higher risk of being non-adherent to baseline Lung-RADS recommendations.

This chapter is adapted from the Experiment 1 and Supplement Experiment of the article, "Factors associated with nonadherence to lung cancer screening across multiple screening time points," published in JAMA Network Open, 2023.[184]

5.1 Overview

Our systematic review and meta-analysis (Chapter 3) found that patient adherence to baseline Lung-RADS recommendations was 57-65% in clinical LCS programs, with a significantly lower annual adherence rate among patients with Lung-RADS 1 or 2 (45-49%) as opposed to early follow-up adherence among Lung-RADS 3 or 4 (74-78%)[99]. Similarly, a recent study reported adherence to recommendations from baseline and first annual screen were 48% and 44%, respectively, among patients with Lung-RADS 1 or 2 screens in a large national cohort (N=30,166)[185]. Failing to maintain annual adherence to LCS recommendations may diminish the ability of clinical screening programs to achieve the same mortality benefits found in large clinical trials. Patients

with interval lung cancers, diagnosed between screening episodes, with a preceding negative (Lung-RADS 1-2) screen, are more likely to be aggressive, emphasizing the importance of regular screening intervals.[102]

This chapter aimed to identify risk factors of patients at risk for non-adherence to Lung-RADS recommendations at baseline. In a preliminary analysis, we showed that patient demographics and Lung-RADS score are predictive of adherence to baseline Lung-RADS recommendations.[186] In this chapter, we included more variables and conducted the analysis in a larger cohort. We investigated whether patient demographics, socioeconomic status, and health status were factors of non-adherence to baseline Lung-RADS recommendations. Further, we evaluated whether machine learning models including these factors could accurately predict non-adherence at the follow-up screen.

5.2 Methods

5.2.1 Patient Enrollment

Institutional review board (IRB) approval was obtained at the University of California, Los Angeles to conduct this retrospective study, and informed consent was waived (IRB#19-000627). A total of 2496 patients were eligible for this analysis (see Section 4.1.2 for details).

5.2.2 Data Collection and Patient Outcome

The independent variables were the 14 baseline patient characteristics, and adherence to baseline Lung-RADS recommendations was the patient outcome (see Section 4.2 in Chapter 4 for details).

5.2.3 Statistical Analyses

In Experiment 1, we used a multivariable logistic regression model to identify significant factors of non-adherence to baseline Lung-RADS recommendations. Patients who had missing values in some characteristics were excluded from the analysis. A comparison of the observed baseline characteristics between included and excluded patients is shown in **Table S5.1** in the Appendix. No significant differences were found for any variables except the family history of lung cancer. A sensitivity analysis was implemented using multiple imputation (i.e., the 'mice'[187] package in R) data and found similar results.

In Experiment 2, we trained and evaluated five machine learning models to predict patient non-adherence to baseline Lung-RADS recommendations (**Fig. 5.1**). The inputs into the models were significant (i.e., z test, two-sided p-value<0.05) baseline factors from Experiment 1. This experiment aimed to validate whether these factors could correctly classify patients who were non-adherent to baseline Lung-RADS recommendations. We also experimented with feature selection using the least absolute shrinkage and selection operator (LASSO), which yielded lower test performance than using significant features from Experiment 1. Logistic regression, random forest, support vector machine, naïve Bayes, and XGBoost were trained using data without missing values in all input variables. Naïve Bayes was also trained using data with missing values left as-is. We used nested 10-fold cross-validation, repeated five times to select the best models based on the primary evaluation metric, area under the receiver operating characteristic curve (ROC-AUC), in the validation sets, which measures the discriminative ability of prediction models. The best-performing model was then retrained and tested on the hold-out test cases (n=278 from data with no

missing values in significant factors from Experiment 1). Secondary evaluation metrics included recall/sensitivity, precision/positive predictive value (PPV), and accuracy.

Python version 3.7.3 and R version 3.6.1[119] were used for data analyses.

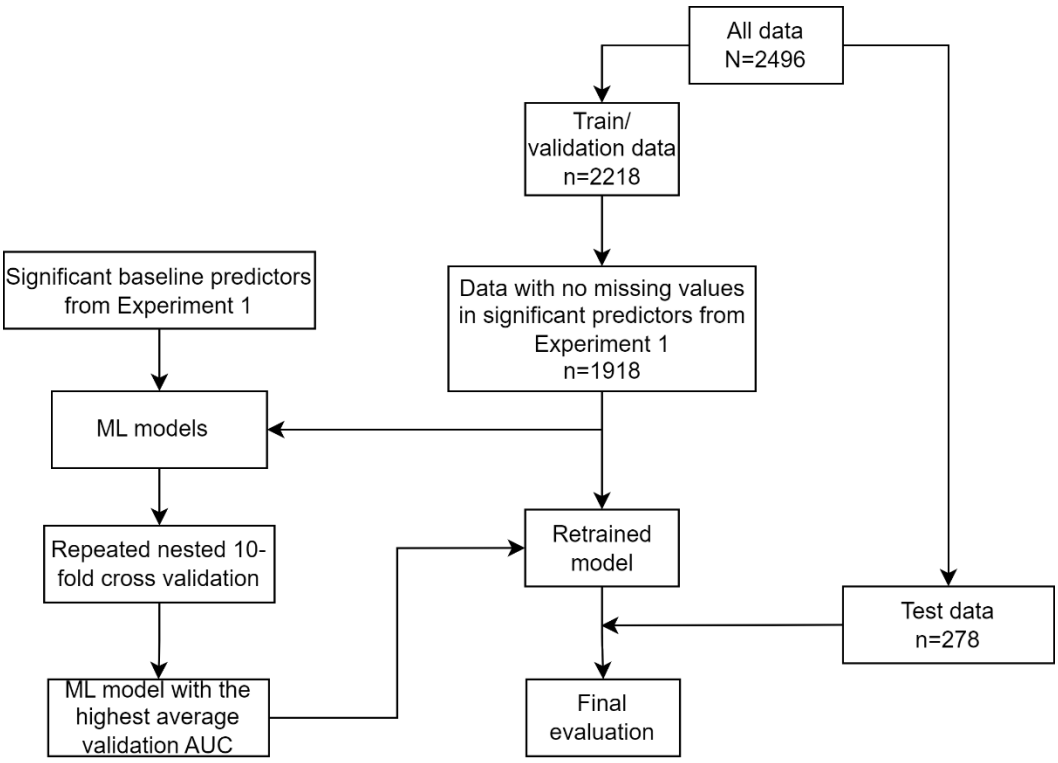

Fig. 5.1 The overall pipeline of Experiment 2. Using ML models to predict patient adherence to baseline Lung-RADS recommendations. Lung-RADS: Lung CT Screening Reporting & Data System. ML: Machine learning; AUC: area under the receiver operating characteristic curve. Note: Test data only included patients with no missing significant factors from Experiment 1.

5.3 Results

5.3.1 Experiment 1 Result

Among the 2496 eligible patients, 1979 had no missing values in all baseline characteristics. The majority had a negative baseline screen (83.9%), were ≥ 65 years of age (56.1%), male (59.4%), White (77.1%), and former smokers (61.1%). Patient characteristics at the baseline screen are summarized in **Table 5.1**. The rates of non-adherence to baseline Lung-RADS recommendations were 70.5% (1170/1660), 46.1% (71/154), 32.3% (32/99), and 19.7% (13/66) for Lung-RADS 1-2, 3, 4A, and 4B/X, respectively. The odds of being non-adherent among patients with a positive baseline Lung-RADS score decreased compared with those with a negative baseline score (referent: 1-2, 3-4: adjusted odds ratio [aOR]: 0.35, 95% confidence interval [CI] 0.25, 0.50, 4A: aOR: 0.21, 95% CI: 0.13, 0.33, and 4B/X: aOR: 0.10, 95% CI: 0.05, 0.19) (see **Table 5.2**). Lower odds of non-adherence were also observed among patients with a postgraduate degree (referent: college graduate, aOR:0.70, 95% CI 0.53, 0.92), with a family history of lung cancer (referent: no, aOR: 0.74, 95% CI 0.59, 0.93), in the high age-adjusted CCI category (referent: low, aOR:0.67, 95% CI 0.46, 0.98), in the high-income category (referent: low, aOR: 0.80, 95% CI: 0.65, 0.98), and referred by physicians from pulmonary or thoracic-related departments (i.e., Thoracic Oncology/Radiology/Surgery) (referent: other department, aOR: 0.56, 95% CI 0.44, 0.73).

Table 5.1 Baseline patient characteristics (Experiment 1).

	Individual, No. (%)		
Variable	Overall (N=1979)	Adherent (n=693)	Non-adherent (n=1286)
Lung-RADS			
1-2	1660 (83.9)	490 (70.7)	1170 (91.0)
3	154 (7.8)	83 (12.0)	71 (5.5)
4A	99 (5.0)	67 (9.7)	32 (2.5)
4B/X	66 (3.3)	53 (7.6)	13 (1.0)
Age in years			
<65	868 (43.9)	268 (38.7)	600 (46.7)
≥65	1111 (56.1)	425 (61.3)	686 (53.3)
Sex			
Female	803 (40.6)	276 (39.8)	527 (41.0)
Male	1176 (59.4)	417 (60.2)	759 (59.0)
Race/ethnicity			
Asian	169 (8.5)	59 (8.5)	110 (8.6)
Black	130 (6.6)	49 (7.1)	81 (6.3)
Hispanic/Latino	111 (5.6)	35 (5.1)	76 (5.9)
White	1526 (77.1)	540 (77.9)	986 (76.7)
Other [a]	43 (2.2)	10 (1.4)	33 (2.6)
Education level			

Table 5.1 Baseline patient characteristics (Experiment 1).

Variable	Individual, No. (%)		
	Overall (N=1979)	Adherent (n=693)	Non-adherent (n=1286)
Less than college	958 (48.4)	337 (48.6)	621 (48.3)
College Graduate	590 (29.8)	186 (26.8)	404 (31.4)
Postgraduate	431 (21.8)	170 (24.5)	261 (20.3)
Family history of lung cancer			
Yes	466 (23.5)	187 (27.0)	279 (21.7)
No	1513 (76.5)	506 (73.0)	1007 (78.3)
Smoking status			
Current	769 (38.9)	246 (35.5)	523 (40.7)
Former	1210 (61.1)	447 (64.5)	763 (59.3)
Primary insurance			
Medicare/Medicaid	830 (41.9)	328 (47.3)	502 (39.0)
Private or Commercial	1121 (56.6)	358 (51.7)	763 (59.3)
Other [b]	28 (1.4)	7 (1.0)	21 (1.6)
Age adjusted CCI			
Low (0-1)	287 (14.5)	72 (10.4)	215 (16.7)
Intermediate (2-3)	1152 (58.2)	403 (58.2)	749 (58.2)
High (≥4)	540 (27.3)	218 (31.5)	322 (25.0)

Table 5.1 Baseline patient characteristics (Experiment 1).

Variable	Individual, No. (%)		
	Overall (N=1979)	Adherent (n=693)	Non-adherent (n=1286)
Distance to screening center [c]			
Short (≤ median)	994 (50.2)	346 (49.9)	648 (50.4)
Long (> median)	985 (49.8)	347 (50.1)	638 (49.6)
Median household income [c]			
Low (≤ median)	1029 (52.0)	340 (49.1)	689 (53.6)
High (> median)	950 (48.0)	353 (50.9)	597 (46.4)
ADI state rank [c]			
Low (≤ median)	1072 (54.2)	387 (55.8)	685 (53.3)
High (> median)	907 (45.8)	306 (44.2)	601 (46.7)
Type of referring physician			
Pulmonology, Thoracic Oncology/Radiology/Surgery	369 (18.6)	176 (25.4)	193 (15.0)
Other [d]	1610 (81.4)	517 (74.6)	1093 (85.0)
Expected follow-up exam			
Pre-COVID	1468 (74.2)	513 (74.0)	955 (74.3)
During COVID pause	53 (2.7)	11 (1.6)	42 (3.3)
Post-COVID pause	458 (23.1)	169 (24.4)	289 (22.5)

Table 5.1 Baseline patient characteristics (Experiment 1).

Variable	Individual, No. (%)		
	Overall (N=1979)	Adherent (n=693)	Non-adherent (n=1286)

Notes: [a] Subcategories in other race: American Indian or Alaska Native, Native Hawaiian or Pacific Islander, more than one race, or other racial and ethnic groups not otherwise stated.

[b] Subcategories in other insurance: Veterans Administration (N=1), self-pay (N=27), and other insurance not specified (N=1).

[c] Median distance to screening center: 6.84 miles.; median household income: $73,478; median ADI state rank: 3.

[d] Subcategories in other referring physician types: family medicine, general internal medicine, and obstetrics and gynecology.

Abbreviations: Lung-RADS: Lung CT Screening Reporting & Data System; CCI: Charlson Comorbidity Index; ADI: Area Deprivation Index.

Table 5.2 Multivariable logistic regression analysis on patient non-adherence to baseline Lung-RADS recommendations (Experiment 1, N=1979).

Variable	aOR (95% CI)	p-value
Intercept	9.17 (4.12, 21.65)	<0.001
Lung-RADS (Referent: 1-2)		
3	0.35 (0.25, 0.50)	<0.001
4A	0.21 (0.13, 0.33)	<0.001
4B/X	0.10 (0.05, 0.19)	<0.001
Age in years (Referent: <65)		
≥65	1.00 (0.78, 1.28)	0.98
Sex (Referent: Female)		
Male	0.95 (0.77, 1.16)	0.60
Race/ethnicity (Referent: White)		
Asian	0.98 (0.69, 1.41)	0.90
Black	0.84 (0.56, 1.25)	0.37
Hispanic/Latino	1.10 (0.71, 1.73)	0.67
Other [a]	1.55 (0.77, 3.39)	0.24
Education (Referent: College graduate)		
Less than college	0.88 (0.69, 1.11)	0.28
Postgraduate	0.70 (0.53, 0.92)	0.01

Table 5.2 Multivariable logistic regression analysis on patient non-adherence to baseline Lung-RADS recommendations (Experiment 1, N=1979).

Variable	aOR (95% CI)	p-value
Smoking status (Referent: Current smoker)		
Former smoker	0.84 (0.68, 1.03)	0.10
Family history of lung cancer (Referent: No)		
Yes	0.74 (0.59, 0.93)	0.010
Primary insurance (Referent: Medicare/Medicaid)		
Private or Commercial	1.10 (0.88, 1.38)	0.41
Other [b]	1.41 (0.60, 3.70)	0.46
Age-adjusted CCI (Referent: Low (0-1))		
Intermediate (2-3)	0.73 (0.52, 1.02)	0.07
High (≥4)	0.67 (0.46, 0.98)	0.042
Distance to screening center (Referent: Short ≤50 percentile)		
Long (>50 percentile)	1.01 (0.81, 1.25)	0.95
ADI state rank (Referent: Low ≤50 percentile)		
High (>50 percentile)	1.12 (0.90, 1.40)	0.30
Median annual income (Referent: Low ≤50 percentile)		
High (>50 percentile)	0.79 (0.65, 0.98)	0.030

Table 5.2 Multivariable logistic regression analysis on patient non-adherence to baseline Lung-RADS recommendations (Experiment 1, N=1979).

Variable	aOR (95% CI)	p-value
Type of referring physician (Referent: Other [c])		
Pulmonology, Thoracic Oncology/Radiology/Surgery	0.56 (0.44, 0.73)	<0.001
Expected follow-up exam (Referent: During COVID-19 pause)		
Pre-COVID-19	0.56 (0.27, 1.08)	0.10
Post-COVID-19 pause	0.52 (0.24, 1.02)	0.07

Notes: [a] Subcategories in other race: American Indian or Alaska Native, Native Hawaiian or Pacific Islander, more than one race, or other racial and ethnic groups not otherwise stated.

[b] Subcategories in other insurance: Veterans Administration, self-pay, and other insurance not specified.

[c] Subcategories in other referring physician types: family medicine, general internal medicine, and obstetrics and gynecology.

Abbreviations: Lung-RADS: Lung CT Screening Reporting & Data System; CCI: Charlson Comorbidity Index; ADI: Area Deprivation Index; aOR: adjusted odds ratio; CI: confidence interval.

5.3.2 Experiment 2 Result

Among 2496 eligible patients, 278 with no missing values in significant factors from Experiment 1 were used as the hold-out test set. Of the remaining 2218 patients, 300 patients had missing values in some significant factors from Experiment 1, leaving 1918 patients with no missing values in the significant factors from Experiment 1. 2218 (with missing values) and 1918

(without missing values) patients were used for cross-validation (see **Fig. 5.1**). The inputs into the machine learning models were the six significant baseline factors from Experiment 1. Model performance on the validation sets of the five machine learning models is shown in **Table 5.3**. Most models achieved greater than 90% recall/sensitivity and similar performance in other evaluation metrics. The final retrained logistic regression model achieved recall/sensitivity: 0.939, precision/PPV: 0.712, accuracy: 0.716, and ROC-AUC: 0.667 on the hold-out test cases.

Table 5.3 Validation performance of machine learning models using repeated (n=5) 10-fold cross-validation (Experiment 2).

Model/Metric (SD)	Recall/sensitivity	Precision/PPV	Accuracy	AUC
Complete case training/validation data n=1918				
Logistic regression	0.939 (0.027)	0.682 (0.032)	0.679 (0.030)	0.662 (0.039)
Naïve Bayes	0.916 (0.029)	0.691 (0.034)	0.682 (0.033)	0.662 (0.039)
XGBoost	0.912 (0.028)	0.692 (0.030)	0.682 (0.027)	0.656 (0.038)
SVM	0.909 (0.026)	0.694 (0.032)	0.684 (0.030)	0.622 (0.047)
Random forest	0.896 (0.031)	0.688 (0.033)	0.670 (0.031)	0.626 (0.039)
All training/validation data with missing values n=2218				
Naïve Bayes	0.919 (0.019)	0.694 (0.027)	0.686 (0.023)	0.590 (0.020)

Input variables: significant baseline factors from Experiment 1 including Lung-RADS, family history of lung cancer, education level, median household income, age-adjusted Charlson Comorbidity Index, and type of referring physician.

SD: standard deviation; PPV: positive predictive value; AUC: area under the receiver operating characteristics curve; SVM: support vector machine.

5.4 Discussion

As the volume of patients participating in clinical LCS practices increases, the challenge of addressing low adherence to Lung-RADS recommendations is magnified, as observed among patients with negative screens in this study. Identifying factors of non-adherence may help resource-constrained health systems to direct targeted outreach to patients who are at a higher risk of non-adherence and thus likely to receive the greatest benefit from targeted interventions. Appointment reminders and/or LCS educational materials sent to patients by mail or via patient health portals in the electronic medical record as well as reinforcement of LCS-related benefits by the screening program are possible interventions to mitigate non-adherence.

Our findings that Lung-RADS scores and type of referring physician were associated with patient non-adherence to baseline Lung-RADS recommendations aligned with previous studies.[123, 128, 138] The baseline Lung-RADS score was the most important variable when predicting whether a patient would be adherent in returning for their initial follow-up screening exam. Patients with a negative baseline screen are at a higher risk for non-adherence. A study by Wildstein et al.[43] found that higher education level (e.g., individuals with at least a college degree) was associated with annual adherence to LCS, though the study was conducted prior to the release date of the Lung-RADS recommendations. Our study found that positive family history of lung cancer, comorbidity (high vs. low score), and lower income were statistically significant factors of non-adherence at the first follow-up, a finding that has not been previously reported in LCS literature. These factors have been previously studied in colorectal and breast cancer screening,[46, 188, 189] but with sometimes conflicting results, as in the case of comorbidity.[46, 188] As such, further investigation into the clinical significance of these factors is necessary.

We show that machine learning models trained on significant factors identified in Experiment 1 can capture most non-adherent patients (i.e., high recall/sensitivity), only missing 6% of non-adherent patients. We also included all 14 baseline factors in the models, which achieved similar performance. Given that some factors may not be routinely collected in medical records (e.g., income), the model that handles missing values (i.e., naïve Bayes) is useful for making classification when values of certain variables are missing. We should note that the analysis was influenced by the screening population that is seen at our institution; other institutions may identify specific factors that affect adherence in their LCS population.

A recent study developed a gradient boosting model that achieved a high AUC (0.89) when predicting non-adherence to baseline Lung-RADS recommendations in a community setting LCS program.[190] To our knowledge, this was the first and only published study on this topic. In our analysis, however, the test AUC was 0.66. Their sample size and non-adherent rate were similar to those in our study; they used similar machine learning models with 10-fold cross-validation. There was only one variable in their model that we did not include in our models, which was the service location or site. The ten screening sites at our institution were managed in a centralized manner by the LCS team. Thus, there should not be any operational differences among these sites. Instead, we accounted for other geographical factors that could affect adherence, such as distance from the patient's residence to the screening center and ADI state rank. The following factors potentially caused the differences in the model performance between the two studies, 1) inherent differences, such as in the patient populations and characteristics, between a community setting (theirs) and an academic institution (ours), 2) differences in the definitions of non-adherence for each Lung-RADS category, and 3) different reminding systems at the two institutions.

This study has some limitations. Several potential factors were not considered in our investigation due to a lack of data. Carter-Harris et al.[20] proposed additional important precursors to LCS behaviors, including psychological, cognitive, social, environmental, and healthcare provider recommendations. These variables were previously shown to be associated with behaviors in the lung or other types of cancer screening.[171, 173, 174, 176, 191-194] Unlike factors (e.g., demographic variables) that are not modifiable, psychological and cognitive factors can change over time, providing opportunities for an outreach intervention. Another group of potential risk factors is SDH variables.[94, 97] Despite a high recall/sensitivity, the accuracy of the prediction models was around 70%, resulting in some patients who are likely to be adherent in practice being misidentified as having a high risk of non-adherence. In a targeted approach to adherence interventions, these individuals may receive unnecessary outreach; in this scenario, the negative impact is minimal to the patient but may divert critical resources away from other essential services. Moreover, it was not possible to track patients who had permanently moved but continued LCS at outside institutions. Additionally, comorbidities were considered in aggregate using the Charlson Comorbidity Index, and we did not know which specific diseases directly contributed to non-adherence. The factors we assessed were limited to data elements that were captured routinely in the medical records. Future work is needed to evaluate other life circumstances (e.g., personal such as health [e.g., had other medical issues, LCS was not a priority]), professional activities, and social environmental factors (e.g., childcare and family responsibilities) that might affect adherence.

The lack of primary care physician involvement may be another major determinant of patients' adherence behaviors in LCS. Primary care physicians may be less familiar with LCS, its relative risks and benefits, and eligibility requirements for reimbursement as compared to other

cancer screening examinations. Although an annual review of preventive health measures is inherent to primary care, LCS is nascent in practice, and there are myriad reasons why primary care referrals may be associated with less adherence. Relative to other preventive measures, LCS requires a greater time commitment for shared decision-making, smoking cessation counseling, and formal documentation. Our study only examined a high-level variable to distinguish primary care and subspecialty referrals, which cannot capture nuances of physician awareness or practice constraints.

In the future, the findings of this study can be incorporated into a temporal model that helps predict adherence status at each screening time point, adding time-varying variables into the temporal model to achieve better performance by considering the changes in patients' health statuses at each screen (e.g., age-adjusted CCI, smoking status, and insurance status). Finally, the use of specific types of outreach intervention (e.g., reminders, consultations, educational materials) to improve adherence will vary based on the underlying reason why an individual may be non-adherent. While reminders and educational outreach have been helpful in other screening contexts[195, 196], a greater understanding of the psychological, cognitive, social, and healthcare provider factors that influence screening adherence may be essential to optimize outreach interventions. Further studies that explicitly examine these factors are needed.

5.5 Conclusion

We identify factors of patients at risk for non-adherence to baseline Lung-RADS recommendations. We show that the Lung-RADS score at baseline was the most important factor of non-adherence in the initial follow-up screen. Prediction models, including Lung-RADS score, demographic, socioeconomic status, and health status variables as features, can identify over 90% of

truly non-adherent patients. Our study provides evidence that can be used as the basis of a decision support tool to identify non-adherent patients and inform future outreach interventions designed to improve patient adherence to LCS. Nevertheless, further improvement in model precision, accuracy, and AUC is needed before this model can be implemented as part of a clinical decision-making support tool in our LCS program.

CHAPTER 6

Predicting Patient Longitudinal Non-adherence to Lung-RADS Recommendations

Chapter 5 is an effort to predict non-adherence at the first follow-up screen (i.e., adherence to the baseline/prevalence Lung-RADS recommendations). Screening for lung cancer is a process that must be done regularly and repeatedly in high-risk individuals; however, to our knowledge, no work has focused on predicting patient non-adherence to Lung-RADS recommendations across multiple screening time points. We are among the first groups to present three novel approaches to model patient non-adherence to LCS longitudinally. In this chapter, we aim to answer the following questions.

1) Are changes in Lung-RADS scores associated with patient non-adherence?
2) Can data from the EMR (i.e., demographic, socioeconomic, health status, and Lung-RADS score) accurately predict non-adherence over time?

6.1 The Role of Changes in Lung-RADS Scores between Screens

This section is adapted from Experiment 2 of the article, "Factors associated with nonadherence to lung cancer screening across multiple screening time points," published in JAMA Network Open, 2023.[184]

6.1.1 Overview

To our knowledge, no studies have investigated risk factors of patient non-adherence to Lung-RADS recommendations over multiple screening intervals. Specifically, Lung-RADS scores may vary over time. Previous work has shown that Lung-RADS score was a significant factor of

non-adherence to baseline Lung-RADS recommendations[99]; however, evidence on whether longitudinal patterns of Lung-RADS scores affect the risk of non-adherence to screening in the future is lacking. This analysis adjusts for significant baseline factors mentioned in Chapter 5 Experiment 1 and evaluates the hypothesis that adherence would increase/decrease as Lung-RADS scores upgraded/downgraded, respectively, and adherence would be stable when Lung-RADS scores remained unchanged. We have shown that changes in Lung-RADS scores between screens were associated with patient non-adherence.[197, 198] In this work, we adjusted for patient baseline characteristics and included adherence statuses up to the third screening time point.

6.1.2 Methods

Institutional review board (IRB) approval was obtained at the University of California, Los Angeles to conduct this retrospective study, and informed consent was waived (IRB#19-000627). Patient enrollment, data collection, and patient outcome sections have been described in Chapter 5 Experiment 1 Section 5.2.

This section focuses on the statistical methods we used to examine whether baseline Lung-RADS scores and the pattern of subsequent Lung-RADS scores were associated with non-adherence to Lung-RADS recommendations over time. Patients who underwent at least two screening examinations were included in this analysis. The Lung-RADS score was binary: a score of 1-2 was defined as a negative screen, and a score of 3-4 screen was defined as a positive screen. Patients were categorized into subgroups based on their longitudinal patterns of Lung-RADS scores (see **Table S6.1** in the Appendix): unchanged, upgraded (score going from negative to positive), and downgraded (score going from positive to negative). Patients whose Lung-RADS scores were first upgraded and then downgraded or vice versa were excluded. A generalized estimating equations

(GEE) model with a logit link and an unstructured working correlation accounting for repeated measurements within the same patient was used. The fixed effects included in this model were baseline Lung-RADS score (1-2 vs. 3-4), longitudinal patterns of Lung-RADS scores (changed vs. unchanged), screening time point (T0, T1, T2), three two-way interaction terms, one three-way interaction term among the three variables, and significant baseline risk factors from Experiment 1 (i.e., z-test, two-sided p-value<0.05). Less than 10% of patients who had missing values of some factors were excluded from this analysis. No significant differences in the observed variables were found between the included and excluded patients. Python version 3.7.3 and R version 3.6.1[119] were used for data analyses.

6.1.3 Results

In total, 830 patients had no missing values in all significant baseline factors from Experiment 1 and monotonic changes in Lung-RADS scores over time **(see Fig 6.1).** Most patients (79.2%) were in the unchanged category (631 negative, 26 positive); 11.3% and 9.5% were in the downgraded and upgraded categories, respectively. Patient baseline characteristics stratified by patterns of subsequent Lung-RADS scores are shown in **Table 6.1**. Fewer patients were ≥ 65 years of age in the negative screen-unchanged group compared to the other three groups combined (54% vs. 66%, p=0.002) and were referred by pulmonary medicine or thoracic-related subspecialists (16% vs. 24%, p=0.011). More patients were younger in the negative screen-unchanged group, which could be that the overall health of younger patients was better than older patients. Patients with two consecutive negative screens might not have had existing lung conditions that needed to be followed by a pulmonologist, and therefore, fewer were referred by pulmonary-related subspecialties.

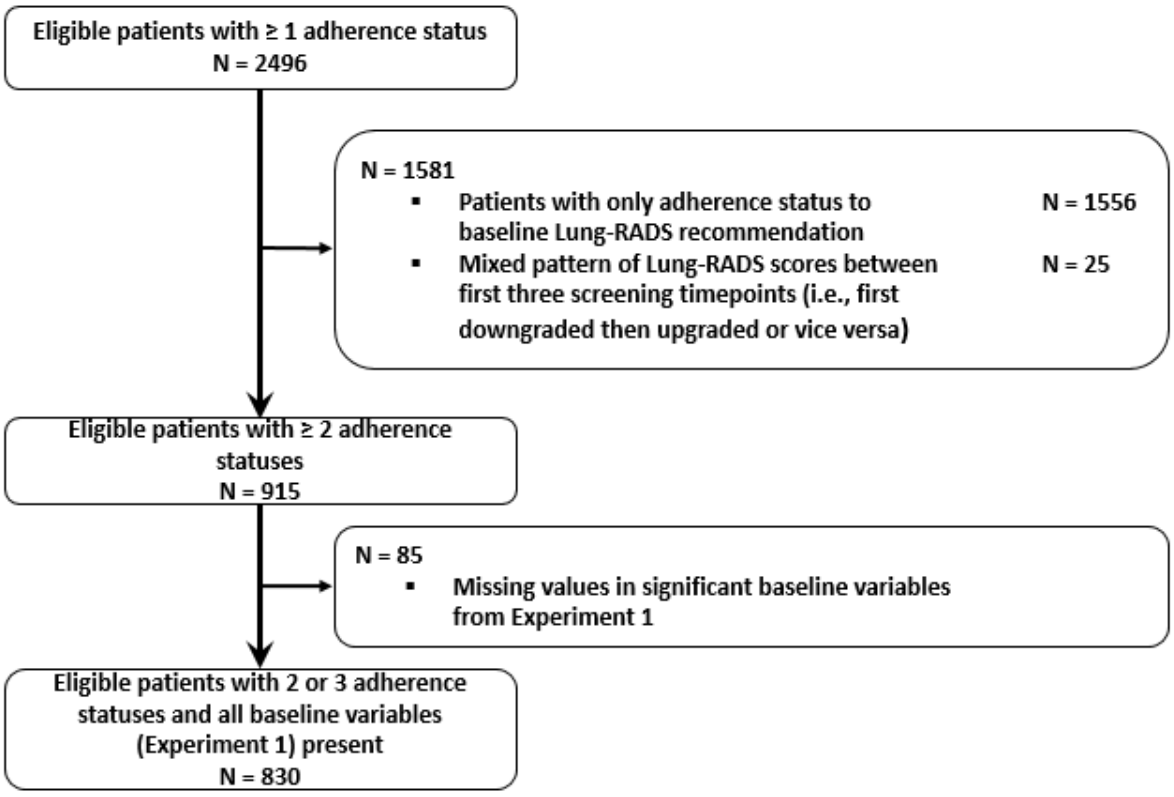

Fig 6.1 The flow diagram of patient enrollment for the analysis in Section 6.1.

Table 6.1 Patient characteristics at baseline, stratified by changes in Lung-RADS scores across three screening time points (Experiment 2, N=830).

Group	Negative Un-changed	Positive Un-changed	Lung-RADS Downgraded	Lung-RADS Upgraded
n (%)	631 (76.0)	26 (3.1)	94 (11.3)	79 (9.5)
Lung-RADS category [b]				
1-2	631 (100.0)	0 (0.0)	0 (0.0)	79 (100.0)
3-4	0 (0.0)	26 (100.0)	94 (100.0)	0 (0.0)
Age in years [c]				
<65	293 (46.4)	5 (19.2)	37 (39.4)	25 (31.6)
≥65	338 (53.6)	21 (80.8)	57 (60.6)	54 (68.4)
Sex (%)				
Female	250 (39.6)	10 (38.5)	33 (35.1)	36 (45.6)
Male	381 (60.4)	16 (61.5)	61 (64.9)	43 (54.4)
Race/ethnicity				
Asian	56 (8.9)	2 (7.7)	10 (10.6)	5 (6.3)
Black	46 (7.3)	2 (7.7)	5 (5.3)	5 (6.3)
Hispanic/Latino	27 (4.3)	1 (3.8)	6 (6.4)	5 (6.3)
White	472 (74.8)	20 (76.9)	69 (73.4)	61 (77.2)
Other [d]	16 (2.5)	0 (0.0)	2 (2.1)	2 (2.5)
Missing	14 (2.2)	1 (3.8)	2 (2.1)	1 (1.3)

Table 6.1 Patient characteristics at baseline, stratified by changes in Lung-RADS scores across three screening time points (Experiment 2, N=830).

Group	Negative Un-changed	Positive Un-changed	Lung-RADS Downgraded	Lung-RADS Upgraded
n (%)	631 (76.0)	26 (3.1)	94 (11.3)	79 (9.5)
Education [b]				
Less than college	281 (44.5)	17 (65.4)	42 (44.7)	43 (54.4)
College Graduate	196 (31.1)	5 (19.2)	34 (36.2)	19 (24.1)
Postgraduate	154 (24.4)	4 (15.4)	18 (19.1)	17 (21.5)
Smoking status (%)				
Current	253 (40.1)	7 (26.9)	42 (44.7)	37 (46.8)
Former	364 (57.7)	19 (73.1)	52 (55.3)	41 (51.9)
Missing	14 (2.2)	0 (0.0)	0 (0.0)	1 (1.3)
Family history of lung cancer [b]				
Yes	140 (22.2)	4 (15.4)	20 (21.3)	21 (26.6)
No	491 (77.8)	22 (84.6)	74 (78.7)	58 (73.4)

Table 6.1 Patient characteristics at baseline, stratified by changes in Lung-RADS scores across three screening time points (Experiment 2, N=830).

Group	Negative Un-changed	Positive Unchanged	Lung-RADS Downgraded	Lung-RADS Upgraded
n (%)	631 (76.0)	26 (3.1)	94 (11.3)	79 (9.5)
Age-adjusted CCI [b]				
Low (0-1)	84 (13.3)	2 (7.7)	9 (9.6)	6 (7.6)
Intermediate (2-3)	407 (64.5)	16 (61.5)	58 (61.7)	48 (60.8)
High (≥4)	140 (22.2)	8 (30.8)	27 (28.7)	25 (31.6)
Primary insurance				
Medicare/Medicaid	272 (43.1)	18 (69.2)	47 (50.0)	30 (38.0)
Private or Commercial	348 (55.2)	8 (30.8)	45 (47.9)	47 (59.5)
Other [e]	9 (1.4)	0 (0.0)	2 (2.1)	2 (2.5)
Missing	2 (0.3)	0 (0.0)	0 (0.0)	0 (0.0)
Distance to screening center [a]				
Short (≤ median)	301 (47.7)	14 (53.8)	45 (47.9)	40 (50.6)
Long (> median)	325 (51.5)	12 (46.2)	48 (51.1)	39 (49.4)
Missing	5 (0.8)	0 (0.0)	1 (1.1)	0 (0.0)
Median household income [a, b]				
Low (≤ median)	309 (49.0)	15 (57.7)	52 (55.3)	44 (55.7)
High (> median)	322 (51.0)	11 (42.3)	42 (44.7)	35 (44.3)

Table 6.1 Patient characteristics at baseline, stratified by changes in Lung-RADS scores across three screening time points (Experiment 2, N=830).

Group	Negative Un-changed	Positive Unchanged	Lung-RADS Downgraded	Lung-RADS Upgraded
n (%)	631 (76.0)	26 (3.1)	94 (11.3)	79 (9.5)
ADI state rank (%) [a]				
Low (≤ median)	362 (57.4)	14 (53.8)	40 (42.6)	44 (55.7)
High (> median)	231 (36.6)	11 (42.3)	50 (53.2)	31 (39.2)
Missing	38 (6.0)	1 (3.8)	4 (4.3)	4 (5.1)
Type of referring physician [b, c]				
Pulmonology, Thoracic Oncology/Radiology/Surgery	102 (16.2)	4 (15.4)	20 (21.3)	24 (30.4)
Other [f]	529 (83.8)	22 (84.6)	74 (78.7)	55 (69.6)
Expected follow-up exam				
Pre-COVID	595 (94.3)	25 (96.2)	89 (94.7)	69 (87.3)
During COVID pause	8 (1.3)	0 (0.0)	1 (1.1)	2 (2.5)
Post-COVID pause	28 (4.4)	1 (3.8)	4 (4.3)	8 (10.1)

Notes: [a] Median distance to screening center: 5.48 miles; median household income: $74,011; median ADI state rank: 3

[b] Variables adjusted for in Experiment 2 (i.e., significant baseline factors from Experiment 1).

[c] p value <0.05 from the Chi-square test.

Table 6.1 Patient characteristics at baseline, stratified by changes in Lung-RADS scores across three screening time points (Experiment 2, N=830).

Group	Negative Un-changed	Positive Unchanged	Lung-RADS Downgraded	Lung-RADS Upgraded
n (%)	631 (76.0)	26 (3.1)	94 (11.3)	79 (9.5)

[d] Subcategories in other race: American Indian or Alaska Native, Native Hawaiian or Pacific Islander, more than one race, or other racial and ethnic groups not otherwise stated.

[e] Subcategories in Other: Subcategories in other insurance: Veterans Administration, self-pay, and other insurance not specified.

[f] Subcategories in other referring physician types: family medicine, general internal medicine, and obstetrics and gynecology.

Abbreviations: Lung-RADS: Lung CT Screening Reporting & Data System; CCI: Charlson Comorbidity Index; ADI: Area Deprivation Index.

In patients with a negative screen at baseline, results from the GEE model suggested that the odds of being non-adherent to the Lung-RADS recommendations at the second screening increased in the unchanged-negative category (adjusted OR: 1.38, 95% CI: 1.12, 1.69) but decreased in the upgraded category (adjusted OR: 0.29, 95% CI: 0.14, 0.60) (see **Table 6.2**). As opposed to the upgraded category, more patients were less than 65 years old at baseline, and fewer patients were referred by physicians from a pulmonary or thoracic-related department in the unchanged-negative category, respectively. Among those with a positive baseline screen, the odds of being non-adherent following the subsequent negative interval screening increased (adjusted OR: 5.08, 95% CI: 1.28, 20.1). There was no significant change in adherence in the unchanged-positive category at the second screen. In addition, no significant difference in adherence at the third screen was found across the four subgroups.

Table 6.2 Summary of findings from generalized estimating equations analysis of non-adherence to Lung-RADS recommendations measured over time (Experiment 2, N=830).

Comparisons of interest	Non-adherence to T1 Lung-RADS recommendations		Non-adherence to T2 Lung-RADS recommendations	
	aOR (95% CI)	p-value	aOR (95% CI)	p-value
Baseline Lung-RADS 1-2				
Unchanged subsequently (Referent: T0)	1.38 (1.12, 1.69)	0.002	1.17 (0.90, 1.52)	0.23
Upgraded subsequently (Referent: T0)	0.29 (0.14, 0.60)	<0.001	0.44 (0.19, 1.01)	0.054

Table 6.2 Summary of findings from generalized estimating equations analysis of non-adherence to Lung-RADS recommendations measured over time (Experiment 2, N=830).

Comparisons of interest	Non-adherence to T1 Lung-RADS recommendations		Non-adherence to T2 Lung-RADS recommendations	
	aOR (95% CI)	p-value	aOR (95% CI)	p-value
Baseline Lung-RADS 3-4				
Unchanged subsequently (Referent: T0)	1.81 (0.62, 5.22)	0.28	1.34 (0.16, 10.9)	0.78
Downgraded subsequently (Referent: T0)	5.08 (1.28, 20.1)	0.021	6.99 (0.66, 74.1)	0.11

Notes: Adjusted baseline variables included baseline Lung-RADS, family history of lung cancer, education, median household income, age-adjusted Charlson Comorbidity Index, and type of referring physician.

Abbreviations: Lung-RADS: Lung-RADS: Lung CT Screening Reporting & Data System; aOR: adjusted odds ratio; CI: confidence interval, T0: first screening time point, T1: second screening time point, T2: third screening time point.

6.1.4 Discussion

Our analysis provides insights into which groups of patients may be more likely to be non-adherent in subsequent screening exams. Specifically, if patients have had consecutive negative screens, their adherence diminishes over time. Individuals in this group tend to be younger at base-line and referred by physicians from non-pulmonary or thoracic subspecialty departments. These observations help to inform which patients are at highest risk of non-adherence to annual screening, which can delay the diagnosis of lung cancer[102, 199]. Of note, cancers first observed on incidence

screens tend to be faster growing and more aggressive in behavior than those identified at prevalence screens[102], increasing the importance of adherence to follow-up recommendations. The GEE model also suggests that patients with a positive baseline screen followed by a negative screen may also need assistance in maintaining adherence at the first annual screen (i.e., non-adherence increases over time). However, further investigation is needed, given the wide confidence interval. Our findings regarding changes in adherence, as patients undergo subsequent screens, underscore the need for screening programs to provide ongoing patient education and reminders, to facilitate adherence by providing screening locations near the patient, and to minimize patient inconvenience through timely scheduling and efficient patient throughput.

The study grouped Lung-RADS scores into negative (Lung-RADS 1 or 2) versus positive (Lung-RADS 3 or 4). This approach is limited in that we could not capture changes in Lung-RADS scores within the positive screen group. For example, a Lung-RADS 3 interpretation followed by a Lung-RADS 4A interpretation was considered unchanged in this analysis because both were recorded as positive screens when, in fact, the level of suspicion and likelihood of cancer both increased. We have sought to model changes more granularly, where we defined 3 to 4 as upgraded (i.e., 3 to 4A, 4A to 4B) and 4 to 3 as downgraded (4B to 4A, 4B to 3). The analysis is not currently possible due to limited data points in some subgroups, which we are actively collecting.

Additional limitations of this analysis have been discussed in Chapter 5 Section 5.4. In summary, patients with consecutive negative screens were at the greatest risk of being non-adherent in a subsequent screen. The findings of our analysis can inform decision support tools to identify potentially non-adherent patients over multiple screening time points to guide future patient or physician interventions to improve adherence.

6.2 Three Approaches to Predict Non-adherence across Three Screening Time Points

6.2.1 Overview

LDCT screening is not a "one and done" event but a process that should occur annually for the duration of the individual's eligibility. One important characteristic of LCS is the longitudinal pattern of Lung-RADS scores, whereby a patient's adherence status is measured repeatedly at each screen until the patient is no longer eligible for LCS, drops out, or is lost to follow-up. To our knowledge, there has been no work focusing on predicting patient non-adherence to Lung-RADS recommendations over multiple screening time points. We propose three novel approaches to test the hypothesis that non-adherence to the second and third Lung-RADS recommendations can be accurately predicted using demographic, socioeconomic, health status, and Lung-RADS information from the medical records.

6.2.2 Methods

6.2.2.1 Patient Enrollment

Institutional review board (IRB) approval was obtained at the University of California, Los Angeles to conduct this retrospective study, and informed consent was waived (IRB#19-000627). Patient enrollment was mentioned in Chapter 5 Section 5.2.1. Depending on the approach, different subsets of the eligible patients were used in different models (see **Fig. 6.2**). The goal of developing these prediction models is to deploy them in clinical settings; however, at that time, COVID-19 shutdown may not be an issue anymore. Therefore, patients whose expected follow-up examination was during the COVID-19 shutdown period were excluded, and the COVID-19 variable was not included in the models.

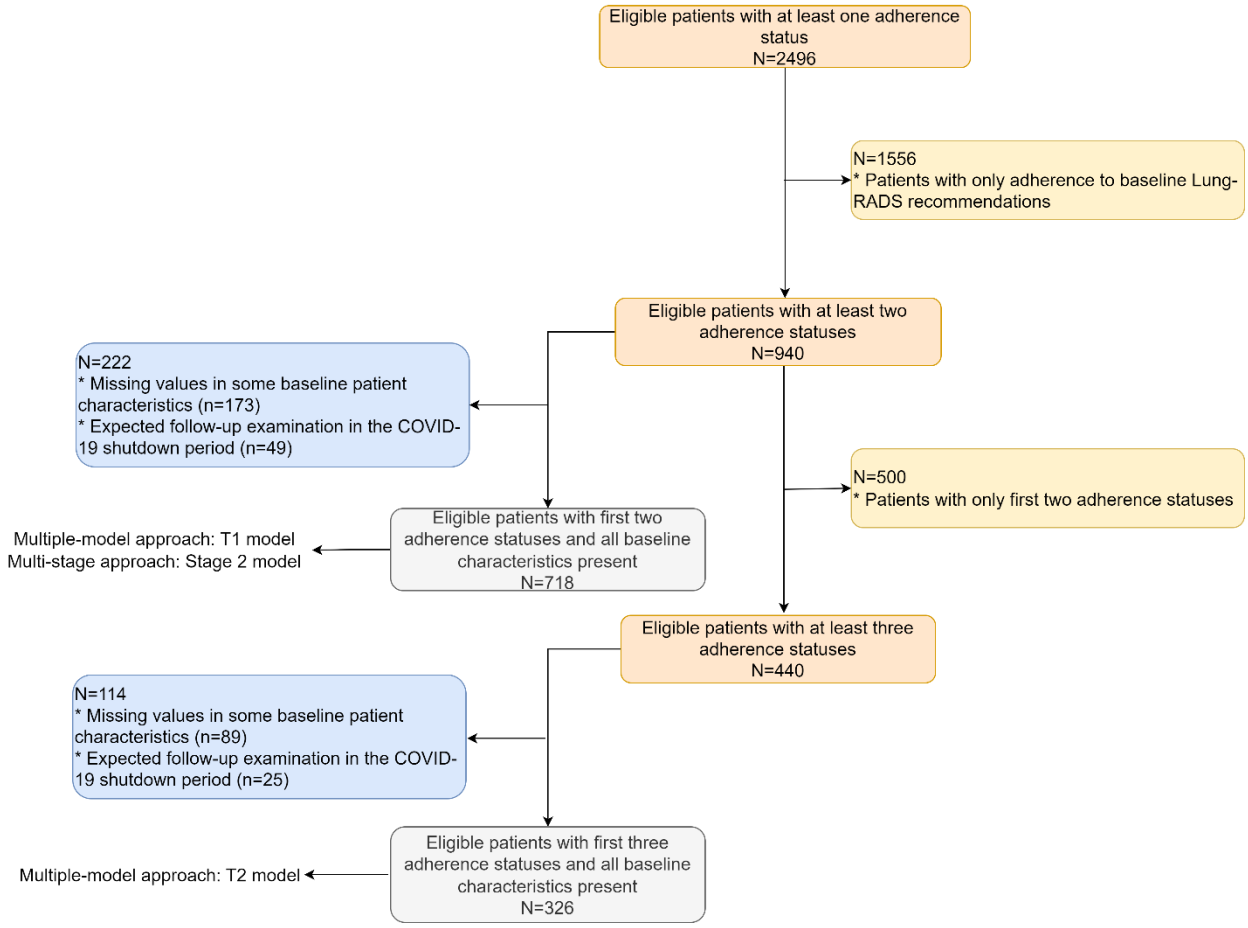

Fig. 6.2 The flow diagram of patient enrollment for the three modeling approaches. LDCT: low-dose computed tomography; Lung-RADS: Lung CT Screening Reporting & Data System.

6.2.2.2 Data Collection

Section 4.2.1 in Chapter 4 provides a description of the independent variables for this analysis. Among the 13 baseline predictors, there were two time-varying variables, including the Lung-RADS score and age-adjusted Charlson Comorbidity Index (CCI). For these variables, data were collected at each screening time point. In Section 6.1, we showed that patterns in Lung-RADS scores between screens were associated with patient non-adherence over time. However, given

that Lung-RADS scores at each screening time point were included as features in the prediction models, we did not further include changes in Lung-RADS scores between screens as a feature because this information could be obtained by knowing Lung-RADS scores. The available predictors at each screening time point are shown in **Fig. 6.3**.

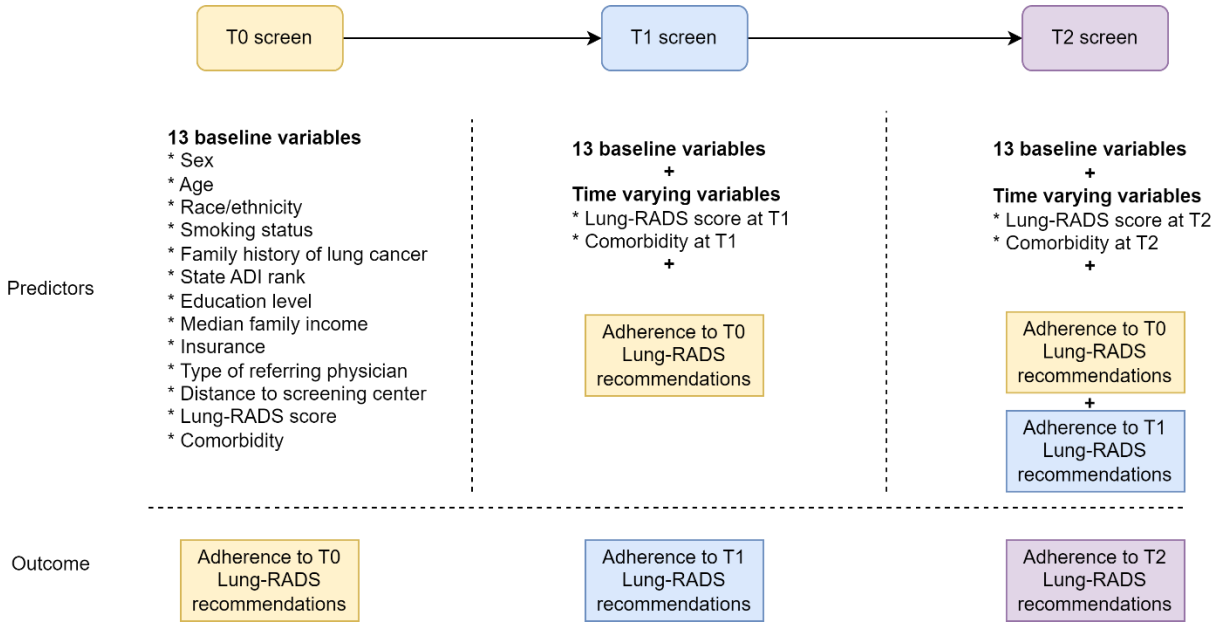

Fig. 6.3 The predictors and outcome at each screening time point. Comorbidity was measured by the age-adjusted Charlson Comorbidity score. ADI: area deprivation index, Lung-RADS: Lung CT Screening Reporting & Data System, T0: first screen, T1: second screen, T2: third screen.

6.2.2.3 Patient Outcomes

The outcome was adherence to Lung-RADS recommendations at a specific screening time point (see **Fig. 6.2**). Section 4.2.2 in Chapter 4 provides a description of the patient outcome. We defined the patient's second and third LDCT screens as T1 and T2 screens. Adherence to T1 and T2 Lung-RADS recommendations were assessed based on the definition mentioned in Chapter 4

Section 4.2.2. In this analysis, patients' adherence statuses were assessed up to the third screening time point (i.e., adherence to the T2 Lung-RADS recommendations) because only 8% of all 2496 eligible patients had four or more adherence statuses.

6.2.2.4 Statistical Analyses

We proposed three modeling approaches to predict patient non-adherence to Lung-RARDS recommendations at the second and third screening time points. Patients with missing values in baseline predictors were excluded. Comparisons of observed variables at baseline between the included and excluded patients were shown in **Tables S6.2 and S6.3** for the T1 and T2 models, respectively. No significant differences in observed baseline characteristics were found for all variables. Among the 13 baseline predictors, the input into the models were the six significant baseline factors (Chapter 5 Experiment 1), time-varying variables, and prior knowledge of non-adherence. Feature selection of baseline predictors with the least absolute shrinkage and selection operator (LASSO) yielded poorer performance on the test set than using a multivariable logistic regression to select features (i.e., z test, two-sided p-value<0.05). A Bayesian network was used in the unified model approach, while five machine learning models, including logistic regression, random forest, support vector machine, naive Bayes, and XGBoost, were used in the separate models and baseline & follow-up models approaches. In the three modeling approaches, repeated (n=5) cross-validation (5-fold) was used on 80% of the data, while the remaining 20% was used as holdout test sets (**Fig 6.4**). The primary evaluation metric was the area under the receiver operating curve (ROC-AUC). Recall/sensitivity, precision/positive predictive value, and accuracy were secondary metrics. For the three approaches, results were reported for the second and third screening time points only. Python version 3.7.3 and R version 3.6.1[119] were used for data analyses.

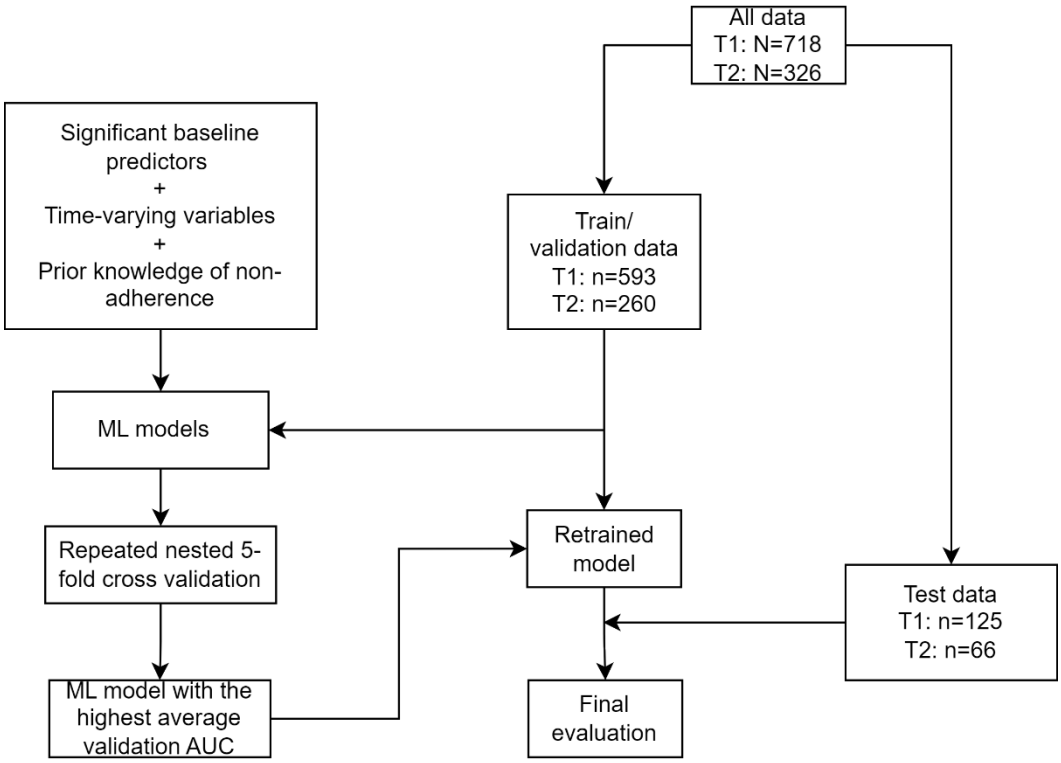

Fig 6.4 The overall pipeline of predicting patient non-adherence to the second and third Lung-RADS recommendations. Lung-RADS: Lung CT Screening Reporting & Data System; ML: Machine learning; AUC: area under the receiver operating characteristic curve.

6.2.2.4.1 Unified Model

A Bayesian network is a probabilistic graphical network where each node represents a random variable, and each edge corresponds to the conditional probability for the corresponding random variables. We built a Bayesian Network to predict non-adherence at the first three screening time points (**Fig 6.5**). In this network, we assumed the recommended follow-up time intervals were equal for all Lung-RADS categories (i.e., fixed intervals between time points). The outcome nodes were adherence to the first, second, and third Lung-RADS recommendations. To predict adherence to first Lung-RADS recommendation, the network structure was similar to the Naïve Bayes model

described in Chapter 5. In this analysis, our focus was on predicting non-adherence to the second and third Lung-RADS recommendations.

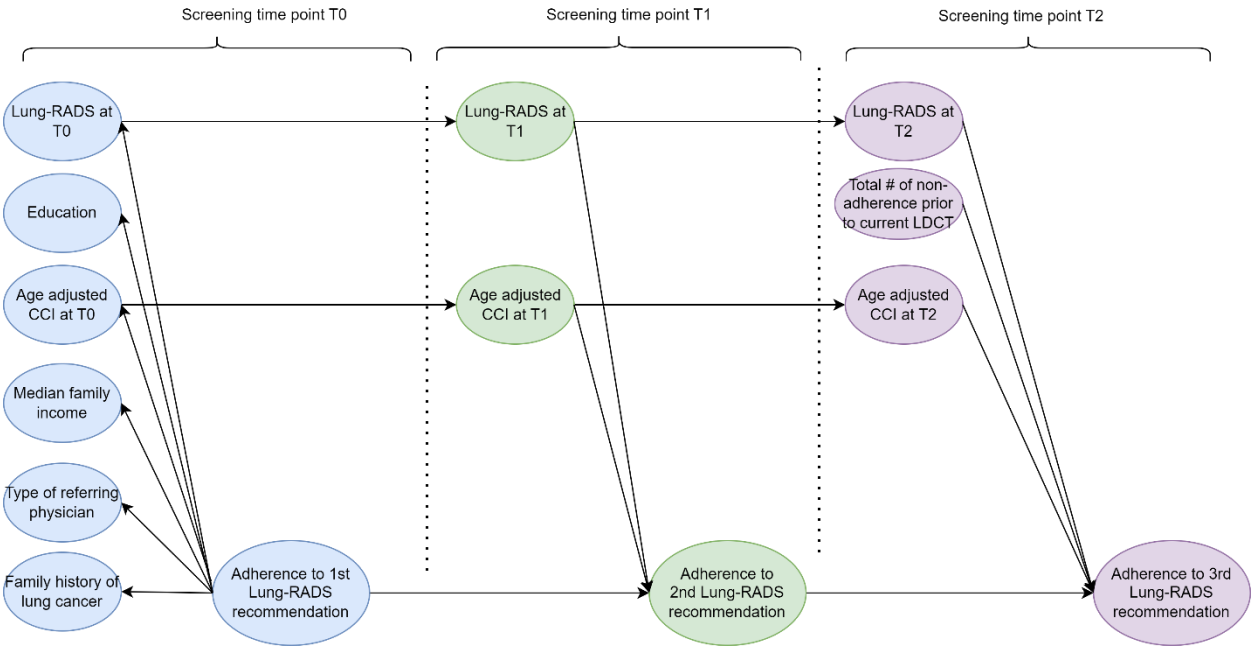

Fig. 6.5 The structure of the Bayesian Network to predict patient non-adherence to Lung-RADS recommendations across three screening time points. CCI: Charlson Comorbidity Index, ADI: area deprivation index, Lung-RADS: Lung CT Screening Reporting & Data System, T0: first screen, T1: second screen, T2: third screen.

6.2.2.4.2 Separate Models

At each screening time point, we built one model to predict non-adherence. The T0 model has been discussed in Chapter 5. In the T1 model, the predictors were the six significant baseline variables, time-varying variables at T1, and patient adherence status to T0 Lung-RADS recommendations (**Fig. 6.6**). The predictors of the T2 model included the six significant baseline variables, time varying variables at T2, and patient adherence statuses to both T0 and T1 Lung-RADS

recommendations (**Fig. 6.6**). In the T1 model, the adherence status to T0 Lung-RADS recommendations was considered as prior knowledge of non-adherence; while adherence statuses to the T0 and T1 Lung-RADS recommendations were deemed as prior knowledge in the T2 model.

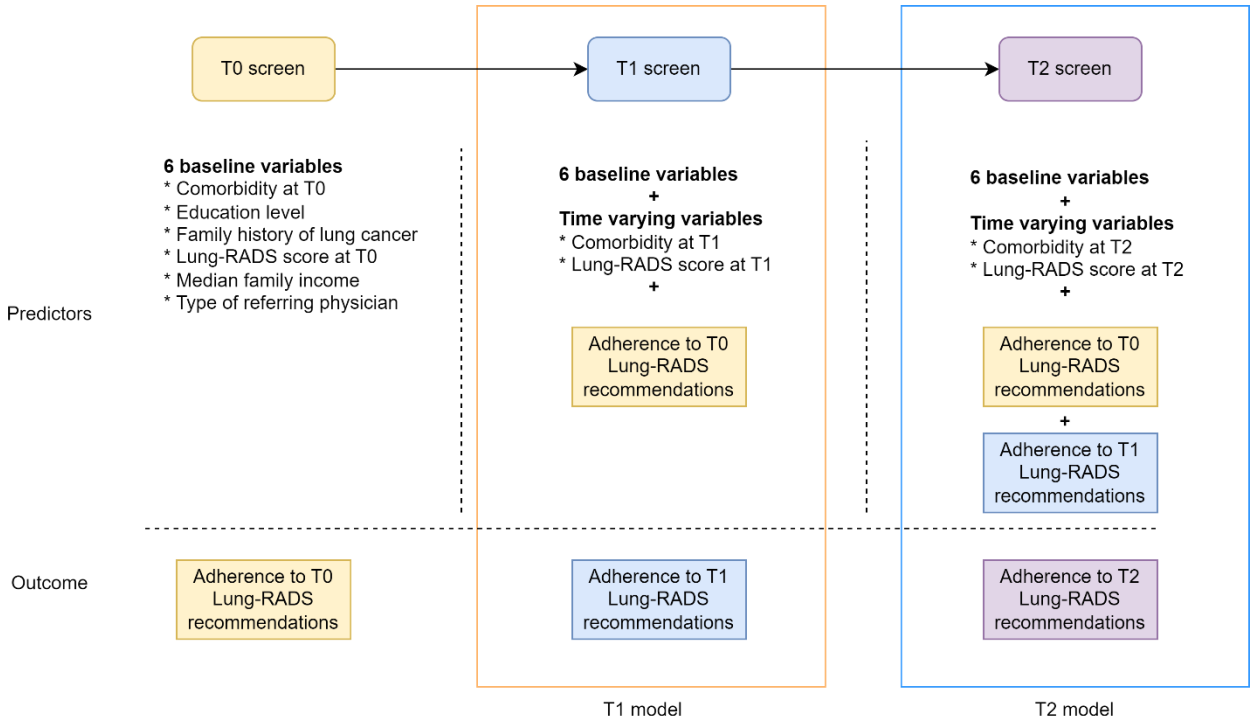

Fig. 6.6 The predictors and outcome of the T1 and T2 models, respectively. Comorbidity was measured by the age-adjusted Charlson Comorbidity score. Lung-RADS: Lung CT Screening Reporting & Data System, T0: first screen, T1: second screen, T2: third screen.

6.2.2.4.3 Baseline & Follow-up Models

Because adherence to screening recommendations might be challenging at the beginning and become stable over time, we hypothesized that 1) patient adherence to T0 Lung-RADS recommendations was different from that to T1 and T2 Lung-RADS recommendations, and 2) there was no difference between adherence to T1 and T2 Lung-RADS recommendations. To test our

hypotheses, we built mixed effects random intercept logistic regression model using patients with one, two, or three adherence statuses, where we adjusted for patient baseline characteristics (i.e., all independent variables in **Table 4.2**) and three time-varying variables (i.e., Lung-RADS score, comorbidity, COVID-19 shutdown) as fixed effects. The mixed effects model included 1979 patients (patient enrollment see Section 5.2.1) with no missing values in all covariates. We found that patients' adherence statuses to the baseline Lung-RADS recommendations were significantly lower than that to the T1 screen (referent: T0, odds ratio [OR] =0.55, $p<0.001$) and T2 (referent: T0, OR=0.54, $p<0.001$) Lung-RADS recommendations. We also found that adherence to T1 Lung-RADS recommendations was not significantly different from that at the T2 Lung-RADS recommendation (referent: T1, OR=0.98, $p=0.92$). Therefore, we could build models for T0 data alone and T1&T2 data combined. The T0 model was the baseline model, while the T1 & T2 model was considered the follow-up model. In the follow-up model, we cross-validated machine learning models using data from the second and third screening time points from patients with two or three adherence statuses. Because the mixed effects model suggested no difference between adherence to the second and third Lung-RADS recommendations in our data, we assumed independence between the patient's second and third screens. Thus, each patient's characteristics and adherence outcomes at T1 and T2 were included as two independent observations. Adherence to the baseline Lung-RADS recommendations was included as a predictor in the models, alongside the baseline patient characteristics and time-varying variables. Because some patients only had two adherence statuses, therefore, adherence to the T1 Lung-RADS recommendations was not included as a feature in this approach. The outcome was adherence to T1 or T2 Lung-RADS recommendations.

6.2.3 Results

6.2.3.1 Patient Characteristics at Baseline Screen

The unified model approach included 1926 patients with at least one adherence status (see **Table 6.3** for patients' characteristics at baseline screen), with 718 (see **Table S6.4** in the Appendix) and 326 (see **Table S6.5** in the Appendix) patients having two and three adherence statuses, respectively. The T1 and T2 models of the separate models approach were 718 and 326 patients (see **Tables S6.4 and S6.5** in the Appendix), respectively. In the baseline & follow-up models approach, the input was 1044 second and third adherence statuses from 718 patients, among which 718 (see **Table S6.4** in the Appendix) had the second adherence status, and 326 (see **Table S6.5** in the Appendix) had the second and third adherence statuses.

Table 6.3 Baseline patient characteristics in the unified model approach (N=1926).

	Individual, No. (%)		
Variable	Overall (N=1926)	Adherent (n=682)	Non-adherent (n=1244)
Lung-RADS			
1-2	1611 (83.6)	481 (70.5)	1130 (90.8)
3	151 (7.8)	82 (12.0)	69 (5.5)
4A	99 (5.1)	67 (9.8)	32 (2.6)
4B/X	65 (3.4)	52 (7.6)	13 (1.0)
Age in years			

Table 6.3 Baseline patient characteristics in the unified model approach (N=1926).

	Individual, No. (%)		
Variable	Overall (N=1926)	Adherent (n=682)	Non-adherent (n=1244)
<65	837 (43.5)	261 38.3)	576 (46.3)
≥65	1089 (56.5)	421 (61.7)	668 (53.7)
Sex			
Female	781 (40.6)	271 (39.7)	510 (41.0)
Male	1145 (59.4)	411 (60.3)	734 (59.0)
Race/ethnicity [b]			
Asian	163 (8.5)	55 (8.1)	108 (8.7)
Black	125 (6.5)	48 (7.0)	77 (6.2)
Hispanic/Latino	107 (5.6)	35 (5.1)	72 (5.8)
White	1488 (77.3)	534 (78.3)	954 (76.7)
Other	43 (2.2)	10 (1.5)	33 (2.7)
Education level			
Less than college	926 (48.1)	333 (48.8)	593 (47.7)
College Graduate	578 (30.0)	182 (26.7)	396 (31.8)
Postgraduate	422 (21.9)	167 (24.5)	255 (20.5)
Family history of lung cancer			
Yes	452 (23.5)	185 (27.1)	267 (21.5)

Table 6.3 Baseline patient characteristics in the unified model approach (N=1926).

Variable	Individual, No. (%)		
	Overall (N=1926)	Adherent (n=682)	Non-adherent (n=1244)
No	1474 (76.5)	497 (72.9)	977 (78.5)
Smoking status			
Current	748 (38.9)	243 (35.6)	505 (40.6)
Former	1178 (61.2)	439 (64.4)	739 (59.4)
Primary insurance			
Medicaid/Medicaid	817 (42.4)	327 (47.9)	490 (39.4)
Private or Commercial or other [c]	1109 (57.6)	355 (52.1)	754 (60.6)
Age-adjusted CCI			
Low (0-1)	278 (14.4)	71 (10.4)	207 (16.6)
Intermediate (2-3)	1124 (58.4)	397 (58.2)	727 (58.4)
High (≥4)	524 (27.2)	214 (31.4)	310 (24.9)
Distance to screening center [a]			
Short (≤ median)	972 (50.5)	341 (50.0)	631 (50.7)
Long (> median)	954 (49.5)	341 (50.0)	613 (49.3)
Median household income [a]			
Low (≤ median)	1002 (52.0)	335 (49.1)	667 (53.6)

Table 6.3 Baseline patient characteristics in the unified model approach (N=1926).

	Individual, No. (%)		
Variable	Overall (N=1926)	Adherent (n=682)	Non-adherent (n=1244)
High (> median)	924 (48.0)	347 (50.9)	577 (46.4)
ADI state rank a			
Low (≤ median)	1050 (54.5)	382 (56.0)	668 (53.7)
High (> median)	876 (45.5)	300 (44.0)	576 (46.3)
Type of referring physician			
Pulmonology, Thoracic Oncology/Radiology/Surgery	360 (18.7)	173 (25.4)	187 (15.0)
Other	1566 (81.3)	509 (74.6)	1057 (85.0)

[a] Median distance to the screening center: 6.84 miles.; median household income: $73,478; median ADI state rank: 3.

[b] Subcategories in Other: American Indian or Alaska Native, more than one race, Native Hawaiian or Pacific Islander, or other racial and ethnic groups that were not mentioned here. [c] Subcategories in Private or Commercial or other: private or commercial, VA, self-pay, other insurance that was not mentioned here.

Lung-RADS: Lung CT Screening Reporting & Data System; CCI: Charlson Comorbidity Index; ADI: Area Deprivation Index.

6.2.3.2 Rates of Non-Adherence

The rates of non-adherence for each screening time point are summarized in **Table 6.4**.

Table 6.4 Rates of non-adherence stratified by screening time points and Lung-RADS category.

Time point	No. Patients	Lung-RADS	Non-adherence rate % (n adherent/n total)
T1	718	1 to 2	0.54 (342/634)
		3	0.34 (12/35)
		4A	0.24 (5/21)
		4B/X	0.36 (10/28)
T2	326	1 to 2	0.47 (135/287)
		3	0.37 (7/19)
		4A	0.33 (3/9)
		4B/X	0.55 (6/11)

T0, T1, T2: the first, second, and third screening time points; Lung-RADS: Lung CT Screening Reporting & Data System.

6.2.3.3 Model Performances

The average model performances on the validation sets for each screening time point are shown in **Tables 6.5** and **6.6**. In general, the AUCs suggested poor discrimination (lower than 0.7) between the adherent and non-adherence patients for all models. The models with the highest AUCs were chosen as the final model at each time point, T1: AUC=0.618 (Naive Bayes from the baseline & follow-up models approach, **Table 6.5**), and T2: AUC=0.627 (XGBoost from the separate models approach, **Table 6.6**). The final models were then retrained using the 80% data and

tested on the holdout test sets. On the holdout test sets, the final T1 model achieved recall: 0.567, precision: 0.615, accuracy: 0.615, and AUC: 0.614; the final T2 model achieved recall: 0.613, precision: 0.679, accuracy: 0.682, and AUC: 0.678. When lowering the prediction threshold, the models captured more false negative cases (i.e., truly non-adherent but misclassified as adherent) at the cost of adding more false positives (i.e., truly adherent but misclassified as non-adherent) (**Table 6.7**).

Table 6.5 Average validation performance (standard deviation) for adherence to T1 Lung-RADS recommendations.

Approach	Model	Recall/sensitivity	Precision/PPV	Accuracy	AUC
Unified model	Bayesian Network	0.550 (0.108)	0.561 (0.073)	0.547 (0.044)	0.553 (0.039)
Separate models	Logistic regression	0.695 (0.068)	0.577 (0.048)	0.573 (0.042)	0.603 (0.051)
	Random forest	0.563 (0.050)	0.545 (0.056)	0.521 (0.045)	0.537 (0.041)
	SVM	0.701 (0.117)	0.568 (0.050)	0.562 (0.041)	0.582 (0.047)
	Naïve Bayes	0.681 (0.068)	0.591 (0.053)	0.586 (0.044)	0.605 (0.051)
	XGBoost	0.706 (0.076)	0.581 (0.046)	0.578 (0.034)	0.600 (0.042)
Baseline & Follow-up models (T1+T2)	Logistic regression	0.568 (0.098)	0.581 (0.066)	0.572 (0.033)	0.616 (0.043)
	Random forest	0.595 (0.065)	0.547 (0.059)	0.554 (0.039)	0.590 (0.047)
	SVM	0.550 (0.100)	0.591 (0.072)	0.578 (0.041)	0.611 (0.039)
	Naïve Bayes	0.586 (0.094)	0.583 (0.061)	0.577 (0.036)	0.618 (0.043)

Table 6.5 Average validation performance (standard deviation) for adherence to T1 Lung-RADS recommendations.

Approach	Model	Recall/sensitivity	Precision/PPV	Accuracy	AUC
	XGBoost	0.574 (0.096)	0.581 (0.057)	0.574 (0.033)	0.603 (0.036)

T1: the second screening time point; Lung-RADS: Lung CT Screening Reporting & Data System; PPV: positive predictive value; AUC: area under the receiver operating characteristic curve; SVM: support vector machine.

Table 6.6 Average validation performance (standard deviation) for adherence to T2 Lung-RADS recommendations.

Approach	Model	Recall/sensitivity	Precision/PPV	Accuracy	AUC
Unified model	Bayesian Network	0.304 (0.104)	0.628 (0.163)	0.624 (0.066)	0.580 (0.053)
Separate models	Logistic regression	0.464 (0.134)	0.572 (0.148)	0.580 (0.068)	0.619 (0.080)
	Random forest	0.518 (0.106)	0.566 (0.102)	0.587 (0.073)	0.619 (0.076)
	SVM	0.444 (0.103)	0.560 (0.111)	0.581 (0.065)	0.621 (0.077)
	Naïve Bayes	0.516 (0.101)	0.554 (0.112)	0.581 (0.069)	0.619 (0.079)
	XGBoost	0.476 (0.123)	0.567 (0.114)	0.579 (0.064)	0.627 (0.069)
Baseline & Follow-up	Logistic regression	0.568 (0.098)	0.581 (0.066)	0.572 (0.033)	0.616 (0.043)
	Random forest	0.595 (0.065)	0.547 (0.059)	0.554 (0.039)	0.590 (0.047)
	SVM	0.550 (0.100)	0.591 (0.072)	0.578 (0.041)	0.611 (0.039)

Table 6.6 Average validation performance (standard deviation) for adherence to T2 Lung-RADS recommendations.

Approach	Model	Recall/sensitivity	Precision/PPV	Accuracy	AUC
models (T1+T2)	Naïve Bayes	0.586 (0.094)	0.583 (0.061)	0.577 (0.036)	0.618 (0.043)
	XGBoost	0.574 (0.096)	0.581 (0.057)	0.574 (0.033)	0.603 (0.036)

T1: the second screening time point; Lung-RADS: Lung CT Screening Reporting & Data System; PPV: positive predictive value; AUC: area under the receiver operating characteristic curve; SVM: support vector machine.

Table 6.7 Model performances on the test sets given varying prediction thresholds.

Threshold	Recall	No. false negatives	Precision	No. false positives
		T1		
0.5	0.57	45	0.61	37
0.4	0.79	22	0.54	70
0.3	0.96	4	0.52	94
0.2	1	0	0.49	107
0.1	1	0	0.48	109
		T2		
0.5	0.61	12	0.68	9

Table 6.7 Model performances on the test sets given varying prediction thresholds.

Threshold	Recall	No. false negatives	Precision	No. false positives
0.4	0.61	12	0.66	10
0.3	0.65	11	0.57	15
0.2	0.71	9	0.54	19
0.1	0.84	5	0.51	25

T1: first screening time point; T2: second screening time point.

Notes: The numbers of total test cases were 126 and 66 for the T1 and T2 models, respectively.

6.2.4 Discussion

We evaluated three approaches to predicting patient non-adherence to T1 and T2 Lung-RADS recommendations. However, the discriminative power of all models was low (test AUCs<0.7). This suggests that the variables currently included in the models are insufficient to classify adherent and non-adherent patients. Some of the potential predictors missing from our models include the antecedent variables (i.e., psychological, cognitive, social, and environmental) from the Carter-Harris conceptual model[20] and SDH[94, 97]. Besides missing patient-level factors, provider and systemic barriers were not accounted for in the analysis. The T0 model achieved higher test AUC (i.e., 0.67) and recall (i.e., 0.94) than the T1 and T2 models, which could suggest

that missing these psychosocial variables had more impact on the T1 and T2 models than the T0 model.

During testing, the false positives were truly adherent but misclassified as non-adherent. In the real world, false-positive patients may receive redundant reminders for their next recommended follow-up examination. In this scenario, the harm to the patient is minimal but will increase the workload of the staff in the LCS program. On the other hand, the false negatives in the test sets were truly non-adherent but misclassified as adherent. The consequence of false negatives is more severe than false positives in clinical practice because false-negative patients will not receive appropriate reminders and are at higher risk of not adhering to the screening recommendation. Being non-adherent to Lung-RADS recommendations may cause a delay in lung cancer diagnosis, especially for patients with highly suspicious lung nodules. Unlike the T0 model with high recall (i.e., 0.94, very few truly non-adherent patients were misclassified), the test recalls in the T1 and T2 models were only 0.57 and 0.61. Lowering the prediction threshold in the T1 and T2 models can help identify more truly non-adherent patients who will receive proper reminders; in turn, the number of false positives will increase, meaning that some adherent patients will receive unnecessary reminders.

The major limitation of this analysis was a lack of truly discriminative features, which led to our model being underspecified. Our data was limited to available variables in the medical records. Due to the retrospective design, collecting additional data elements was not an option. Future prospective studies incorporating psychosocial variables and social determinants of health information may be essential to achieving better performance in predicting patient non-adherence over time. In designing surveys to collect additional psychosocial variables, from the behavioral science

perspective, we could also assess patient intention and commitment to adhering to Lung-RADS recommendations because they have been shown to be associated with individual adherence in other domains.[200, 201] Moreover, insurance status, which could change over time for some LCS participants, was only collected at the time of the baseline screen in our dataset. Patients who lost their insurance status before the recommended follow-up examination might decided not to complete the scheduled follow-up (i.e., non-adherence). Insurance data should be collected longitudinally in prospective studies in the future. Besides prior knowledge of non-adherence at prior screening time points, patient adherence to other types of examinations (e.g., adherence to breast cancer screening recommendations) may be predictive of non-adherence to LCS recommendations, and this information can be retrieved from the medical records. In addition, previous studies have examined the association between personality and patient adherence in other disease domains.[202-204] Personality traits may be associated with patient behaviors in LCS, including adherence status. More research is needed in this regard.

The coding of adherence status was binary in this analysis. In future studies, we may consider more subcategories (i.e., on-time, late, no follow-up) or use continuous coding. The models were evaluated using data from a single academic center. Given the heterogeneous settings of LCS programs across the nation (Chapter 3), our findings may not be generalizable to LCS programs implemented in non-academic settings or to LCS programs with patient characteristics different from our institution. We are actively working to seek collaborators for multi-center data to validate our results. Since we were the first group to predict patient non-adherence across multiple screening time points, comparing our results with the literature was not possible. We encourage other research groups to implement our models and report their findings.

6.3 Conclusion

This chapter delineates our investigations of predicting patient non-adherence to Lung-RADS recommendations over multiple screening time points. Demographic variables, socioeconomic status, health status, and Lung-RADS scores are insufficient to accurately predict non-adherence. Future work should focus on including psychosocial and social determinants of health variables as features in the prediction models and conducting prospective studies using multi-center data. As well, we have addressed only patient-centered variables; the influence of provider beliefs and behaviors is likely critical to the adherence of patients to LCS recommendations.

CHAPTER 7

Conclusion

This chapter summarizes the results and contributions from this dissertation and important takeaways. Based on the findings, we suggest research directions to further improve patient adherence to LCS recommendations.

7.1 Summary of Research

This dissertation advances our understanding of the current status of patient adherence to LCS recommendations in the US. In this dissertation, we provide the following research developments that address factors contributing to patient non-adherence to LCS:

1. An understanding of current adherence rates to Lung-RADS recommendations. Existing systematic review and meta-analysis' reported adherence rates and predictors of non-adherence in LCS programs[103-105] have not specifically examined patient adherence to Lung-RADS recommendations. We conducted a stratified pooled analysis based on Lung-RADS scores due to perceived differences in adherence behaviors among positive (Lung-RADS 3 or 4, risk of malignancy 5-15% or >15%) and negative (Lung-RADS 1 or 2, risk of malignancy <1% or 1-2%) patients. We further performed meta-regression to identify factors that contribute to the heterogeneous adherence rates reported in the literature. Through this (Chapter 3), we achieved a more precise understanding of the current state of LCS adherence.
2. Individualized prediction of LCS non-adherence using medical records data. We build machine-learning models using data from our medical records to predict non-adherence across the first three screening time points (Chapters 5 and 6). Our work sheds light on the extent of

validity of using routinely collected electronic medical records data to predict LCS non-adherence. We also identified the most important factors associated with non-adherence over time. This finding may aid in the understanding of patient behaviors in LCS and provide the basis for tailored interventions to improve adherence.

7.2 Considerations and Lessons Learned

An individual must undergo multiple steps to complete cancer screening successfully.[98] The maximum benefits of cancer screening can be achieved by repeated screens at specified intervals. The necessity of repetition may complicate this process due to non-adherence to cancer screening recommendations. In this dissertation, we stopped at determining factors associated with non-adherence to LCS recommendations, we did not examine potential reasons for failing to complete each patient step to successful cancer screening. For example, we did not contact the patient to ask about reasons for canceled or re-scheduled follow-up examinations. Such information might allow us to determine the true reasons for screening discontinuation.

Analyses in this dissertation were conducted using data from the first decade of LCS implementation. During this stage, LCS participation among high-risk individuals was extremely low, with a national average of 6%.[24] Factors of non-adherence were identified in this work. However, determining factors of non-adherence is a continuing process. As more screen-eligible adults initiate LDCT screening, the factors may change over time. As such, the factors identified in this work require further verification in future research.

7.3 Future Directions

We identify limitations in analyses of this dissertation and subsequently suggest directions for extending this work to improve patient adherence to LCS recommendations.

- Emphasizing LCS adoption. Currently, the LCS participation rates remain low among high-risk individuals in the United States. Adherence to LCS guidelines would benefit from improved LCS participation in the following two aspects. First, LCS participation serves as a precursor or antecedent for maintaining adherence to screening guidelines. Undergoing the first LDCT scan reflects the patient's awareness of and knowledge about LCS, which sets the stage for adhering to screening recommendations. Second, barriers to LCS participation can also influence patients' adherence to cancer screening guidelines. Some of the shared barriers may include fear of cancer diagnosis, perceived stigma, cost concerns, and skepticism about the benefits of screening.[143] Addressing barriers to LCS participation helps with the patient's downstream behaviors in LCS, including adhering to screening guidelines.
- Prospectively collecting psychosocial variables in a standardized manner to enable more accurate predictions of non-adherence to LCS. The psychosocial antecedent variables mentioned in the Carter-Harris conceptual model have been found to influence breast, cervical, and colorectal cancer screening adherence. Incorporating these variables as features in the prediction models has the potential to achieve better model performance. Nevertheless, the works in this dissertation reveal a lack of standardized instruments for collecting these data elements. Societies and professional organizations should promote the development of these social determinants of health common data elements to ensure interoperability of collected data across sites. When these standardized variables are readily available for use in clinical research, researchers

can verify them in prospective studies, creating more opportunities to refine and improve our knowledge in predicting patient adherence to LCS guidelines.

- Leveraging data from national LCS registries. Because we are among the first groups to identify factors and predict non-adherence to LCS, most of our findings have not been verified in other studies in the literature. We should note that while our approach to identifying factors and training machine learning models is generalizable, other institutions may identify specific factors that affect adherence in their own LCS population. One of our next steps is to repeat the experiments using data from more diverse populations across multiple settings. As of 2020, the American College of Radiology (ACR) Lung Cancer Screening Registry (LCSR) manages LCS data submitted from 3404 facilities across 50 states to help clinicians improve their own quality of care and refine LCS care for everyone at the national level.[205] This national data registry contains rich information on LDCT scans and the corresponding follow-ups, with over 610,000 LDCT records currently stored in the database. Leveraging data from the ACR LCSR, we seek to validate our findings with the goal of increasing rates of adherence by patients who have already entered the LCS program.
- Assessing the impact of non-adherence on patient outcome. In this dissertation, we focused on identifying factors associated with patient non-adherence to Lung-RADS recommendations. For instance, we found that patients with negative screens were more likely to be non-adherent to both baseline recommendations and annual screens. But we did not further assess whether non-adherence was associated with patient outcomes, such as time to lung cancer diagnosis, time to lung cancer treatment, lung cancer stage, and survival. The patients who are most likely to benefit from this analysis are those non-adherent patients with screen-detected lung cancers.

Such evidence is more profound when informing the decision support tool for identifying non-adherent patients across multiple time points as well as informing future outreach efforts to improve patient adherence to LCS.

- Implementing multilevel tailored interventions to improve adherence. While identifying factors of non-adherence is essential to knowing which subgroups of patients are more likely to be non-adherent to LCS recommendations, tailored interventions are the key to achieving better adherence. Multilevel interventions have been shown to be effective in increasing the rates of adherence to screening guidelines in breast, cervical, and colorectal cancer screenings, including outreach, navigation, patient and physician education, patient and physician reminders, and financial incentives. Such interventions may be adopted in clinical LCS programs for further evaluation.

APPENDIX

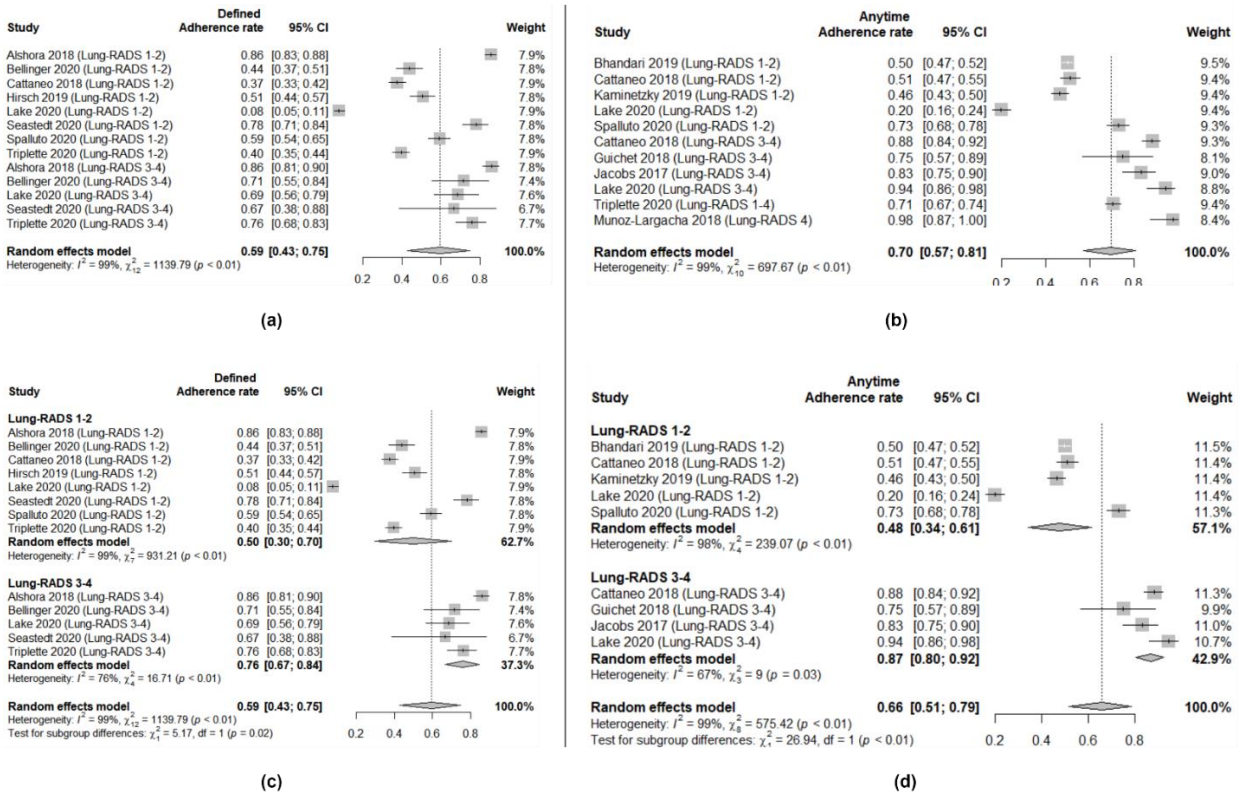

Fig. S3.1 Forest plots of the pooled adherence rate to Lung-RADS recommended screening intervals at T1 from journal articles. (a) Forest plot of defined adherence rates from journal articles (total n=3582). (b) Forest plot of anytime adherence rates from journal articles (total n=4636). (c) Forest plot of defined adherence rates from journal articles stratified by Lung-RADS categories (total n= 3582, Lung-RADS 1-2 n=3048, Lung-RADS 3-4 n=534). (d) Forest plot of anytime adherence rates from journal articles stratified by Lung-RADS categories (total n=3926, Lung-RADS 1-2 n=3446, Lung-RADS 3-4 n=480). Defined adherence: Adherence was defined as completion of an annual incidence screen or early follow-up exam within a specified time interval from recommended date. Anytime adherence: Patients are considered adherent as long as they received a follow-up exam anytime during the course of the study period. Lung-RADS: Lung CT Screening Reporting & Data System; T1: annual incidence screen at one year; CI: confidence interval.

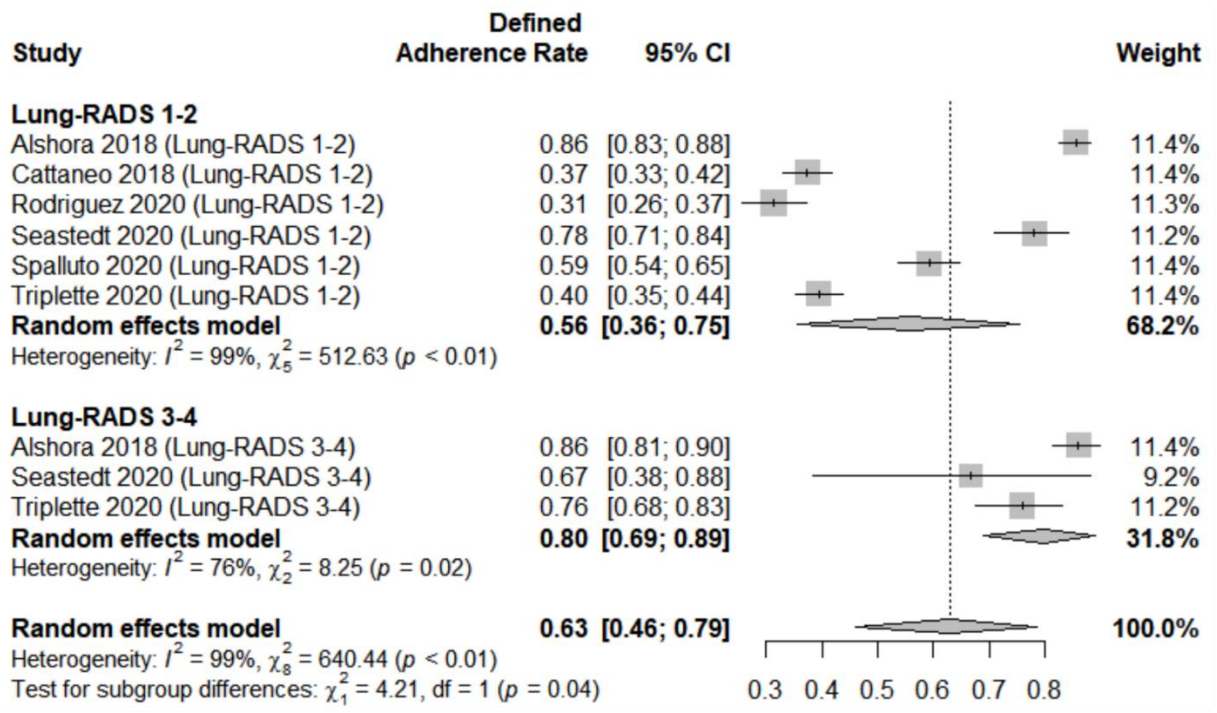

Fig. S3.2 Forest plot of the pooled adherence rates to Lung-RADS recommended screening intervals at T1 of a subset of the studies in which adherence was defined as completion of an annual incidence screen or early follow-up within three months of recommended date (total n=2836, Lung-RADS 1-2 n=2414, Lung-RADS 3-4 n=422). Defined adherence: Adherence was defined as completion of an annual incidence screen or early follow-up exam within a specified time interval from recommended date. Lung-RADS: Lung CT Screening Reporting & Data System; T1: annual incidence screen at one year; CI: confidence interval.

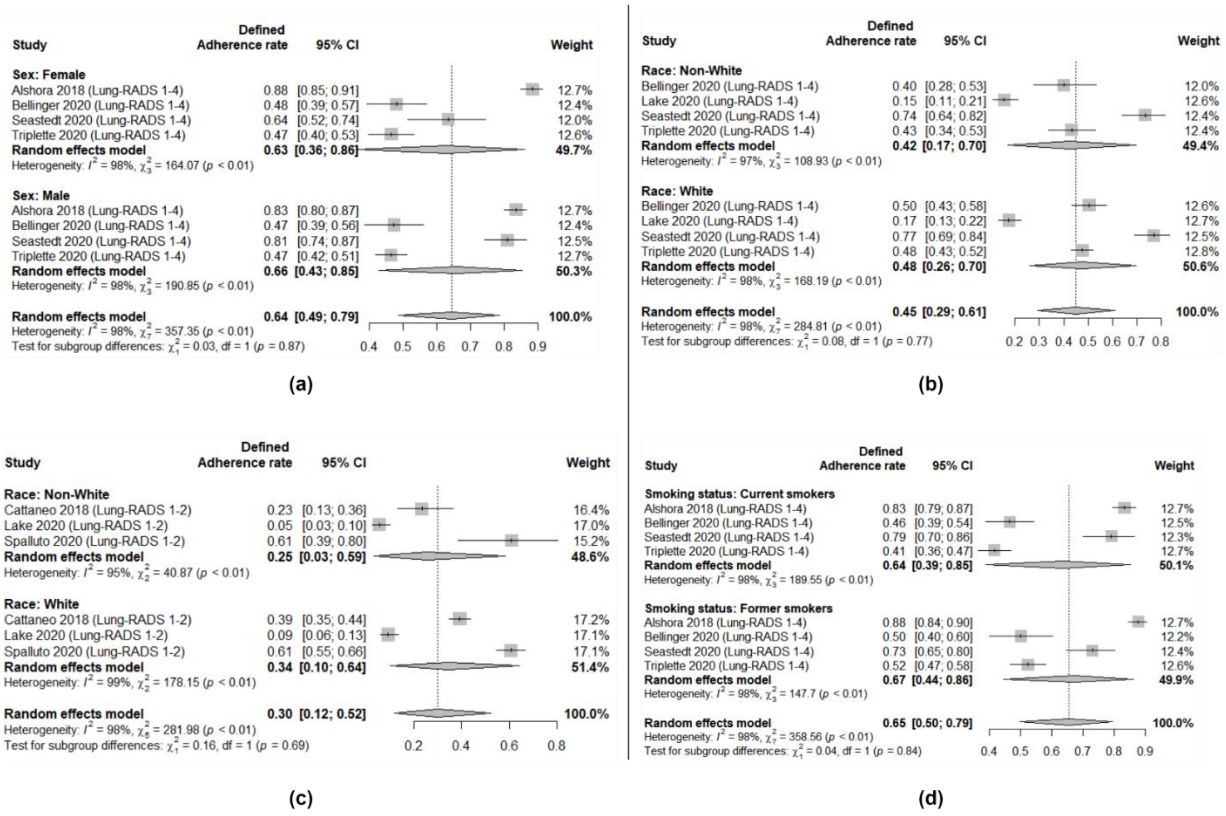

Fig. S3.3 Forest plots of the pooled adherence rates to Lung-RADS recommended screening intervals at T1 in sub-groups. (a) Forest plot of defined adherence rates stratified by sex among Lung-RADS 1-4 (total n=2079, male n=1255, female n=824). (b) Forest plot of defined adherence rates stratified by race among Lung-RADS 1-4 (total n=1607, White n=1133, non-White n=474). (c) Forest plot of defined adherence rates stratified by race among Lung-RADS 1-2 (total n=1218, White n=973, non-White n=245). (d) Forest plot of defined adherence rates stratified by smoking status among Lung-RADS 1-4 (total n=2079, current smokers n=1051, former smokers n=1028). Defined adherence: Adherence was defined as completion of an annual incidence screen or early follow-up exam within a specified time interval from recommended date. Lung-RADS: Lung CT Screening Reporting & Data System; T1: annual incidence screen at one year; CI: confidence interval. Notes: Adherence rates assessed among patients with unknown race or smoking status were excluded from the analyses. The inconsistent reporting of pooled adherence rates for sex, race, or smoking status stratified by Lung-RADS categories was due to data scarcity (e.g., insufficient data for pooling defined adherence rates stratified by sex among Lung-RADS 1-2).

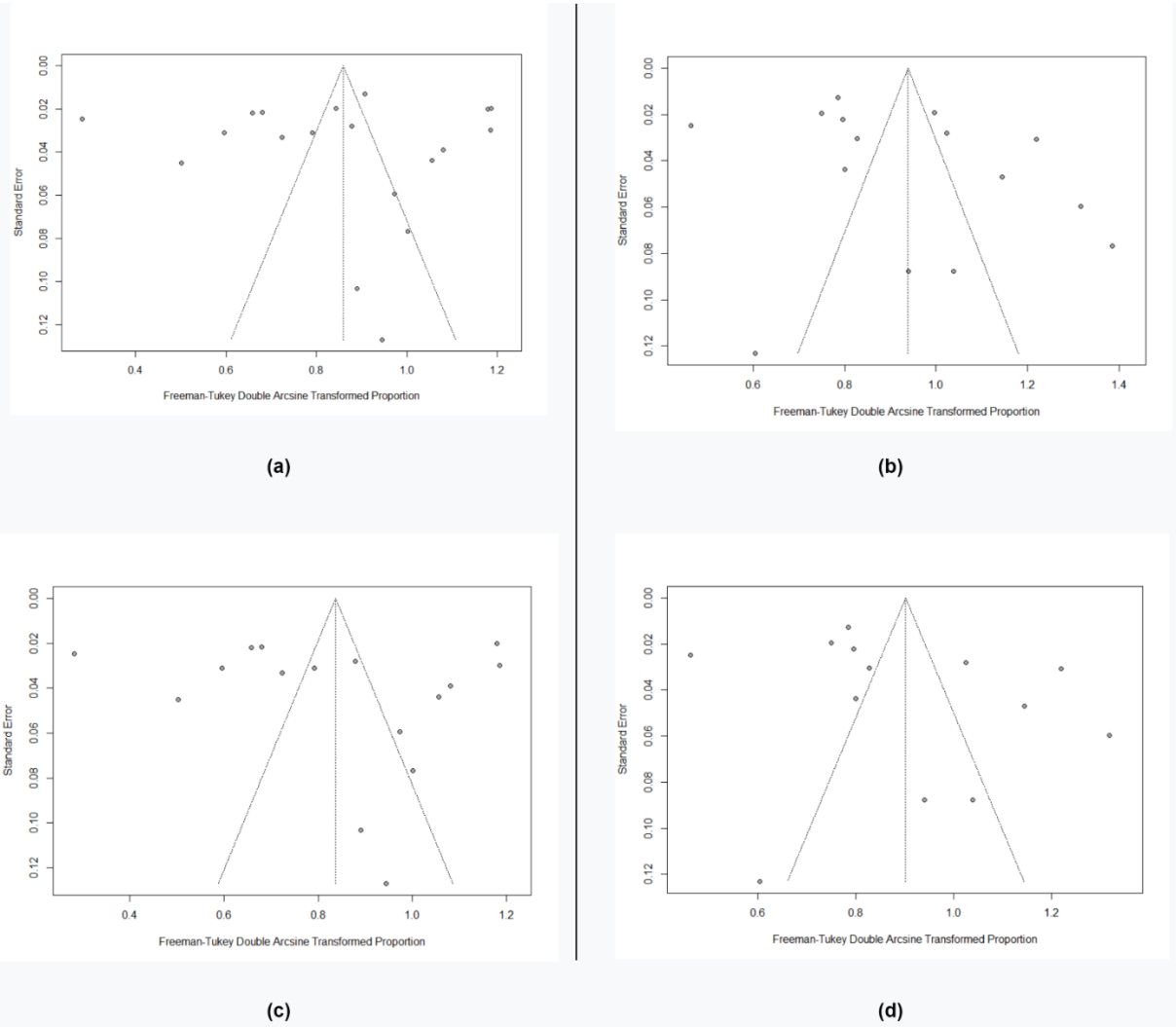

Fig. S3.4 Funnel plots for meta-analyses of pooled adherence rates to Lung-RADS recommended screening intervals at T1. (a) Funnel plot of defined adherence rates. (b) Funnel plot of anytime adherence rates. (c) Funnel plot of defined adherence rates stratified by Lung-RADS categories. (d) Funnel plot of anytime adherence rates stratified by Lung-RADS categories. Defined adherence: Adherence was defined as completion of an annual incidence screen or early follow-up exam within a specified time interval from recommended date. Anytime adherence: Patients are considered adherent as long as they received a follow-up exam anytime during the course of the study period. Lung-RADS: Lung CT Screening Reporting & Data System; T1: annual incidence screen at one year.

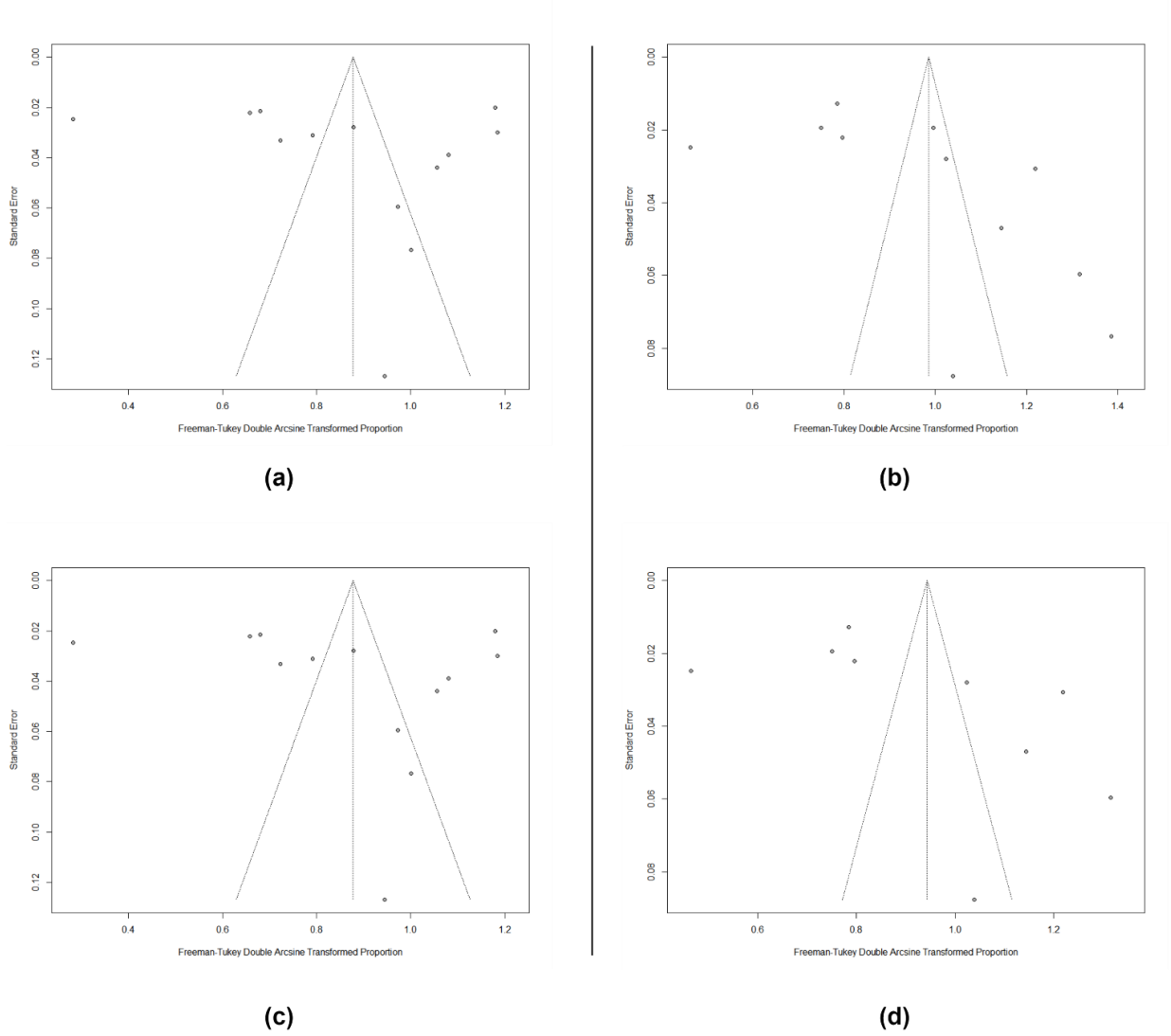

Fig. S3.5 Funnel plots for meta-analyses of pooled adherence rates to Lung-RADS recommended screening intervals at T1 from journal articles. (a) Funnel plot of defined adherence rates from journal articles. (b) Funnel plot of anytime adherence rates from journal articles. (c) Funnel plot of defined adherence rates stratified by Lung-RADS categories from journal articles. (d) Funnel plot of anytime adherence rates stratified by Lung-RADS categories from journal articles. Defined adherence: Adherence was defined as completion of an annual incidence screen or early follow-up exam within a specified time interval from recommended date. Anytime adherence: Patients are considered adherent as long as they received a follow-up exam anytime during the course of the study period. Lung-RADS: Lung CT Screening Reporting & Data System; T1: first follow-up after the initial screen.

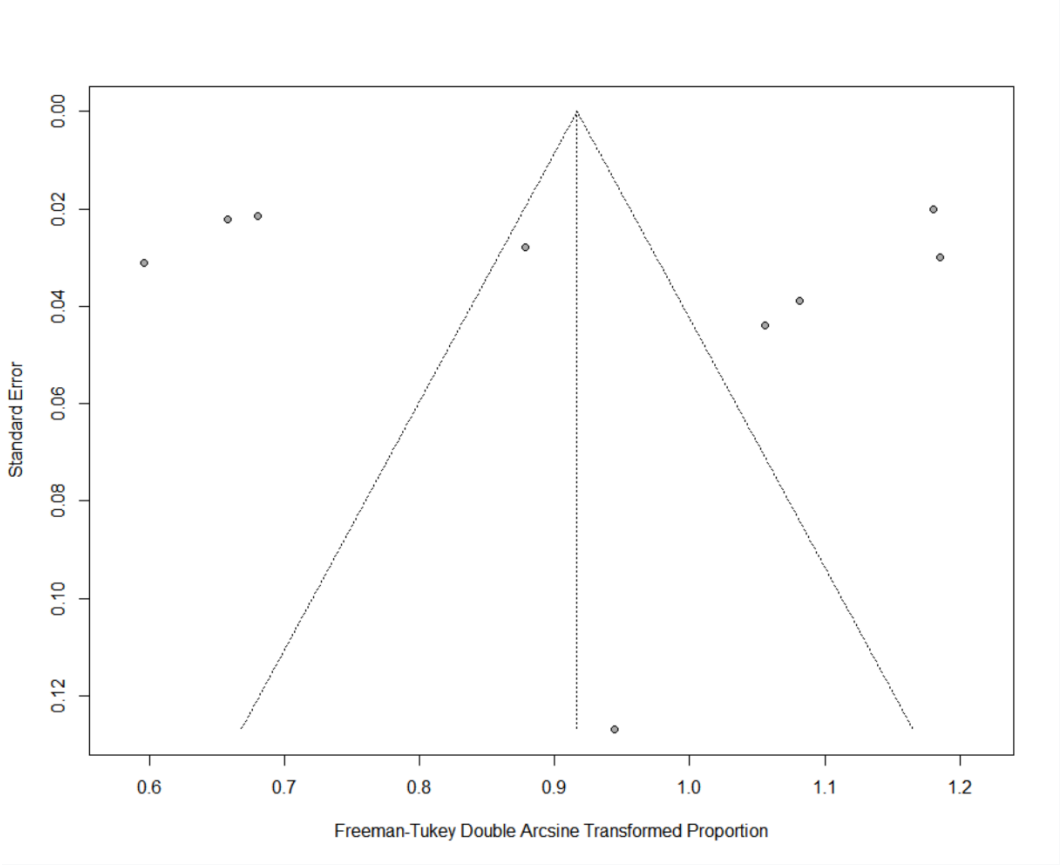

Fig. S3.6 Funnel plot for a meta-analysis of adherence rates to Lung-RADS recommended screening intervals at T1 of a subset of the studies in which adherence was defined as completion of an annual incidence screen or early follow-up exam within three months of recommended date. Lung-RADS: Lung CT Screening Reporting & Data System; T1: annual incidence screen at one year.

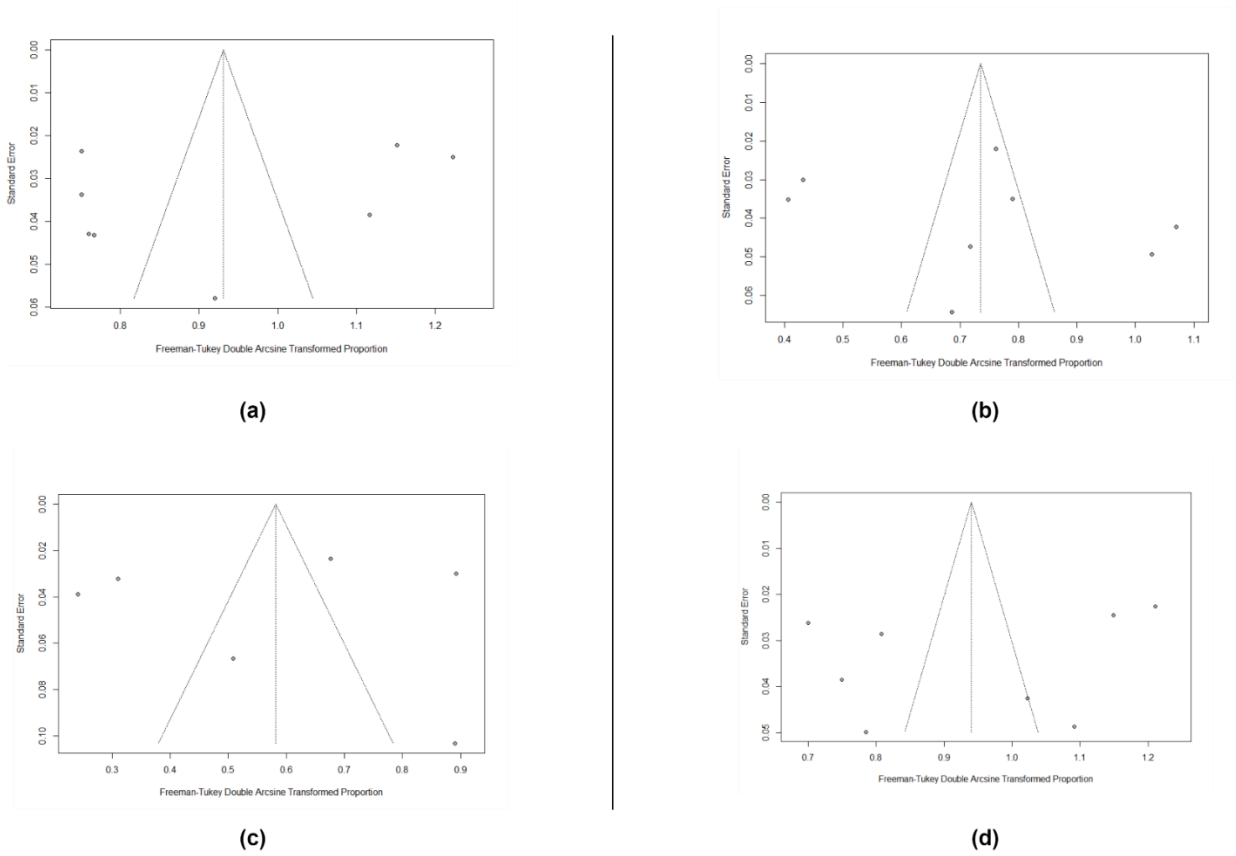

Fig. S3.7 Funnel plots for meta-analyses of pooled adherence rates to Lung-RADS recommended screening intervals at T1 in subgroups. (a) Funnel plot of defined adherence rates stratified by sex among Lung-RADS 1-4. (b) Funnel plot of defined adherence rates stratified by race among Lung-RADS 1-4. (c) Funnel plot of defined adherence rates stratified by race among Lung-RADS 1-2. (d) Funnel plot of defined adherence rate stratified by smoking status among Lung-RADS 1-4. Defined adherence: Adherence was defined as completion of an annual incidence screen or early follow-up exam within a specified time interval from recommended date. Anytime adherence: Patients are considered adherent as long as they received a follow-up exam anytime during the course of the study period. Lung-RADS: Lung CT Screening Reporting & Data System; T1: annual incidence screen at one year.

Table S3.1 Search strategy in PubMed.

MESH	"Lung neoplasms"[MeSH Terms] AND "Early detection of cancer"[MeSH Terms] AND ("Guideline adherence"[MeSH Terms] OR "Patient compliance"[MeSH Terms] OR "Patient dropouts"[MeSH Terms]) Filters: English, publication date 2014-04-28 to 2020-12-17
Manual	("lung neoplasms"[All Fields] OR "pulmonary neoplasms"[All Fields] OR "lung neoplasm"[All Fields] OR "pulmonary neoplasm"[All Fields] OR "lung cancer"[All Fields] OR "lung cancers"[All Fields] OR "pulmonary cancer"[All Fields] OR "pulmonary cancers"[All Fields] OR "cancer of the lung"[All Fields] OR "cancer of lung"[All Fields]) AND ("early detection of cancer"[All Fields] OR "cancer early detection"[All Fields] OR "cancer screening"[All Fields] OR "cancer screening test"[All Fields] OR "cancer screening tests"[All Fields] OR "cancer early detection"[All Fields] OR "early diagnosis of cancer"[All Fields] OR "cancer early diagnosis"[All Fields] OR "early cancer diagnosis"[All Fields]) AND ("guideline adherence"[All Fields] OR "patient compliance"[All Fields] OR "protocol compliance"[All Fields] OR "patient adherence"[All Fields] OR "patient non-compliance"[All Fields] OR "patient non-compliance"[All Fields] OR "patient noncompliance"[All Fields] OR "patient non-adherence"[All Fields] OR "patient non adherence"[All Fields] OR "patient nonadherence"[All Fields] OR "patient dropouts"[All Fields] OR "patient dropout"[All Fields] OR "loss to follow up"[All Fields]) Filters: English, publication date 2014-04-28 to 2020-12-17

Table S3.2 Quality assessment criteria based on the Newcastle-Ottawa Scale for cohort studies.

Category	Item	Scale
Selection	1) Representativeness of the Exposed Cohort	a) Truly representative of the average LCS population in the community *
		b) Somewhat representative of the average LCS population in the community *
		c) Selected group of users
		d) No description of the derivation of cohort
	2) Selection of the non-exposed cohort	Irrelevant
	3) Ascertainment of exposure	a) Secure record (e.g., medical records) *
		b) Structured interview *
		c) Written self-report
		d) No description
	4) Demonstration that outcome of interest was not present at start of study	a) Yes *
		b) No
Comparability	1) Comparability of cohorts on the basis of the design or analysis	Irrelevant
Outcome	1) Assessment of outcome	a) Independent blind assessment *
		b) Record linkage *
		c) Self-report
		d) No description

Table S3.2 Quality assessment criteria based on the Newcastle-Ottawa Scale for cohort studies.

Category	Item	Scale
	2) Was follow-up long enough for outcomes to occur	a) Yes * b) No
	3) Adequacy of follow-up of cohorts	Irrelevant

*A star is awarded. Note: A study can be awarded a maximum of one star for each numbered item within the Selection and Outcome categories. A maximum of two stars can be given for Comparability.

LCS: lung cancer screening.

Table S3.3 Additional characteristics of included studies (N=24).

Study	Publication type	Additional inclusion criteria	Exclusion criteria	Referral type	Retrospective assignment of Lung-RADS	Adherence determination in certain subgroups	Reasons for non-adherence
Alshora 2018[127]	Journal article	Not reported	(1) Had known metastatic disease; (2) Had lung cancer within the past 5 years; (3) Had symptoms concerning for lung cancer or acute infection; (4) Referred from outside authors' institution due to limited follow-up data.	HCP	Yes	Patients who died, were diagnosed with cancer, exceeded the program age limit, or became otherwise ineligible for additional CTLS were	N=129 (1) Refusal of follow-up exam: 66.7%; (2) Inability to contact the patient: 20.9%; (3) Inability to obtain a follow-up CTLS exam order from the ordering provider: 7.8%; (4) Went elsewhere: 5.0%.

Table S3.3 Additional characteristics of included studies (N=24).

Study	Publication type	Additional inclusion criteria	Exclusion criteria	Referral type	Retrospective assignment of Lung-RADS	Adherence determination in certain subgroups	Reasons for non-adherence
						considered adherent.	
Angotti 2020[110]	Conference abstract	Not reported	Not reported	PCP or through a dedicated LCS program	No	Not reported	Not reported
Barbosa 2020[122]	Journal article	Only patients who underwent 2 or more consecutive LCS examinations	(1) Had treatment for or evidence of any cancer other than non-melanoma skin cancer or	Not reported	No	Not reported	Not reported

Table S3.3 Additional characteristics of included studies (N=24).

Study	Publication type	Additional inclusion criteria	Exclusion criteria	Referral type	Retrospective assignment of Lung-RADS	Adherence determination in certain subgroups	Reasons for non-adherence
		performed at authors' institution were included.	carcinomas in situ within the past 5 years; (2) Had any diagnostic chest CT in the past 12 months.				
Bellinger 2020[128]	Journal article	Not reported	Not reported	Not reported	No	Not reported	Patients had follow-up studies at other institutions.
Bernstein 2019[123]	Conference abstract	Not reported	(1) Diagnosed with another malignancy and therefore ineligible for screening scans;	Pulmonary medicine and thoracic surgery services	No	Patients who became ineligible (e.g., diagnosed with an-	Not reported

Table S3.3 Additional characteristics of included studies (N=24).

Study	Publication type	Additional inclusion criteria	Exclusion criteria	Referral type	Retrospective assignment of Lung-RADS	Adherence determination in certain subgroups	Reasons for non-adherence
			(2) Aged out of screening eligibility; (3) Had a CT scan for reasons other than LCS; (4) Had an initial scan but did not reach the designated time interval for follow-up study during the study period.	or other physicians		other malignancy, aged-out) for LCS were excluded.	

Table S3.3 Additional characteristics of included studies (N=24).

Study	Publication type	Additional inclusion criteria	Exclusion criteria	Referral type	Retrospective assignment of Lung-RADS	Adherence determination in certain subgroups	Reasons for non-adherence
Bhandari 2019[6]	Journal article	(1) Baseline Lung-RADS 1-2; (2) Patients who were recommended to continue with annual screening.	Patients with missing information on demographics or LDCT screen.	Not reported	No	Not reported	Not reported
Brillante 2019[129]	Conference abstract	Baseline Lung-RADS 3-4	Not reported	Not reported	Not specified	Not reported	Not reported
Cattaneo 2018[7]	Journal article	Patients who were recommended to continue with annual screening.	Not reported	PCP	Yes	Not reported	Not reported

Table S3.3 Additional characteristics of included studies (N=24).

Study	Publication type	Additional inclusion criteria	Exclusion criteria	Referral type	Retrospective assignment of Lung-RADS	Adherence determination in certain subgroups	Reasons for non-adherence
Deepak 2020[109]	Conference abstract	Not reported	Not reported	Not reported	Not specified	Not reported	Not reported
Guichet 2018[130]	Journal article	(1) 55-74 years old with at least a 30-pack-year smoking history and were either current smokers or former smokers who had quit smoking within the past 15 years; (2) 50-80 years old with at least a 20-	(1) Patients who refused to participate in the study; (2) Patients who had home addresses outside the required zip codes; (3) Patients who were referred for LDCT did not undergo baseline LDCT during the study	Community partner clinics	No	Patients who died were excluded.	Not reported

Table S3.3 Additional characteristics of included studies (N=24).

Study	Publication type	Additional inclusion criteria	Exclusion criteria	Referral type	Retrospective assignment of Lung-RADS	Adherence determination in certain subgroups	Reasons for non-adherence
		pack-year smoking history were also eligible if they had one additional lung cancer risk factor other than secondhand smoke exposure.	period: (4) Death.				

Table S3.3 Additional characteristics of included studies (N=24).

Study	Publication type	Additional inclusion criteria	Exclusion criteria	Referral type	Retrospective assignment of Lung-RADS	Adherence determination in certain subgroups	Reasons for non-adherence
Hirsch 2019[131]	Journal article	Not reported	(1) Ineligible for screening by CMS guidelines; (2) Died before eligible for annual screening; (3) Aged out (>77 yo) after baseline screen by CMS guidelines; (4) Reached >15 yr since quitting smoking; (5) Declined annual screening due to comorbid conditions;	PCP or through a pulmonology-staffed LCS clinic	No	Not reported	Not reported

Table S3.3 Additional characteristics of included studies (N=24).

Study	Publication type	Additional inclusion criteria	Exclusion criteria	Referral type	Retrospective assignment of Lung-RADS	Adherence determination in certain subgroups	Reasons for non-adherence
			(6) Re-screened >18 months after baseline scan; (7) Baseline Lung-RADS 3-4.				
Jacobs 2017[126]	Journal article	Not reported	Not reported	Not reported	No	Not reported	Refusal of follow-up exam: n=19
Kaminetzky 2019[132]	Journal article	Not reported	(1) Age criteria not met; (2) Too few pack-years;	Local physicians	Yes	Not reported	Not reported

Table S3.3 Additional characteristics of included studies (N=24).

Study	Publication type	Additional inclusion criteria	Exclusion criteria	Referral type	Retrospective assignment of Lung-RADS	Adherence determination in certain subgroups	Reasons for non-adherence
			(3) Cancer within 5 years; (4) Lung cancer within 5 years; (5) Chest CT within 1 year; (6) Quit smoking > 15 years.				
Lake 2020[133]	Journal article	Not reported	(1) Neither Black nor White; (2) Never screened.	PCP or specialist	No	Not reported	Not reported

Table S3.3 Additional characteristics of included studies (N=24).

Study	Publication type	Additional inclusion criteria	Exclusion criteria	Referral type	Retrospective assignment of Lung-RADS	Adherence determination in certain subgroups	Reasons for non-adherence
Li 2018[134]	Conference abstract	Not reported	Not reported	Not reported	No	Not reported	Not reported
Muñoz-Largacha 2018[124]	Journal article	A small proportion were <55 or >80 years but were screened based on the ordering physician's clinical judgment based on other risk factors (e.g., strong smoking history, lung nodule follow-up,	Not reported	PCP, internist, or pulmonologist	No	Patients who died were considered as non-adherent.	Not reported

Table S3.3 Additional characteristics of included studies (N=24).

Study	Publication type	Additional inclusion criteria	Exclusion criteria	Referral type	Retrospective assignment of Lung-RADS	Adherence determination in certain subgroups	Reasons for non-adherence
		family history of lung cancer)					
Plank 2018[111]	Conference abstract	Not reported	Not reported	Not reported	Not specified	Not reported	Not reported
Rodriguez 2020 [38]	Conference abstract	Not reported	Not reported	Not reported	No	Not reported	Not reported
Sakoda 2018[136]	Conference abstract	Continuous health plan enrollment for at least 14 months post-baseline	Not reported	PCP	No	Not reported	Not reported

Table S3.3 Additional characteristics of included studies (N=24).

Study	Publication type	Additional inclusion criteria	Exclusion criteria	Referral type	Retrospective assignment of Lung-RADS	Adherence determination in certain subgroups	Reasons for non-adherence
Seastedt 2020[112]	Journal article	Not reported	Not reported	Not reported	Yes	Not reported	N=31 (1) Not contacted to schedule a follow-up exam: n=24; (2) Had other medical issues, LCS was not a priority: n=4; (3) Continued screening elsewhere: n=3.
Spalluto 2020[8]	Journal article	Not reported	(1) Baseline Lung-RADS 3-4; (2) Death; (3) Were diagnosed with cancer;	Not reported	Yes	Patients who died were excluded.	(1) Lack of transportation; (2) Financial cost; (3) Lack of communication;

Table S3.3 Additional characteristics of included studies (N=24).

Study	Publication type	Additional inclusion criteria	Exclusion criteria	Referral type	Retrospective assignment of Lung-RADS	Adherence determination in certain subgroups	Reasons for non-adherence
			(4) Had LDCT follow-up recommendation other than 12 months; (5) Had LDCT performed for follow-up rather than baseline purposes.				(4) Lack of current symptoms.
Stowell 2020[137]	Journal article	Not reported	Lung-RADS 0 or 4	Not reported	No	Patients who died, aged out of screening eligibility, or became ineligible for LCS were	Not reported

Table S3.3 Additional characteristics of included studies (N=24).

Study	Publication type	Additional inclusion criteria	Exclusion criteria	Referral type	Retrospective assignment of Lung-RADS	Adherence determination in certain subgroups	Reasons for non-adherence
						considered adherent.	
Triplette 2020[138]	Journal article	Not reported	(1) Death; (2) Did not initially qualify for screening; (3) Now outside of smoking or age range; (4) Documented move outside region/state; (5) Other.	Not reported	Yes	Not reported	Not reported
Wernli 2020[125]	Conference abstract	Not reported	Baseline Lung-RADS 4	Not reported	No	Not reported	Not reported

Table S3.3 Additional characteristics of included studies (N=24).

Study	Publication type	Additional inclusion criteria	Exclusion criteria	Referral type	Retrospective assignment of Lung-RADS	Adherence determination in certain subgroups	Reasons for non-adherence

Lung-RADS: Lung CT Screening Reporting & Data System; HCP: health care provider; CTLS: computed tomography lung screening; PCP: primary care provider; LCS: lung cancer screening; CT: computed tomography; LDCT: low-dose computed tomography; CMS: Centers for Medicare & Medicaid Services; yo: years old; yr: years.

Table S3.4 Summary of values of outcome and independent variables for each study included in meta-regression analyses at T1 (N=17).

No.	Study	Lung-RADS	Adherence type	Adherence rate	Institutional setting	Program coordinators/navigators	Shared decision-making	Smoking cessation	Interventions for adherence	Publication type
1	Alshora 2018[127]	1-2	Defined	0.86	Academic	Yes	Yes	Yes	Yes	Article
1	Alshora 2018[127]	3-4	Defined	0.86	Academic	Yes	Yes	Yes	Yes	Article
2	Bellinger 2020[128]	1-2	Defined	0.44	Academic	Yes	Not reported	Not reported	Yes	Article
2	Bellinger 2020[128]	3-4	Defined	0.71	Academic	Yes	Not reported	Not reported	Yes	Article
3	Bhandari 2019[6]	1-2	Anytime	0.5	Non-academic	Not reported	Not reported	Not reported	Not reported	Article

Table S3.4 Summary of values of outcome and independent variables for each study included in meta-regression analyses at T1 (N=17).

No.	Study	Lung-RADS	Adherence type	Adherence rate	Institutional setting	Program coordinators/navigators	Shared decision-making	Smoking cessation	Interventions for adherence	Publication type
4	Brillante 2019[129]	3-4	Anytime	0.66	Academic	Not reported	Not reported	Not reported	Not reported	Abstract
5	Cattaneo 2018[7]	1-2	Defined	0.37	Non-academic	Yes	Yes	Yes	Yes	Article
5	Cattaneo 2018[7]	1-2	Anytime	0.51	Non-academic	Yes	Yes	Yes	Yes	Article
5	Cattaneo 2018[7]	3-4	Anytime	0.88	Non-academic	Yes	Yes	Yes	Yes	Article
6	Deepak 2020[109]	1-2	Anytime	0.52	Academic	Not reported	Not reported	Not reported	Not reported	Abstract

Table S3.4 Summary of values of outcome and independent variables for each study included in meta-regression analyses at T1 (N=17).

No.	Study	Lung-RADS	Adherence type	Adherence rate	Institutional setting	Program coordinators/navigators	Shared decision-making	Smoking cessation	Interventions for adherence	Publication type
6	Deepak 2020[109]	3-4	Anytime	0.31	Academic	Not reported	Not reported	Not reported	Not reported	Abstract
7	Guichet 2018[130]	3-4	Anytime	0.75	Academic	Yes	Not reported	Not reported	Not reported	Article
8	Hirsch 2019[131]	1-2	Defined	0.51	Academic	Yes	Yes	Not reported	Yes	Article
9	Jacobs 2017[126]	3-4	Anytime	0.83	Non-academic	Not reported	Yes	Yes	Not reported	Article
10	Kaminetzky 2019[132]	1-2	Anytime	0.46	Academic	Yes	Not reported	Not reported	Not reported	Article

Table S3.4 Summary of values of outcome and independent variables for each study included in meta-regression analyses at T1 (N=17).

No.	Study	Lung-RADS	Adherence type	Adherence rate	Institutional setting	Program coordinators/navigators	Shared decision-making	Smoking cessation	Interventions for adherence	Publication type
11	Lake 2020[133]	1-2	Defined	0.08	Academic	Yes	Yes	Not reported	Yes	Article
11	Lake 2020[133]	3-4	Defined	0.69	Academic	Yes	Yes	Not reported	Yes	Article
11	Lake 2020[133]	1-2	Anytime	0.2	Academic	Yes	Yes	Not reported	Yes	Article
11	Lake 2020[133]	3-4	Anytime	0.94	Academic	Yes	Yes	Not reported	Yes	Article
12	Li 2018[134]	1-2	Anytime	0.54	Academic	Yes	Not reported	Not reported	Not reported	Abstract

Table S3.4 Summary of values of outcome and independent variables for each study included in meta-regression analyses at T1 (N=17).

No.	Study	Lung-RADS	Adherence type	Adherence rate	Institutional setting	Program coordinators/navigators	Shared decision-making	Smoking cessation	Interventions for adherence	Publication type
13	Rodriguez 2020[135]	1-2	Defined	0.31	Academic	Not reported	Yes	Not reported	Not reported	Abstract
14	Sakoda 2018[136]	1-2	Defined	0.23	Non-academic	Not reported	Not reported	Not reported	Not reported	Abstract
14	Sakoda 2018[136]	3-4	Defined	0.61	Non-academic	Not reported	Not reported	Not reported	Not reported	Abstract
15	Seastedt 2020[112]	1-2	Defined	0.78	Non-academic	Not reported	Not reported	Yes	Yes	Article
15	Seastedt 2020[112]	3-4	Defined	0.67	Non-academic	Not reported	Not reported	Yes	Yes	Article

Table S3.4 Summary of values of outcome and independent variables for each study included in meta-regression analyses at T1 (N=17).

No.	Study	Lung-RADS	Adherence type	Adherence rate	Institutional setting	Program coordinators/navigators	Shared decision-making	Smoking cessation	Interventions for adherence	Publication type
16	Spalluto 2020[8]	1-2	Defined	0.59	Academic	Yes	Yes	Yes	Yes	Article
16	Spalluto 2020[8]	1-2	Anytime	0.73	Academic	Yes	Yes	Yes	Yes	Article
17	Triplette 2020[138]	1-2	Defined	0.4	Academic	Not reported	Not reported	Not reported	Yes	Article
17	Triplette 2020[138]	3-4	Defined	0.76	Academic	Not reported	Not reported	Not reported	Yes	Article

T1: annual incidence screen at one year; Lung-RADS: Lung CT Screening Reporting & Data System; Defined adherence: Adherence was defined as completion of an annual screen or early follow-up exam within a specified time interval from recommended date; Anytime adherence: Patients are considered adherent as long as they received a follow-up exam anytime during the course of the study period.

Table S3.5 Summary of values of outcome and independent variables for each study included in meta-analyses adjusting for predictors of LCS non-adherence at T1 (N=18).

No.	Study	Lung-RADS	Adherence type	Adherence rate	Mean age	Percent of females	Percent of Whites	Percent of Lung-RADS 1-2	Percent of former smokers
1	Alshora 2018[127]	1-4	Defined	0.857	Not reported	0.442	0.95*	0.691	0.541
2	Bellinger 2020[128]	1-4	Defined	0.481	Not reported	0.496	0.761	0.843	0.373
3	Bernstein 2019[123]	1-4	Defined	0.558	Not reported	0.487	Not reported	Not reported	Not reported
4	Bhandari 2019[6]	1-2	Anytime	0.499	Not reported	Not reported	Not reported	1	Not reported
5	Brillante 2019[129]	3-4	Anytime	0.656	64.8	Not reported	Not reported	0	Not reported
6	Cattaneo 2018[7]	1-2	Defined	0.374	Not reported	0.548	0.89	1	0.483

Table S3.5 Summary of values of outcome and independent variables for each study included in meta-analyses adjusting for predictors of LCS non-adherence at T1 (N=18).

No.	Study	Lung-RADS	Adherence type	Adherence rate	Mean age	Percent of females	Percent of Whites	Percent of Lung-RADS 1-2	Percent of former smokers
6	Cattaneo 2018[7]	1-4	Anytime	0.638	Not reported	Not reported	Not reported	0.659	Not reported
7	Deepak 2020[109]	1-4	Anytime	0.493	Not reported	Not reported	Not reported	0.89	Not reported
8	Guichet 2018[130]	3-4	Anytime	0.750	Not reported	Not reported	Not reported	0	Not reported
9	Hirsch 2019[131]	1-2	Defined	0.506	64.1	0.429	0.826	1	0.452
10	Jacobs 2017[126]	3-4	Anytime	0.832	Not reported	Not reported	Not reported	0	Not reported

Table S3.5 Summary of values of outcome and independent variables for each study included in meta-analyses adjusting for predictors of LCS non-adherence at T1 (N=18).

No.	Study	Lung-RADS	Adherence type	Adherence rate	Mean age	Percent of females	Percent of Whites	Percent of Lung-RADS 1-2	Percent of former smokers
11	Kaminetzky 2019[132]	1-2	Anytime	0.465	Not reported	Not reported	Not reported	1	Not reported
12	Lake 2020[133]	1-4	Defined	0.166	64.3	0.53	0.579	0.853	0.411
12	Lake 2020[133]	1-4	Anytime	0.308	64.3	0.53	0.579	0.853	0.411
13	Li 2018[134]	1-2	Anytime	0.542	Not reported	Not reported	Not reported	1	Not reported
14	Rodriguez 2020[135]	1-2	Defined	0.314	Not reported	Not reported	Not reported	1	Not reported

Table S3.5 Summary of values of outcome and independent variables for each study included in meta-analyses adjusting for predictors of LCS non-adherence at T1 (N=18).

No.	Study	Lung-RADS	Adherence type	Adherence rate	Mean age	Percent of females	Percent of Whites	Percent of Lung-RADS 1-2	Percent of former smokers
15	Sakoda 2018[136]	1-4	Defined	0.290	Not reported	0.39	0.71	0.841	Not reported
16	Seastedt 2020[112]	1-4	Defined	0.771	Not reported	Not reported	Not reported	0.916	Not reported
17	Spalluto 2020[8]	1-2	Defined	0.592	64.1	0.492	0.868	1	Not reported
17	Spalluto 2020[8]	1-2	Anytime	0.730	64.1	0.492	0.868	1	Not reported
18	Triplette 2020[138]	1-4	Defined	0.466	Not reported	0.328	0.768	0.807	0.455
18	Triplette 2020[138]	1-4	Anytime	0.705	Not reported	0.328	0.768	0.807	0.455

Table S3.5 Summary of values of outcome and independent variables for each study included in meta-analyses adjusting for predictors of LCS non-adherence at T1 (N=18).

No.	Study	Lung-RADS	Adherence type	Adher-ence rate	Mean age	Percent of females	Percent of Whites	Percent of Lung-RADS 1-2	Percent of former smokers

*Alshora et al.[127] reported >95% Whites.

LCS: lung cancer screening; T1: annual incidence screen at one year; Lung-RADS: Lung CT Screening Reporting & Data System. Defined adherence: Adherence was defined as completion of an annual incidence screen or early follow-up exam within a specified time interval from recommended date. Anytime adherence: Patients are considered adherent as long as they received a follow-up exam anytime during the course of the study period.

T**able S5.1** Comparison of observed baseline characteristics between included patients and excluded patients (due to missing values in predictors) for Experiment 1.

	Included	Excluded	p
n (%)	1979	517	
Lung-RADS			
1-2	1660 (83.9)	433 (83.8)	0.997
3-4	319 (16.1)	84 (16.2)	
Age in years			
<65	868 (43.9)	207 (40.0)	0.130
>=65	1111 (56.1)	310 (60.0)	
Sex			
Female	803 (40.6)	207 (40.0)	0.864
Male	1176 (59.4)	310 (60.0)	
Family history of lung cancer			
Yes	466 (23.5)	92 (17.8)	0.006
No	1513 (76.5)	425 (82.2)	
Age-adjusted CCI			
Low (0-1)	287 (14.5)	68 (13.2)	0.477
Intermediate or high (>=1)	1692 (85.5)	449 (86.8)	
Expected follow-up exam			
Pre-COVID-19	1468 (74.2)	381 (73.7)	0.555

T**able S5.1** Comparison of observed baseline characteristics between included patients and excluded patients (due to missing values in predictors) for Experiment 1.

	Included	Excluded	p
n (%)	1979	517	
During COVID-19 pause	53 (2.7)	10 (1.9)	
Post-COVID-19 pause	458 (23.1)	126 (24.4)	

[a] p: two-sided p values of Chi-square tests.

Lung-RADS: Lung CT Screening Reporting & Data System; CCI: Charlson Comorbidity Index.

Table S6.1 Possible scenarios of longitudinal patterns in Lung-RADS scores.

Category	Lung-RADS score		
	Time point 1	Time point 2	Time point 3
Unchanged	1 or 2	1 or 2	NA
	1 or 2	1 or 2	1 or 2
	3 or 4	3 or 4	NA
	3 or 4	3 or 4	3 or 4
Downgraded	3 or 4	1 or 2	NA
	3 or 4	1 or 2	1 or 2
	3 or 4	3 or 4	1 or 2
Upgraded	1 or 2	3 or 4	NA
	1 or 2	3 or 4	3 or 4
	1 or 2	1 or 2	3 or 4

[a] When a Lung-RADS score is NA, it can either be that the recommended date of the patient's third screen was scheduled after the last follow-up date of this study or the patient had a third screen but with insufficient follow-up time to determine adherence status to the third Lung-RADS recommendation.

Lung-RADS: Lung CT Screening Reporting & Data System, NA: not available.

Table S6.2 Comparison of observed baseline characteristics between included patients and excluded patients (due to missing values in predictors) for the T1 model from the multiple-model approach.

	Included	Excluded	p
n (%)	767	173	
Lung-RADS			
1-2	648 (84.5)	153 (88.4)	0.331
3	73 (9.5)	10 (5.8)	
4A	35 (4.6)	9 (5.2)	
4B/X	11 (1.4)	1 (0.6)	
Age in years			
<65	327 (42.6)	68 (39.3)	0.474
>=65	440 (57.4)	105 (60.7)	
Sex			
Female	307 (40.0)	64 (37.0)	0.515
Male	460 (60.0)	109 (63.0)	
Family history of lung cancer			
Yes	173 (22.6)	40 (23.1)	0.952
No	594 (77.4)	133 (76.9)	
Age-adjusted CCI			
Low (0-1)	95 (12.4)	20 (11.6)	0.864
Intermediate or high (>=1)	672 (87.6)	153 (88.4)	

Table S6.2 Comparison of observed baseline characteristics between included patients and excluded patients (due to missing values in predictors) for the T1 model from the multiple-model approach.

	Included	Excluded	p
n (%)	767	173	

[a] p: two-sided p values of Chi-square tests.

Lung-RADS: Lung CT Screening Reporting & Data System; CCI: Charlson Comorbidity Index.

Table S6.3 Comparison of observed baseline characteristics between included patients and excluded patients (due to missing values in predictors) for the T2 model from the multiple-model approach.

	Included	Excluded	p
n (%)	351	89	
Lung-RADS			
1-2	302 (86.0)	83 (93.3)	0.204
3	31 (8.8)	2 (2.2)	
4A	13 (3.7)	3 (3.4)	
4B/X	5 (1.4)	1 (1.1)	
Age in years			
<65	156 (44.4)	31 (34.8)	0.129
>=65	195 (55.6)	58 (65.2)	
Sex			
Female	156 (44.4)	39 (43.8)	1
Male	195 (55.6)	50 (56.2)	
Family history of lung cancer			

Yes	87 (24.8)	22 (24.7)	1
No	264 (75.2)	67 (75.3)	
Age-adjusted CCI			
Low (0-1)	44 (12.5)	11 (12.4)	1
Intermediate or high (>=1)	307 (87.5)	78 (87.6)	

[a] p: two-sided p values of Chi-square tests.

Lung-RADS: Lung CT Screening Reporting & Data System; CCI: Charlson Comorbidity Index.

Table S6.4 Baseline characteristics of patients used to predict non-adherence to T1 Lung-RADS recommendations (N=718).

Variable	Individual, No. (%)		
	Overall (N=718)	Adherent (n=349)	Non-adherent (n=369)
Lung-RADS			
1-2	608 (84.7)	291 (83.4)	317 (85.9)
3	67 (9.3)	35 (10.0)	32 (8.7)
4A	34 (4.7	21 (6.0)	13 (3.5)
4B/X	9 (1.3)	2 (0.6)	7 (1.9)
Age in years			
<65	310 (43.2)	146 (41.8)	164 (44.4)
≥65	408 (56.8)	203 (58.2)	205 (55.6)
Sex			
Female	281 (39.1)	147 (42.1)	134 (36.3)
Male	437 (60.9)	202 (57.9)	235 (63.7)
Race/ethnicity [b]			
Asian	67 (9.3)	32 (9.2)	35 (9.5)
Black	53 (7.4)	25 (7.2)	28 (7.6)
Hispanic/Latino	35 (4.9)	16 (4.6)	19 (5.1)
White	545 (75.9)	266 (76.2)	279 (75.6)

Table S6.4 Baseline characteristics of patients used to predict non-adherence to T1 Lung-RADS recommendations (N=718).

Variable	Individual, No. (%)		
	Overall (N=718)	Adherent (n=349)	Non-adherent (n=369)
Other	18 (2.5)	10 (2.9)	8 (2.2)
Education level			
Less than college	334 (46.5)	158 (45.3)	176 (47.7)
College Graduate	210 (29.2)	106 (30.4)	104 (28.2)
Postgraduate	174 (24.2)	85 (24.4)	89 (24.1)
Family history of lung cancer			
Yes	161 (22.4)	94 (26.9)	67 (18.2)
No	557 (77.6)	255 (73.1)	302 (81.8)
Smoking status			
Current	303 (42.2)	140 (40.1)	163 (33.2)
Former	415 (57.8)	209 (59.9)	206 (55.8)
Primary insurance			
Medicaid/Medicaid	319 (44.4)	171 (49.0)	148 (40.1)
Private or Commercial or other [c]	399 (55.6)	178 (51.0)	221 (59.9)
Age-adjusted CCI			
Low (0-1)	92 (12.8)	39 (11.2)	53 (14.4)

Table S6.4 Baseline characteristics of patients used to predict non-adherence to T1 Lung-RADS recommendations (N=718).

Variable	Individual, No. (%)		
	Overall (N=718)	Adherent (n=349)	Non-adherent (n=369)
Intermediate (2-3)	445 (62.0)	219 (62.8	226 (61.2)
High (≥4)	181 (25.2)	91 (26.1)	90 (24.4)
Distance to screening center [a]			
Short (≤ median)	406 (56.5)	200 (57.3)	206 (55.8)
Long (> median)	312 (43.5)	149 (42.7)	163 (44.2)
Median household income [a]			
Low (≤ median)	354 (49.3)	167 (47.9)	187 (50.7)
High (> median)	364 (50.7)	182 (52.1)	182 (49.3)
ADI state rank a			
Low (≤ median)	427 (59.5)	218 (62.5)	209 (56.6)
High (> median)	291 (40.5)	131 (37.5)	160 (43.4)
Type of referring physician			
Pulmonology, Thoracic Oncology/Radiology/Surgery	126 (17.5)	76 (21.8)	50 (13.6)
Other	592 (82.5)	273 (78.2)	319 (86.4)

Table S6.4 Baseline characteristics of patients used to predict non-adherence to T1 Lung-RADS recommendations (N=718).

Variable	Individual, No. (%)		
	Overall (N=718)	Adherent (n=349)	Non-adherent (n=369)

[a] Median distance to screening center: 6.84 miles.; median household income: $73,478; median ADI state rank: 3.

[b] Subcategories in Other: American Indian or Alaska Native, more than one race, Native Hawaiian or Pacific Islander, or other racial and ethnic groups that were not mentioned here. [c] Subcategories in Private or Commercial or other: private or commercial, VA, self-pay, other insurance that was not mentioned here.

Lung-RADS: Lung CT Screening Reporting & Data System; CCI: Charlson Comorbidity Index; ADI: Area Deprivation Index.

Table S6.5 Baseline characteristics of patients used to predict non-adherence to T2 Lung-RADS recommendations (N=326).

Variable	Individual, No. (%)		
	Overall (N=326)	Adherent (n=175)	Non-adherent (n=151)
Lung-RADS			
1-2	278 (85.3)	150 (85.7)	128 (84.8)
3	30 (9.2)	12 (6.9)	18 (11.9)
4A	13 (4.0)	9 (5.1)	4 (2.6)
4B/X	5 (1.5)	4 (2.3)	1 (0.7)
Age in years			
<65	151 (46.3)	76 (43.4)	75 (49.7)
≥65	175 (53.7)	99 (56.6)	76 (50.3)
Sex			
Female	142 (43.6)	74 (42.3)	68 (45.0)
Male	184 (56.4)	101 (57.7)	83 (55.0)
Race/ethnicity [b]			
Asian	29 (8.9)	15 (8.6)	14 (9.3)
Black	27 (8.3)	14 (8.0)	13 (8.6)
Hispanic/Latino	18 (5.5)	12 (6.9)	6 (4.0)
White	241 (73.9)	128 (73.1)	113 (74.8)

Table S6.5 Baseline characteristics of patients used to predict non-adherence to T2 Lung-RADS recommendations (N=326).

Variable	Individual, No. (%)		
	Overall (N=326)	Adherent (n=175)	Non-adherent (n=151)
Other	11 (3.4)	6 (3.4)	5 (3.3)
Education level			
Less than college	140 (42.9)	76 (43.4)	64 (42.4)
College Graduate	98 (30.1)	53 (30.3)	45 (29.8)
Postgraduate	88 (27.0)	46 (26.3)	42 (27.8)
Family history of lung cancer			
Yes	82 (25.2)	47 (26.9)	35 (23.2)
No	244 (74.8)	128 (73.1)	116 (76.8)
Smoking status			
Current	150 (46.0)	80 (45.7)	70 (46.4)
Former	176 (54.0)	95 (54.3)	81 (53.6)
Primary insurance			
Medicaid/Medicaid	138 (42.3)	82 (46.9)	63 (41.7)
Private or Commercial or other [c]	181 (55.5)	93 (53.1)	88 (58.3)
Age-adjusted CCI			

Table S6.5 Baseline characteristics of patients used to predict non-adherence to T2 Lung-RADS recommendations (N=326).

Variable	Individual, No. (%)		
	Overall (N=326)	Adherent (n=175)	Non-adherent (n=151)
Low (0-1)	43 (13.2)	20 (11.4)	23 (15.2)
Intermediate (2-3)	217 (66.6)	114 (65.1)	103 (68.2)
High (≥4)	66 (20.2)	41 (23.4)	25 (16.6)
Distance to screening center [a]			
Short (≤ median)	199 (61.0)	102 (58.3)	97 (64.2)
Long (> median)	127 (39.0)	73 (41.7)	54 (35.8)
Median household income [a]			
Low (≤ median)	151 (46.3)	88 (50.3)	63 (41.7)
High (> median)	175 (53.7)	87 (49.7)	88 (58.3)
ADI state rank a			
Low (≤ median)	208 (63.8)	106 (60.6)	102 (67.5)
High (> median)	118 (36.2)	69 (39.4)	49 (32.5)
Type of referring physician			
Pulmonology, Thoracic Oncology/Radiology/Surgery	63 (19.3)	43 (24.6)	20 (13.2)
Other	263 (80.7)	132 (75.4)	131 (86.8)

Table S6.5 Baseline characteristics of patients used to predict non-adherence to T2 Lung-RADS recommendations (N=326).

Variable	Individual, No. (%)		
	Overall (N=326)	Adherent (n=175)	Non-adherent (n=151)

[a] Median distance to screening center: 6.84 miles.; median household income: $73,478; median ADI state rank: 3.

[b] Subcategories in Other: American Indian or Alaska Native, more than one race, Native Hawaiian or Pacific Islander, or other racial and ethnic groups that were not mentioned here.

[c] Subcategories in Private or Commercial or other: private or commercial, VA, self-pay, other insurance that was not mentioned here.

Lung-RADS: Lung CT Screening Reporting & Data System; CCI: Charlson Comorbidity Index; ADI: Area Deprivation Index.

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