Examples of Funded Grants in Healthcare Delivery Research

Overview
The National Cancer Institute (NCI) frequently receives requests for examples of funded grant applications. Several investigators and their organizations agreed to let the Healthcare Delivery Research Program (HDRP) post excerpts of their healthcare delivery research grant applications online.

About
We are grateful to the investigators and their institutions for allowing us to provide this important resource to the community. We only include a copy of the SF 424 R&R Face Page, Project Summary/Abstract (Description), Project Narrative, Specific Aims, and Research Strategy; we do not include other SF 424 (R&R) forms or requisite information found in the full grant application (e.g., performance sites, key personnel, biographical sketches). To maintain confidentiality, we have redacted some information from these documents (e.g., budgets, social security numbers, home addresses, introduction to revised application).

Accessibility
Individuals using assistive technology (e.g., screen reader, Braille reader) who experience difficulty accessing any information should send an email to the Healthcare Delivery Research Program (NCIHDRP@mail.nih.gov).

424 R&R and PHS-398 Specific
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PI: Braithwaite, Dejana K

Grant Number: 1 R01 CA249506-01

Title: Personalized screening for lung cancer: the importance of co-existing chronic conditions to clinical practice and policy

FOA: PA19-056

FOA Title: Research Project Grant (Parent R01 Clinical Trial Not Allowed)

Organization: GEORGETOWN UNIVERSITY

Senior/Key Personnel: Dejana Braithwaite Ph.D

Organization: GEORGETOWN UNIVERSITY

Role Category: PD/PI

Abstract / Summary

Lung cancer is the leading cause of cancer death in the US and worldwide, largely because most patients have advanced, incurable disease at the time of diagnosis. However, lung cancer screening (LCS) with low-dose computed tomography (LDCT) has the potential to revolutionize lung cancer outcomes through early detection. As LCS is disseminated into real-world settings and populations, a key outstanding question is whether the benefits/harms ratio found in clinical trials will apply to an older and sicker population. The basic conundrum facing LCS candidates is that the single risk factor most strongly linked to lung cancer -- smoking history -- is also strongly linked to morbidity and death from non-lung cancer causes (e.g. chronic obstructive pulmonary disease emphysema), which limit life expectancy and increase risk of complications from diagnostic or therapeutic procedures. The overarching goal of our proposed study is to precisely characterize this vulnerable subpopulation with high comorbidity burden, quantifying for them the benefits and harms of LCS to enable more informed decision-making by patients contemplating LCS. Our study will help close this knowledge gap by leveraging real-world data to more fully characterize this subpopulation of “marginal” LCS candidates, reducing the uncertainty currently facing patients and providers. More specifically, we propose to leverage electronic health records and claims data for patients ages 55-80 (n~34,039) undergoing annual screening with LDCT in geographically diverse real-world settings from 2016-2022. We will then use these observational data with validated models in the Cancer Intervention Simulation Network to simulate LCS outcomes in the real-world US population. By generating previously unavailable real-world data for use in validated simulation models, this proposal responds directly to calls to improve patient- centered decision-making in LCS candidates for whom the net benefits of screening are currently highly uncertain.

Public Health Relevance

Currently, there is little knowledge regarding a possible threshold where the benefits of finding early-stage lung cancer no longer outweigh the risk of dying due to a competing cause. Our proposed study has direct value for advancing public health by examining real-world, timely data on the outcomes of LCS.

Specific Aims

Lung cancer is the leading cause of cancer death in the US and worldwide,[1] largely because most patients have advanced, incurable disease at the time of diagnosis.[2] However, lung cancer screening (LCS) with low-dose computed tomography (LDCT) has the potential to revolutionize lung cancer outcomes through early detection.[3-8] In 2011, a large randomized clinical trial (RCT) -- the National Lung Screening Trial (NLST) -- showed that, compared with chest radiography, 3 rounds of annual screening with LDCT reduced the risk of lung cancer death by 20% among high-risk current and former smokers.[9] Consequently, LCS with LDCT is now recommended for those meeting standard risk-based eligibility criteria.[10, 11] While the RCT is a powerful tool for assessing benefits and harms of an intervention, subsequent observational studies are needed to assess how the intervention performs in real-world settings and populations.[12] For LCS, a key outstanding question is whether the benefits/harms ratio found in the NLST will apply to an older and sicker real-world population. Compared with NLST participants, US adults eligible for LCS are nearly twice as likely to be >70 years and are substantially more likely to be a current smoker.[9, 13] And of the nearly 8.6 million LCS-eligible adults in the US, ~3 million have chronic co-existing conditions that may decrease the net benefit of screening for early stage disease.[14] In prior work, we found that elderly stage IA lung cancer patients with ≥2 comorbidities were twice as likely to die within 90 days of lung cancer surgery compared to those with ≤1 comorbidity.[15] The basic conundrum facing LCS candidates is that the single risk factor most strongly linked to lung cancer -- smoking history[2] -- is also strongly linked to morbidity and death from *non-lung cancer* causes (chronic obstructive pulmonary disease (COPD), emphysema, etc.).[16-19] Patients with these diseases are at increased risk of lung cancer and thus should have the most to gain from screening; however, these same diseases also limit life expectancy and increase risk of complications from downstream diagnostic or therapeutic procedures following a positive screen.[16, 17] For some of these patients, the net benefit of LCS appears "marginal", and the tipping point where potential harms begin to outweigh benefits is highly uncertain. We do not know a) what **combination of health-related factors** likely leads to this tipping point, or b) **how many patients** may potentially approach this tipping point. The overarching goal of our proposed study is to precisely characterize this vulnerable subpopulation with high comorbidity burden, quantifying for them the benefits and harms of LCS to enable more informed decision-making by patients contemplating LCS.

We propose to collect and analyze data from real-world populations and settings in order to fully characterize the outcomes of LCS with LDCT, with a focus on evaluating the subpopulation of "marginal" LCS candidates. More specifically, we propose to leverage electronic health records and claims data for patients ages 55-80 (n~34,039) undergoing annual screening with LDCT in geographically diverse real-world settings from 2016- 2019 (retrospective cohort) and 2020-2022 (prospective cohort). We will integrate the data into a unified repository using a common data standard based on the PCORI-funded Watch the Spot (WTS) trial infrastructure. We will then use these real-world data with validated models in the Cancer Intervention Simulation Network (CISNET) to perform simulation modeling of LCS outcomes across the full screening-eligible US population.

Our specific aims with exemplar hypotheses are to:

Aim 1: Characterize the patient population undergoing LCS in real-world settings with regard to the burden of multimorbidity (defined as chronic co-existing conditions, functional limitations and/or impaired pulmonary function) with particular attention to evaluating the subpopulation of marginal patients for whom the net benefit of LCS appears uncertain. *Exploratory sub-aim*: Examine this burden by race/ethnicity, socioeconomic status and age.

Aim 2: Quantify potential harms (e.g., false-positive results, procedure-related complications) and benefits (e.g., early stage disease at diagnosis) of LCS among persons with diverse levels of multimorbidity. *Hypothesis: Chronic co-existing conditions, functional limitations and impaired pulmonary function are associated with an increased risk of LCS harms.*

Aim 3: Compare the effectiveness of LCS in relation to long-term outcomes (both benefits and harms) across subpopulations with diverse levels of multimorbidity using validated CISNET simulation models and refined model parameters based on real-world data. *Hypothesis: LCS will not be effective for subpopulations with moderate to severe comorbidity, functional limitations or severe COPD.*

Anticipated impact: By leveraging previously unavailable real-world data in combination with validated simulation models, this proposal responds directly to calls[20-23] to improve patient-centered decision-making in LCS candidates for whom the net benefits of screening are currently highly uncertain. Our study findings will help inform patients and providers in their discussions regarding LCS. In addition, MPIs, Drs. Silvestri and Gould, members of the American Cancer Society's National Lung Cancer Roundtable will help present our study findings, continuing our team's track record of helping to inform LCS guidelines.[24-27]

Research Strategy

A. SIGNIFICANCE

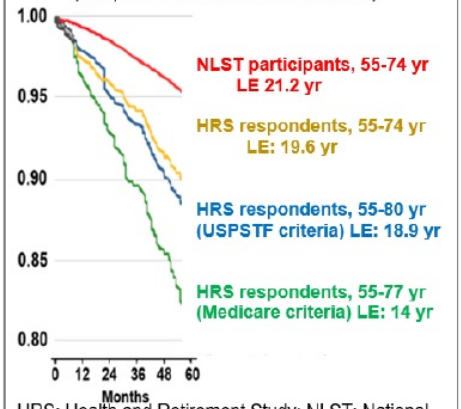
A.1. Implementing lung cancer screening in the "real world": How do screening-eligible adults compare to clinical trial participants? Lung cancer is the leading cause of cancer death in the US and worldwide,[1] largely because most patients have advanced, incurable disease at the time of diagnosis.[2] However, lung cancer screening (LCS) with low-dose computed tomography (LDCT) has the potential to revolutionize lung cancer outcomes through early detection.[3-7] In 2011, the National Lung Screening Trial (NLST) demonstrated a 20% reduction in lung cancer mortality among current and former smokers randomly assigned to 3 rounds of annual LCS with LDCT compared with those assigned to 3 rounds of annual chest radiography.[28] In absolute terms, this translates to approximately 3 fewer deaths from lung cancer for every 1,000 individuals who underwent LDCT screening -- *a magnitude of benefit similar to the estimated 5 per 1,000 reduction in breast cancer deaths associated with 10 years of annual mammographic screening in women ages 50 to 74*.[14] Thus, annual LCS with LDCT is now recommended in the United States (US) for persons age 55-80, who have a 30 pack-year smoking history and currently smoke or have quit within the past 15 years.[11] However, as LCS is implemented more widely in real-world populations and settings, the ratio of benefits to harms may well differ from that observed in the highly-controlled environment and the relatively young participants of the NLST (only 25% of NLST participants were age ≥65, and none were >74 years).[15, 29] To learn how real-world LCS-eligible persons may differ from NLST participants, Howard et al. compared NLST participants with respondents to the 2012 Health and Retirement Study (HRS), a nationally representative survey of US adults age ≥50 years sponsored by the National Institute on Aging.[30] Considering only those HRS respondents who were screening-eligible (i.e., met smoking history and age criteria), Howard et al. found that HRS respondents were older, more likely to be current smokers, and more likely to have been diagnosed with comorbidities than NLST participants (**Table 1**).[30] Also, life expectancy and survival curves were simulated and compared for NLST participants and 3 subgroups of screening-eligible HRS respondents: a subgroup with same age criteria as NLST, ages 55-74; a subgroup meeting USPSTF criteria, ages 55–80; and a subgroup meeting CMS criteria (i.e., disabled Medicare participants age 55-64 and Part B participants ages 65-77).[30] Striking differences were apparent (**Fig 1**). For example, average life expectancy was estimated (based on US life tables) to be 21.2 yr for NLST participants, but only 14 yr for the Medicare screening-eligible HRS subgroup.[30] ***These comorbidity related differences, along with sociodemographic differences noted by others,[4, 31, 32] raise questions about the generalizability of the NLST results to the full screening-eligible US population.***

Table 1: Characteristics of NLST Participants and Participants in the 2012 HRS Survey who met USPSTF and Medicare Criteria (Howard et al. 2013)

	NLST	USPSTF		Medicare FFS	
Characteristic	%	%	P	%	P
55-59 yr	42.8	29.4	<.001	9.3	<.001
60-64 yr	30.6	25.3		12.5	
65-69 yr	17.8	22.3		36.2	
70-74 yr	8.8	14.2		30.8	
≥75 yr	0.0	8.8		11.1	
Male	59.0	56.8	.150	52.3	.009
Black	4.4	7.0	<.001	5.7	.122
Hispanic	1.7	3.9	<.001	3.8	.002
College degree	31.5	12.9	<.001	11.3	<.001
Current smoker	48.2	60.8	<.001	55.9	.003
Diabetes	9.7	21.7	<.001	24.1	<.001
Heart disease	12.7	26.4	<.001	33.2	<.001
Stroke	2.8	8.2	<.001	11.6	<.001

Abbreviations: FFS, fee-for-service; NLST, National Lung Screening Trial; USPSTF, US Preventative Services Task Force.

Fig 1: 5-year survival in 4 subgroups (adapted from Howard et al. 2013)



HRS: Health and Retirement Study; NLST: National Lung Cancer Screening Trial; USPSTF: United States Preventative Services Task Force; LE: Life expectancy; yr: years

A.2. Potential harms of LCS: Is there increased risk for real-world patients considered "marginally" appropriate for screening? A fundamental question is whether the ***benefits / harms ratio*** observed in the NLST is generalizable to the general population of screening-eligible persons, including persons who may be considered marginally appropriate for LCS. Of the nearly 8.6 million Americans estimated to meet standard NLST eligibility criteria for LCS (age 55-74 years, ≥30 pack-year history of cigarette smoking, quit smoking ≤15 years), ~3 million have consequential comorbid conditions (e.g., COPD, congestive heart failure, cardiovascular disease).[14] We know the real-world screening- eligible population is older and sicker than NLST participants, but we do not know how this may affect the risk of harms – i.e., the potential for false-positive results, unnecessary diagnostic procedures, and complication rates from downstream diagnostic or surgical procedures. A false-positive LDCT result, which occurred in almost 40% of NLST participants, was the main harm associated with screening; for each lung cancer death averted, there were approximately 133 false-positive findings.[29] While most false-positive findings were managed conservatively with surveillance imaging, a number of participants in the LDCT study arm underwent one or more invasive procedures and were ultimately found to have a benign

nodule; these procedures included needle biopsy in 66 participants (2 per 1,000 persons screened), bronchoscopic biopsy in 227 participants (9 per 1,000), or surgery in 164 participants (6 per 1,000).[9, 33] (It should be noted that a *post hoc* analysis of NLST data demonstrated that the frequency of false-positive test results in the baseline round of screening could have been reduced from 27% to 13% by adopting a more stringent threshold for nodule size to define a positive LDCT test result; however, the authors also point out that the potential effect of reduced sensitivity on the mortality benefit of screening is unknown[33]). In a separate more recent study – the LCS Demonstration Project (LCSDP) conducted at 8 Veterans Affairs centers – 56% of individuals screened required nodule tracking.[34, 35] Importantly, in the LDCT arm of the NLST, complications occurred in 28% of all procedures for benign nodules, or 7 per 1,000 participants.[36] In a *post hoc* analysis of data from NLST, it was observed that older participants had a higher risk of false-positive results and complications from invasive procedures.[36] ***Given the number of participants experiencing a false-positive result over three years of annual screening, the rate of complications in procedures for benign nodules, the overall healthier status and younger age of NLST participants relative to screening-eligible adults in the real world, and the higher procedure volumes and dedicated thoracic surgery support generally seen in NLST trial centers,[37, 38] it may prove difficult to replicate the relatively low risk of harms as LCS is implemented in real-world*** **populations and settings.**

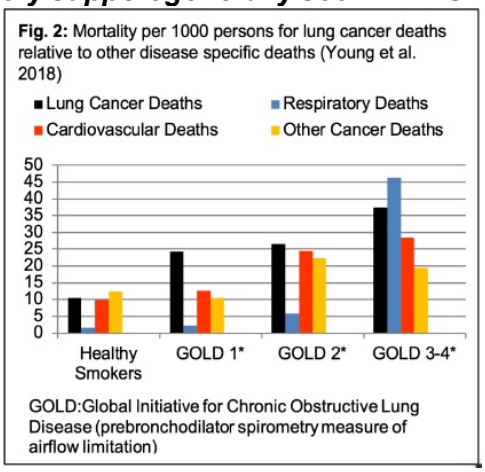


Fig. 2: Mortality per 1000 persons for lung cancer deaths relative to other disease specific deaths (Young et al. 2018)

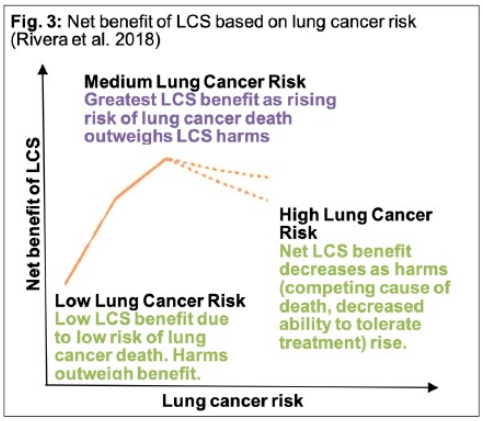


Fig. 3: Net benefit of LCS based on lung cancer risk (Rivera et al. 2018)

A.3. Conceptual framework for examining multimorbidity and LCS outcomes: Is there a potentially vulnerable subpopulation of screening-eligible patients? Patients eligible for LCS face a conundrum not seen in other cancer screening decisions.[27, 39] That is, the single risk factor most strongly linked to lung cancer --- smoking history -- is also strongly linked to morbidity and death from *non-lung cancer* causes. For example, on one hand, persons with COPD face a 2-3 fold higher risk of lung cancer than smokers without COPD and thus should be more likely to benefit from LCS.[40-45] On the other hand, persons with advanced COPD are at a greater risk of complications during evaluation of pulmonary nodules[46], have a higher 30-day mortality after resection of lung cancer (especially after thoracotomy)[47, 48] and have a higher risk of non-lung cancer mortality.[45, 49] Moreover, findings from an NLST sub-study show rates of respiratory deaths are higher than lung cancer deaths in that population[50]. In that study, over 50% participants had risk factors for premature mortality.[50] These results are in in strong contrast to breast cancer screening where comorbid disease is much less prevalent.[51, 52] Indeed, relative to populations at risk of breast cancer, several comorbid conditions are many fold more prevalent in populations at high risk of lung cancer -- including chronic lung disease (4–5 fold), diabetes (2–3 fold) and heart disease (2–4 fold).[51, 53] Taken together, these studies suggest that the benefits from LCS are not linearly related to the risk of developing lung cancer and that smokers at highest risk derive less benefit from screening than those in the intermediate level of risk.[17, 20, 50] Given the lack of the real-world evidence, the benefits of LCS to those with advanced COPD[52] (GOLD grade 3 and 4) and other serious comorbidities are highly uncertain (**Fig 2**). The need for a more thorough and systematic examination of the benefit/harms ratio for this subpopulation with higher levels of multimorbidity was highlighted in a 2018 report by a multidisciplinary group of international clinicians and researchers on behalf of the American Thoracic Society Assembly on Thoracic Oncology.[20] After reviewing available evidence, and considering the complex relationship between baseline risk of lung cancer, potential harms from LCS and downstream diagnostic procedures, treatment-related harms, and risk of death from competing causes, the group described a hypothetical relationship between lung cancer risk and net benefit from LCS, suggesting the possibility that for a subpopulation of screening-eligible patients, the potential harms of LCS could exceed the benefits (**Fig 3**). This expert group also identified knowledge gaps and an overall research framework regarding how to consider comorbidities and related factors when selecting appropriate patients for LCS. ***Our proposed study starts with this framework, and aims to: comprehensively and precisely describe a real-world population currently eligible for LCS, quantity benefits and harms across this real-world population, describe the shape of the benefits/harms ratio curve, and attempt to pinpoint the inflection point where harms may begin to exceed the benefit.***

A.4. Evaluating the rigor of prior research that supports our proposed study. The fundamental premise for our proposed study is the **widely recognized need to monitor interventions when they are implemented in the real world** to ensure that interventions perform as expected – i.e., present a ratio of benefits to harms in line with prior randomized clinical trials.[54] To date, to our knowledge, there has been no large and representative observational study designed to assess the real-world performance of LCS with LDCT. The need for such a study is strongly supported by the Howard et al. findings, which are cited extensively above.[30] They provide a very rigorous scientific basis for our proposed study. Howard et al.[30] studied subgroups from a **highly relevant** population of US adults, those nearing or in retirement; they also used a **high-quality data** source -- the longstanding, rigorously documented HRS, which is sponsored by the National Institute on Aging. The methodology and findings of the Howard et al.[30] study are reported **fully and transparently**. Potential conflict of interests (COI) are disclosed by authors, and the study was funded by the Centers for Disease Control and Prevention, further **minimizing potential sources of COI.** The study is limited, however, by two aspects of the data source – the time frame when data were collected, and the limited nature of health status data considered in the analysis. Data used by Howard et al.[30] were from 2012, the most recent data available at the time the study was conducted; nevertheless, the size and composition of the screening-eligible population continues to change,[55] and thus the 2012 data are limited with regard to fully representing the current real-world population. Perhaps the more important limitation relates to the nature of the health status data used in their analysis. Howard et al.[30] examined only "…comorbidities that are common and reported in both the NLST and HRS data (diabetes, heart disease, and stroke)…" While these health status data are certainly relevant, they do not include key respiratory diseases common among smokers (e.g., COPD, emphysema) – diseases that may increase the level of potential harms associated with LCS, as well as the risk of non-lung cancer causes of death. Moreover, Howard et al.[30] examined screening-eligible patients while we will examine those actually undergoing LCS. But crucially, Howard et al.[30] did not examine harms of LCS. Our study design, which will be described in detail below, will not have these limitations. We will utilize robust electronic health records and claims data that include information on all key health status parameters – including respiratory diseases, pulmonary function, functional limitations, etc. Moreover, we will have both a retrospective and prospective component, collecting timely data (2016-2022) from a large and diverse real-world population.

A.5. Public health relevance of our proposed study. USPSTF guidelines[11] on LCS recommend excluding persons unable to tolerate surgical resection, and other guidelines state that screening should be restricted to those "in reasonably good health"[56] or those able to "tolerate cancer treatment".[16, 27, 57] Notably, all these statements are qualitative and subjective; they do not provide objective or transparent criteria for assessing every patient's suitability for LCS. Clinicians may wish to ensure their higher-risk patients benefit from the detection of early-stage disease that LDCT offers; however, to date, there is **inadequate evidence to guide patient selection when patients present with multimorbidity, i.e., chronic co-existing conditions, functional limitations, and/or impaired pulmonary function**. This presents challenges for clinicians who must assess and communicate risk. It is difficult to engage elderly, frail, or sick patients in informed decision-making if the clinician cannot readily articulate a transparent assessment of the patient's risks. Currently, there is little knowledge regarding a possible threshold where the benefits of finding early-stage lung cancer no longer outweigh the risk of dying due to a competing cause or risk of complications from downstream procedures. Our proposed study has direct value for advancing public health: by analyzing real-world, timely data on the outcomes of LCS we will: i) **characterize the patient factors regarding multimorbidity** that most strongly predict LCS outcomes, ii) **identify subpopulations** for which LCS benefits clearly exceed harms, and subpopulations where harms may exceed benefits, iii) **use newly generated knowledge to refine simulation models** and improve clinical decision-making.

B. INNOVATION

This study is innovative in at least four ways.

1) Our study will be the first to generate real-world evidence regarding multimorbidity and LCS outcomes in a large and representative study population (across 3 diverse health systems) in the US by making efficient use of electronic health record (EHR) and Medicare claims based LCS and outcome data from 2016 to 2022. Relatively little is known about the safety and effectiveness of LCS as delivered in typical clinical settings. The novelty of the proposed study lies in **characterizing the benefit/harm ratio for different subgroups within the overall real-world LCS population**, especially since much work to date has focused solely on characterizing lung cancer risk.[39, 40, 58, 59]

2) Our study will be the first to fully combine empirical real-world LCS cohort data with simulation modeling. Current CISNET lung cancer simulation models have informed USPSTF LCS guidelines[60] but these models are based on inputs from RCTs rather than real-world data.[24, 25, 61] In Aim 3, we propose to calibrate simulation models using input from real-world data collected in Aims 1 and 2.

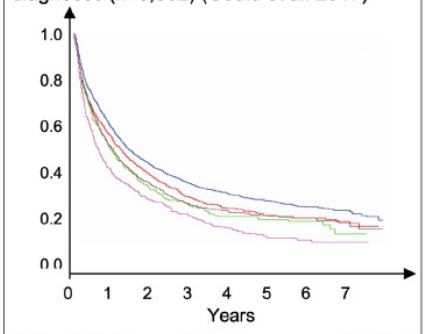
3) Our study will use refined and innovative measures to more precisely characterize the health status of screening-eligible patients; this will address limitations in existing studies, which have focused exclusively on comorbidity type and number.[16, 17] Instead, we will incorporate measures of pulmonary function and novel indicators of functional limitations -- factors that more precisely capture the severity of comorbid conditions. For example, our proposal is among the first to examine surrogates of functional limitations[62, 63] (e.g., wheelchair use, oxygen supplementation) in the LCS setting. Also, we will use pulmonary function tests (e.g., spirometry and ejection fraction data[20]) to assess the severity of respiratory comorbidities. This represents a major innovation and step toward precision LCS.

4) Our study will have a large and racially/ethnically diverse cohort from 3 large and geographically distinct healthcare systems. Our cohort will include racially/ethnically and socioeconomically diverse screening-eligible patients ages 55-80, with approximately a quarter of the cohort comprised of Black patients. Patients will be recruited from 3 large geographically distinct study locations (in Southern California, South Carolina and Oregon) and will include typically difficult-to-reach populations, such as rural Whites in Oregon and Appalachian Blacks in South Carolina. Few, if any, LCS cohorts incorporate this range of diversity. The diverse types of healthcare systems participating in our study will further enhance the generalizability of our study findings to the broader US population.

C. PRELIMINARY STUDIES

C.1. Study Team. We have assembled an outstanding multi-disciplinary study team that includes expertise in thoracic oncology, epidemiology, simulation modeling, health services research, thoracic surgery, health disparities, biostatistics and real-world data analysis. We have also included dedicated lung cancer patient advocates, who will inform translation of our findings into patient-centered clinical decision aids. Our team has extensive expertise with the collection and analysis of real-world cancer screening data, with three large PCORI- and NIH-funded studies using these approaches. Furthermore, we have experience pooling data across multiple institutions for central analysis, and experience analyzing large population-based datasets from both primary and secondary data sources, including SEER-Medicare and other secondary datasets. We also have considerable experience with lung cancer simulation modeling, and unmatched content expertise and research experience in LCS. Of greatest relevance to the proposed research, Drs. Braithwaite, Gould, Silvestri and Slatore were members of an expert panel commissioned by the American Thoracic Society (ATS) that developed an official ATS statement on incorporating co-existing illness into decisions about candidate selection for LCS.[20] Drs. Gould, Silvestri and Slatore have written extensively about the delivery of LCS, including multiple articles that address lung cancer risk, comorbid conditions and LCS eligibility.[6, 22, 27, 34, 64-66] In addition, Drs. Silvestri and Gould recently used NLST data to develop a model to predict positive baseline LDCT screening test results.[16, 17, 19, 39] They also co-authored a paper that identified racial disparities in survival and receipt of surgery in the NLST.[15] This team has also collaborated on recent studies of pulmonary nodule evaluation, including a study that documented high frequencies of invasive sampling of low-risk nodules and surgical resection of benign nodules[67], and another study that demonstrated the potential utility of measuring nodule volume for cancer prediction.[68] Our team has also conducted a cost-effectiveness analysis of the NLST showing that the value of LCS varied across risk quintiles from extremely cost-effective to inefficient [$52,000 vs. $169,000 per quality life year (QALY)].[69]

Fig. 4: Survival by comorbidity class profile for patients with lung cancer with first-time diagnoses (n=6,662) (Gould et al. 2017)



* Five distinct comorbidity classes were identified using specific comorbid conditions from the Charlson comorbidity index

C.2. Comorbidity patterns and lung cancer outcomes: Dr. Gould and colleagues used latent class analysis to identify distinct comorbidity profiles in a large retrospective study of patients with lung cancer at Kaiser Permanente Southern California.[70] They identified 5 classes, defined by progressively higher comorbidity index scores and further distinguished by the presence or absence of specific types of vascular disease and diabetes. These 5 classes were independently associated with both treatment selection and survival (**Fig 4**). *This study demonstrates our team's experience working with electronic health records (EHR) and Medicare claims based comorbidity data as well as an ability*

to clinical phenotype a large and heterogeneous population of lung cancer patients. We will build on this approach in Aim 2 by augmenting comorbidity index scores with data on functional and pulmonary status.

C.3. Comorbidity in relation to surgical outcomes and lung cancer mortality: In comparing surgical outcomes among elderly stage 1A lung cancer patients in SEER-Medicare who had ≤1 comorbid condition (n=3870) versus patients who had ≥2 comorbidities (n=2577), we found that patients with ≥2 comorbid conditions were twice as likely to die within 90 days of surgery and had much lower overall 5-year survival (47% vs 74%). (**Table 2**). These sicker patients would have been excluded from the NLST; however, they may very well be considered marginally appropriate for LCS in community settings. *These findings demonstrate the importance of evaluating comorbidity burden in relation to outcomes in individuals undergoing LCS in community settings (Aims 1 and 2)*.

Table 2: Characteristics of patients with stage 1 lung cancer undergoing surgery (Tanner et al. 2017)

	NLST		SEER NLST eligible		SEER NLST ineligible	
	N	PctN	N	PctN	N	PctN
All	379	100	3870	100	2577	100
Stage						
IA	273	72.03	2268	58.60	1537	59.64
IB	106	27.97	1602	41.40	1040	40.36
Age						
65-69	226	59.63	2042	52.76	1006	39.04
70-74	153	40.37	1828	47.24	1571	60.96
Charlson comorbidity score						
0	247	65.17	2069	53.46		
1	132	34.83	1801	46.54		
2+						
Mortality						
30 day	6	1.58	56	1.45	69	2.68
60 day	8	2.11	90	2.33	112	4.35
90 day	9	2.37	113	2.92	152	5.90
5 year overall survival*		*73.60*		*62.80*		*47.14*

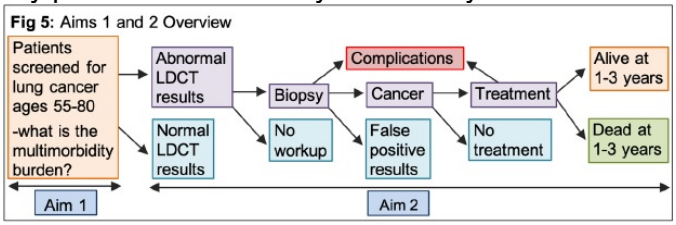
C.4. LCS utilization and results: In the NCI-funded Cancer Research Network Lung Screening Supplement, Dr. Gould and colleagues from three other health care systems developed efficient methods to collect data on LCS practices and outcomes in clinical settings.[71] This research generated a comprehensive description of diverse practices for screening and data collection, and further refinement of a previously developed natural language processing (NLP) algorithm that identified the presence of a pulmonary nodule on a dictated radiology transcript with 96% sensitivity and 92% specificity.[72, 73] The NLP had similar accuracy in a subsequent external validation study[74]. More recently, the functionality of the NLP algorithm has been expanded to enable capture of nodule characteristics, including laterality, lobe, size, attenuation, edge and calcification, all with very high (>95%) sensitivity and specificity (unpublished data). *Our proposed study will use this NLP algorithm to capture the presence and characteristics of screening-detected nodules*.

C.5. Michigan CISNET Lung Cancer Simulation Model: The University of Michigan Lung Cancer Screening model (UM-LCS, described in section E.5 below), led by co-I, Dr. Meza, combines a multistage carcinogenesis model with a discrete-state microsimulation model to evaluate the effect of LCS on lung cancer incidence and mortality, overdiagnosis, and quality of life.[75] This model was used for the 2015 USPSTF lung screening decision analyses,[24, 25] but has been updated considerably to simplify its use and enhance its applicability. *Thus, our preliminary work demonstrates expertise in simulation modeling. In Aim 3, we will refine Dr. Meza's model with real-world data inputs generated in Aims 1 and 2.*

D. APPROACH

D.1. Overview of Observational Study Design (Aims 1 and 2): There is a lack of real-world data about what actually happens after LCS and how outcomes are affected by patient multimorbidity. Guided by the Rivera et al. conceptual framework[20] (section 3.A.3.), we will extract detailed EHR and claims data from 3 major healthcare systems to *characterize the chain of events following LCS in patients with a full range of multimorbidity levels, including severe chronic conditions such as COPD, impaired pulmonary function, etc.* **(Fig 5)**. We will assemble our study cohort using the same methodology published in our *Annals of the American Thoracic Society* article.[71] Below we discuss the characteristics of study participants in our cohort, the data sources to be included in our study and the key variables. We will incorporate two distinct approaches to sampling adults ages 55-80 undergoing LCS at the 3 study sites described below: i) <u>retrospective</u> LCS cohort (2016-2019) and ii) <u>prospective</u> LCS cohort (2020-2022). We chose to focus on this age group (55-80) because this age range is recommended for LCS by USPSTF.[11]

Fig 5: Aims 1 and 2 Overview



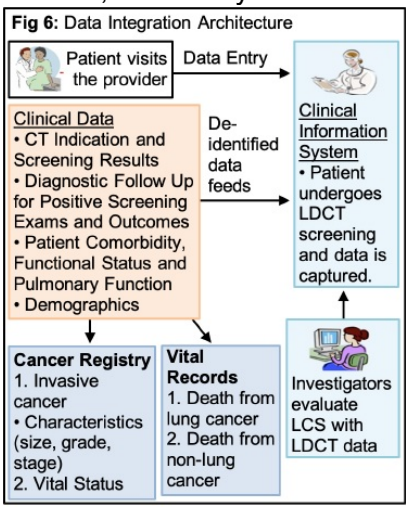
D.2. Eligibility for LCS cohort and description of LCS healthcare systems: Data will be drawn from cohorts of persons who undergo baseline or repeat annual screening with LDCT, and who have had one or more primary care visits at one of 3 participating healthcare systems from 2016 to 2022. Patients ages 55-80 with scans performed for diagnostic purposes and patients with a history of lung cancer within 5 years will be excluded. We will analyze data from ~34,039 persons undergoing LCS with LDCT and ~1,902 early stage lung cancer patients

treated at one of the following 3 institutions participating in our proposed study. Each of our 3 healthcare systems is community-based and provides comprehensive services, including primary and specialty care, to large, diverse populations. In addition, each system has implemented lung cancer screening since at least November 2015. These three healthcare systems represent varied models of care delivery: 2 are integrated models and 1 is a statewide network of community hospitals and clinics. The geographic diversity and varied care delivery models of these 3 healthcare systems enhance our study's ability to evaluate LCS in real-world settings:

Kaiser Permanente Southern Calif. (KPSC) is a fully integrated health care system that serves over 4.6 million members of a (mostly) pre-paid, capitated health plan. Approximately 7,600 physician partners and associates of the Southern California Permanente Medical Group (SCPMG) provide comprehensive primary and specialty care at 15 medical centers and over 230 medical office buildings throughout Southern California. The KPSC membership is racially and ethnically diverse, reflecting the population of the Southern California region from which is it drawn.[76] In March 2019, the total membership (including children) was 43% Hispanic, 35% non-Hispanic White, 9% Black and 12% Asian/Pacific Islander. KPSC implemented LCS in 2014 with a standardized order set for LDCT screening exams. The order set was modified in October 2015 by including specific exam codes to distinguish more effectively between screening exams, diagnostic exams, and exams for follow-up of incidentally-detected or screening-detected lung nodules. The order set for screening LDCT includes check boxes to confirm that the patient meets USPSTF eligibility criteria[11], does not have symptoms of lung cancer, has gone through a process of shared decision-making, and has been referred for smoking cessation counseling (if indicated). In 2018, over 6,000 individuals were screened for lung cancer withLDCT.

Medical University of South Carolina (MUSC). MUSC functions as the state's safety net hospital, caring for a diverse population; over 30% of patients are African-American. LCS eligible individuals are identified through the EHR. PCPs are notified by an alert when a patient meets age and smoking criteria. The provider can order the LDCT or make a referral to the LCS program. At the end of 2015, MUSC launched its LCS Program at the NCI-designated Hollings Cancer Center. The multidisciplinary program is led by a pulmonologist and a smoking cessation expert. In 2018, the program screened more than 700 individuals and is expanding outreach efforts.

Veterans Affairs Hospitals (VAMC). The VA Portland Health Care System in Portland, OR was one of eight sites that participated in the LCS Demonstration Project. The site provides care for close to 60,000 mostly older male Veterans, over 50% of whom are current and former smokers. In addition to the main medical centers, patients are seen in primary care Community-Based Outpatient Clinics (CBOCs). The VAMC implemented LCS in 2013 through a population-based screening program that proactively identified eligible patients ages 55 to 80 years without a prior diagnosis of cancer through an algorithm applied to VHA electronic medical records. Nursing staff receive clinical reminders to collect tobacco pack-year history at the time of PCP visit. Those eligible by age and smoking history trigger an additional clinical reminder through the EHR to the provider, who then decides if the patient is medically fit to undergo screening. The provider then places a consult order for LCS and a dedicated nurse coordinator provides patients without exclusion criteria a risk and benefit brochure one week prior to a shared decision phone call. The VA Portland screened 1,200 patients in 2018.



D.3. Description of Data Coordination and Data Collection

D.3.1. Data Coordinating Center (DCC): The DCC, directed jointly by Drs. Shen (KPSC Lead Statistician) and Gould (KPSC MPI), will be responsible for overseeing all aspects of data capture, management, mapping, transfer and reporting, as well as data analysis in Aims 1 and 2. Dr. Shen will also provide statistical and methodological support for data analysis, drawing on his specific expertise in multilevel modeling, latent-class analysis and causal inference. In addition, Dr. Fan (Professor of Biostatistics, Bioinformatics and Biomathematics) will work closely with Dr. Braithwaite at Georgetown and provide input on statistical analysis. The primary goal of the DCC is to ensure that the required data elements are reliably collected and mapped into a commonly defined, Health Insurance Portability and Accountability Act (HIPAA)-compliant format, and managed in a flexible, secure data system (**Fig 6**). The DCC will establish and maintain systems to collect common data elements across all three participating institutions and provide a secure transfer and distribution infrastructure to meet HIPAA, collaborating institution, and United States federal regulations for data sharing. The DCC will lead the implementation of a single data standard, based on the existing data infrastructure for the PCORI-funded trial, a large (N~35,000), pragmatic clinical trial of strategies Watch the Spot (WTS) for pulmonary nodule evaluation. *It is important to note that there is no scientific or budgetary overlap between this proposal and WTS as WTS is a*

pragmatic trial with distinct aims, and the overwhelming majority of WTS participants will have incidentally-detected (rather than screening-detected) nodules.

D.3.2. Data standardization*:* The WTS data standard is defined by a common vocabulary, which provides a foundation for integrating the data into a unified repository. The common vocabulary is codified in the WTS data codebook, which contains 13 key sets of data elements, including files for participant identification and eligibility, sociodemographic characteristics, smoking history, nodule characteristics, health care utilization, comorbid conditions and vital status. The WTS data model is currently being used by all of the aforementioned participating sites for the proposed study (KPSC, MUSC and VA Portland) to collect standardized data from the EHR of WTS participants. Additional efforts at data standardization will involve a common template that will be used by radiologists at all study centers to report LDCT results by Lung-RADS® category.[77] Lung-RADS®, the Lung Imaging and Reporting System, is a quality assurance tool of the American College of Radiology.[33] It was designed to reduce confusion in lung cancer CT screening interpretations, standardize reporting and management recommendations, and facilitate outcome reporting. To date, our team has collected baseline data from diverse locations for over 21,000 participants, as well as follow-up utilization and adherence data for over 8,000 participants. *Thus, our team has highly relevant experience collecting and sharing standardized data related to LCS and pulmonary nodule evaluation.*

D.3.3. Data sources and data collection: The data model will include both structured and unstructured health information collected at our 3 participating healthcare systems; these 3 systems have developed methods (exports from EHR, NLP, text mining) for extraction of study variables, including demographic characteristics, smoking history, referrals for and receipt of LDCT, LDCT results using Lung-RADS®, diagnostic follow-up procedures, and lung cancer diagnoses. Each participating institution will create a secure database of patients undergoing LCS with LDCT. Patient identifiers (name, medical record number, DOB) linked to a unique study ID number will be kept in a file separate from other study data. Demographic information (age, sex, race/ethnicity) and selected clinical variables from the Radiology Information Systems (RIS) will be linked with information from the EHR to collect relevant clinical data such as smoking history, information about health care utilization (physician visits of different types, imaging), and diagnosis of cancer from medical records, hospital pathology databases and local tumor registries. While the variables will be defined using a single data dictionary, the strategies for populating the database will be developed individually at each institution, depending on available information systems and systems for extracting data to populate the database. Data sources will include administrative records and membership files (demographic characteristics), EHR (e.g., smoking history, pulmonary function), ICD-9 and ICD-10 codes for diagnoses and procedures, Current Procedural Terminology (CPT) codes for procedures, LDCT referral and order codes used by each system, and radiology reports from each system, linked to cancer registry and mortality data. EHR and claims data will be combined and standardized since both use ICD and CPT4 codes; the Healthcare Common Procedure Coding System (HCPCS) used by Medicare includes CPT4.[78, 79] Patient residential zip codes (from EHR) will be linked to US census data. Medicare data will also help identify any patients in our screening cohort who are diagnosed and/or treated for lung cancer outside of our study sites. Our collection of patient- and system-level data will leverage the methods and programs previously developed for the Cancer Research Network Lung Screening Supplement (see section C.4), and the ongoing WTS trial. *It is important to note, however, that there is no scientific or budgetary overlap between this proposal and WTS as WTS is a pragmatic trial with distinct aims, and the overwhelming majority of WTS participants will have incidentally-detected (rather than screening-detected) nodules.*

D.3.4. Data transfer and storage*:* Data elements will be transferred securely to KPSC from MUSC and Portland VA through a web-based portal via REDCap[80], a secure web application for building and managing online surveys and highly customizable data collection instruments. REDCap includes a sophisticated export module that is compatible with all the popular statistical programs, and it supports HIPAA compliance and Title 21 Code of Federal Regulations (21 CFR) Part 11. All data transmissions will be encrypted, and access to the DCC portal will require authentication and authorization.

D.4. Description of Variables

D.4.1. Predictor variables:

Age: Only individuals ages 55-80 at the start of 2016 will be included in our study.

Comorbidity: In this proposal, comorbidity is defined by diseases that are predictive of life expectancy. Since the benefit of LCS comes from finding and treating lung cancer that would have become symptomatic over a

person's remaining years of life while it is at an early stage, individuals with severe comorbidity and limited life expectancy are subjected to the potential harms of LCS with little chance to benefit.[20] Therefore, our measures of comorbidity are focused on prognosis. We have chosen to use the Charlson/Elixhauser comorbidity score using EHR data[81-83] because this combined score has been shown to offer improvements in comorbidity summarization over other existing scores.[84] The Charlson score is a summary measure of 19 diseases that are weighted based on severity.[85, 86] The Elixhauser system was developed to predict hospital charges, length of stay, and in-hospital mortality; it was developed by identifying comorbidities that are relevant to hospitalization, but are not the primary reason for hospitalization, along with the severity of the condition that prompted hospitalization.[84] A diagnosis of lung cancer will be excluded from the calculation of the Charlson/Elixhauser score, consistent with previous studies. The Charlson/Elixhauser score will be calculated from EHR[87, 88] during the 12 months prior to each LDCT. Individuals will be categorized as being in best health if they have a Charlson/Elixhauser score of 0, average health if they have a Charlson/Elixhauser score of 1 and worst health if they have a Charlson/Elixhauser score of ≥2.[89] *We will treat comorbidity status as a time-varying variable[90], as described in section* E.4.

Functional limitations: Consistent with the Segal study,[63, 91] patients' indicators of functional limitations will be derived from claims and EHR data at KPSC and VA, the two systems that comprise nearly 80% of our LCS cohort. As with comorbidity, functional limitations will be ascertained during the 12 months prior to the baseline LDCT. We will examine frequency distributions for each of the following conditions: mobility limitations (defined by claims for cane, walker, wheel chair, hospital bed, etc.), blood transfusion, use of oxygen, supplemental nutrition, hip or pelvic fracture, chronic skin ulcer, pneumonia, delirium/dementia/Alzheimer disease, bone marrow failure/agranulocytosis, depression, use of urinary catheter, respiratory failure/insufficiency/arrest, sepsis, and malnutrition/unintentional weight loss, fall-related injury and syncope. All Function Related Indicators (FRI) will be coded as binary variables (scale 0-13); individuals will receive a score for each aspect of functional limitations with the average score generating the FRI score. Consistent with our aforementioned categorizations of comorbidity status, persons will be categorized as being in best health if they have a FRI score of 0, average health if they have a FRI score of 1 and worst health if they have a FRI score of≥2.

Pulmonary function: We will leverage the infrastructure from Dr. Gould's preliminary work[71] to obtain data from pulmonary function tests – these represent a major innovation toward precision LCS since they assess the severity of pulmonary comorbidities.[92] We will evaluate previously validated structured data on spirometry, which can capture severity of co-existing pulmonary disease such as COPD.[93] We will classify COPD using the new Global Initiative for Obstructive Lung Disease (GOLD) classification: categories A, B, C and D based on spirometry indicators.[94] We will also evaluate data for forced expiratory volume (FEV) and ejection fraction and will perform analyses for patients with heart failure, another common comorbid condition that could influence LCS outcomes. Impaired pulmonary function will be defined as FEV1/FVC<70%.[93, 95]

Other variables that may act as potential confounders or effect modifiers to influence LCS outcomes: i) ***Smoking history*****:** both smoking status and pack-years will be extracted from medical charts based on previously validated methods.[71] Importantly, we have virtually complete data on smoking status and the most important determinant of outcomes is current smoking (and not pack years or quit years for which data are less complete and accurate);
ii) **Race/ethnicity** is based on data recorded in EHR; iii) ***Socioeconomic status (SES)*** measures will be obtained through linkage to the US census to determine the proportion of adults with a college education who lived within a subject's zip code tabulation area.[96] SES measures at the census block group level include: diversity index score (a measure of the racial and ethnic diversity of a geographic area ranging from 0 [no diversity] to 100 [complete diversity]), median disposable income, median household income, average annual health insurance expenditures, average annual public transportation expenditures, proportion with a college degree and proportion with access to the internet.[96]

D.4.2. Outcome Variables: The primary outcome for Aim 1 is the prevalence of multimorbidity in the LCS cohort. Our primary outcomes in Aim 2 are the events that follow LCS with LDCT. The chain of events includes the results of the baseline LDCT and subsequent LDCT tests, biopsies, lung cancer diagnosis and procedure-related complications. These outcomes data will be derived from the EHR and claims-data as well as tumor registries. The primary outcomes include:

i) ***False positive results*****,** biopsies and cancer detection rate will be identified from cancer registry files to determine if a lung cancer occurs within 1 year of LDCT. We will classify each LDCT exam result as true positive, false-positive, true negative or false-negative.[33] Cancer detection rate is defined as the number of cancers found per 1,000 persons screened (screening detection rate).[14]

ii) ***Procedural complications*** will include complications following transthoracic, transbronchial or surgical

biopsies that lead to lung cancer diagnosis. Procedures after the date of lung cancer diagnosis will be excluded. Serious complications within 7 and 30 days of biopsies include pneumothorax, bleeding (pulmonary hemorrhage), acute respiratory failure, acute renal failure, allergic reaction to iodinated contrast material requiring hospitalization, and acute myocardial infarction.[6] We will evaluate procedural complications among all persons undergoing LCS, not only those diagnosed with lung cancer.

iii) ***Lung cancer stage at diagnosis****:* Stage will be ascertained using respective institutional cancer registries (using ICD9/10 codes), and supplemented by the patient's pathology reports obtained through EHR; key clinical variables include the AJCC stage, histology, and presence/absence of metastases.[95, 97] In terms of histology, we will evaluate rates of lung cancers with a bronchioloalveolar carcinoma histology, which are often indolent with very long doubling times and are thus more prone to overdiagnosis.[98, 99]

Other outcomes will include*: i)* ***LDCT results***: Results of the LCS with LDCT will be extracted from Lung RADS® reports, the standardized template for reporting LDCT results.[33] All 3 participating healthcare systems currently use Lung-RADS® for reporting. The receipt and timing of additional CT tests will be examined based on Lung RADS®. *ii)* ***Lung cancer treatment****:* We will include data on treatment modalities focusing on differences in receipt of surgery vs. radiation therapy among patients with early stage lung cancer. Receipt of curative radiotherapy may be a marker of overtreatment due to inappropriate LCS of patients with a high risk of other cause mortality.[100]

D.4.3 Study Design Considerations. We considered several issues in our study design.

First, the observational nature of our assessments limits our ability to make causal inferences due to the likelihood of selection bias and confounding by indication. To account for potential confounders that are inherent in observational research[101] we will adjust for factors associated with the exposure variables of interest (i.e., age, surrogates of functional limitations, COPD status and overall comorbidity) and other relevant variables, including socio- demographics, smoking history, and clinical factors. Given the richness of the available EHR data, we will be able to account for all generally recognized confounders that have been reported in the literature to be associated with both the exposures of interest and LCS outcomes. To achieve this goal, we will use propensity score methods to adjust for confounders.[102-104] Given that some exposures of interest are not binary, the propensity scores will be estimated using multinomial logistic regression models with a generalized logit link and included as covariates in the outcome regression models. This approach gives us flexibility on how to model the propensity scores and it allows for the incorporation of interactions involving the propensity scores, to best account for differences between patients receiving LCS during different time intervals.

Second, while an advantage of this proposal is that it links EHR data with cancer registry data, we acknowledge that EHR data from clinical settings may have limited granularity.[105] However, data sources employed in this proposal are drawn from healthcare systems that mandate the universal adoption of standards-based, interoperable healthcare data, captured seamlessly across the different locations where their patients receive care. Further, EHR-based data offer important advantages because they include large numbers of patients who receive real-world care.[12] Finally, EHR-based data already exist, having been collected as part of routine care, making this study more generalizable and much less expensive than a primary data collection effort.

Third, we specifically selected a centralized data repository model over a distributed model to optimize integration and harmonization of data derived from the 3 diverse healthcare systems participating in our study.

Fourth, we strengthen our study design by combining observational data from real-world diverse settings with an established simulation model[26] to estimate long-term harms and benefits of LCS.

E. ANALYTIC PLAN

E.1. a) Overview: We plan a series of analyses examining the impact of comorbidity, functional limitations and pulmonary function on the benefits and harms of LCS. Under **Aim 1**, we will leverage comprehensive measures of comorbidity, functional limitations and impaired pulmonary function to characterize their burden among individuals undergoing LCS in typical U.S. clinical practice. Under **Aim 2**, we will use previously developed and applied discrete-time survival methods[106] to estimate the risk of false-positive results, procedure related complications and detection of screen-detected lung cancer among persons with varying levels of comorbidity, functional limitations and impaired pulmonary function. Results from these analyses will be used as an input for simulation models in Aim 3. Finally, under **Aim 3**, we will enhance our previously validated lung cancer CISNET model using estimates from Aims 1 and 2 to compare benefits and harms of LCS for persons with diverse levels of multimorbidity -- including diverse levels of chronic coexisting conditions, functional limitations and pulmonary function. **b) Strengthening observational design**: To account for potential confounders and selection bias in cohort data from Aims 1 and 2, we will adjust for important covariates including, but not limited to, geographic

location, race/ethnicity, socioeconomic status, age, smoking history and gender. In addition, we will use propensity scores to adjust for potential selection bias.[104] The generalized propensity score is the probability of a particular LCS interval (e.g. annual, biennial) given pre-screening factors potentially associated with LCS interval (e.g. geographic location, age, smoking history, socioeconomic status, etc.).[102, 107] Propensity scores will be estimated using a multinomial logistic regression model with a generalized logit link and will be included as covariates in regression models. This approach allows us to explore a flexible model for the propensity score, incorporating interactions and other non-linear relationships to best account for possible differences between individuals receiving LCS at various intervals.[108-110]

E.2. Sample size considerations and power analysis: Based on our preliminary data collection from the 3 study sites (2016–2018), we project a total sample size of approximately 34,039 unique persons undergoing LCS, and 902 incident lung cancer cases (based on an estimated 2% lung cancer rate) for the period 2016–2022. We focused our power calculation on the outcome for Aim 2: estimates of procedure-related complications following LCS with LDCT. Based on published literature,[14, 53, 111] we estimate that at least 70% of those undergoing LCS have at least one consequential comorbidity and about 20% have COPD. Based on recently published data from Huo et al.,[112, 113] it is estimated that 20-30% of individuals undergoing LCS without major chronic co-existing conditions will have downstream procedure-related complications.[67, 113-115] Given these assumptions, we will be well powered to identify a minimally detectable risk difference *as small as* 5% for procedure-related complications; this estimate takes into account 80% power and the probability of type I error at 0.05. Based on similar assumptions, we can identify small effect sizes for minimally detectable risk difference of false positive LCS results ranging between 1.3 and 1.9% across levels ofcomorbidity.

E.3. <u>Aim 1 analyses</u>: In a cohort of ~34, 039 individuals undergoing LCS with LDCT at 3 diverse real-world healthcare settings, we will characterize the patient population with regard to the burden of chronic co-existing conditions, functional limitations and impaired pulmonary function, with particular attention to evaluating the subpopulation of marginal patients for whom the net benefit of LCS currently appears uncertain. As an exploratory sub-aim, we will examine this burden by race/ethnicity, SES and age. To this end, we will generate a weighted variable for each observation based on inverse of its selection probability since this can increase the generalizability of the prevalence estimates.[116] We will consider the distribution of important risk factors in the target population when generating the weighted variable[116] and report weighted prevalence estimates of comorbidity, functional limitations, and impaired pulmonary function. We will use descriptive statistics to fully characterize our patient population (including means and standard deviations for continuous covariates, and counts or percentages for categorical covariates), stratified by comorbidity, functional limitations, and impaired pulmonary function. Two-sample proportion tests will be used to examine if the prevalence of comorbidity, functional limitations or impaired pulmonary function differs by race/ethnicity, SES and age. We will fit a multivariable logistic regression model to calculate adjusted odds ratios of comorbidity (Charlson/Elixhauser index 0 vs. ≥1), functional limitations (0 vs. ≥1), and impaired pulmonary function (FEV1/FVC<70% vs. ≥70%) while taking into account race/ethnicity, SES and age as well as relevant covariates (e.g. smoking status, calendar year, and geographic location).

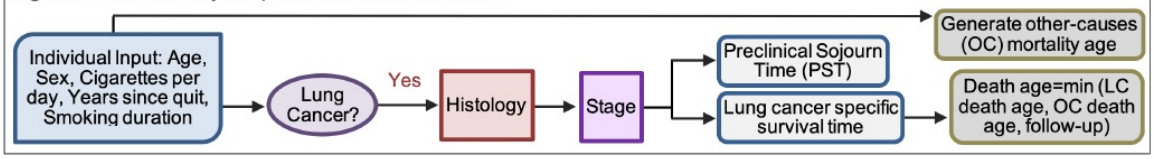
<u>Aim 2 analyses</u>: In a cohort of ~34, 039 individuals undergoing LCS with LDCT at 3 diverse real-world healthcare settings, we will quantify potential harms (e.g. false-positive results, procedure-related complications) and benefits (early stage disease at diagnosis) of LCS among persons with varying levels of comorbidity, functional limitations and pulmonary function. We will estimate the cumulative risk of these LCS outcomes over the course of 6 years of screening performed during 2016-2022. We <u>hypothesize</u> that LCS will not be effective for persons with moderate to severe comorbidity, functional limitations or severe COPD. We will use EHR and claims data from the one year prior to each LCS to estimate the Charlson/Elixhauser comorbidity score, FRIs and pulmonary function. We will collect information on any prevalent and incident comorbid conditions, FRIs and pulmonary function impairments. Similarly to Aim 1, we will compute descriptive statistics for LCS outcomes (see section D.4.2) stratified by the Charlson/Elixhauser comorbidity score, FRIs and impaired pulmonary function at the beginning of follow-up. Discrete-time survival models are the most appropriate approach to estimating the cumulative risk of outcomes associated with screening because they inherently account for the fact that risk of an event only accrues at the time of a screening exam.[117] Thus, time is indexed by the number of prior screening examinations rather than calendar time. Discrete-time survival models allow us to estimate the average number of exams until a person first experiences an event as well as the cumulative probability of experiencing at least one event over the course of 6 years of screening. Using discrete-time survival models, we will estimate the

hazard for each outcome of interest by comorbidity, FRIs, and impaired pulmonary function, adjusted for relevant covariates (e.g. geographic location, SES, race/ethnicity, age, smoking status). Separate models will be constructed for each outcome. If Yk is a binary variable indicating the outcome of interest at the kth exam, our model for the discrete hazard takes the form: logit fk(Xk) = log(P(Yk=1)/(1 - P(Yk = 1)) = Xk βk, where Xk represents a vector of possibly time-varying covariates including comorbidity, age, and other patient characteristics; of note Xk can also include interactions between time-varying covariates and exposure. Since we are modeling each LDCT scan as a separate observation and the probability of an event within the following year, we will model the Charlson/Elixhauser score, FRIs, and pulmonary function at the beginning of each interval for each separate observation; the Charlson/Elixhauser score, FRIs, and pulmonary function measurements will be treated as time-varying because they can change with each observation. Models will be pruned by backward selection using the Akaike Information Criterion[118] to balance the predictive power of the model against model parsimony. This is especially important given the large number of FRIs we will examine. To estimate the cumulative probability of each outcome associated with LCS for persons of a given comorbidity level, functional limitations or pulmonary function level, we will aggregate discrete hazards to estimate cumulative probabilities. Notably, *missing data* on specific covariates (e.g., smoking status) may affect these statistical analyses. Missing data may cause bias in the analyses, loss of power, or both.[119] We will use logistic regression models to identify the factors related to the probability of missing data and determine whether there is a pattern of missingness. Sensitivity analyses will be based on using inverse probability (of having missing data) weights.[112] The issue of loss of power and possible bias will be further addressed by using multiple imputation methods if the variables are missing at random. Before performing the statistical analyses described in the subsequent subsections, we will generate ten imputed datasets, analyze them separately as described below, and then combine the results using established methods.

E.5. <u>Aim 3 Analyses</u>:

E.5.1. Overview of model: The University of Michigan Lung Cancer Screening (UM-LCS) model was developed to evaluate the benefits and harms of LDCT screening, including lung cancer deaths averted, life-years gained, overdiagnosis, false positive tests, and radiation-related lung cancer deaths. The model consists of two main components, a natural history and a screening component, which together generate an individual history. The natural history component simulates individual lung cancer related events as well as age at death from causes other than lung cancer, given an individual's smoking history (**Fig 7**). If an individual develops lung cancer, the model simulates age at lung cancer diagnosis, histologic type (adenocarcinoma+BAC, squamous, small cell, other), and stage (IA, IB, II, IIIA, IIIB, IV). Lung cancer specific survival time is simulated conditioned on sex, age at diagnosis, histology, and stage. Given a lung cancer diagnostic event, the screening component simulates a stage-appropriate preclinical sojourn time (PST) (i.e., the period in which an asymptomatic lung cancer develops before being detected once screening occurs), as well as a screening schedule and screening outcomes (**Fig 8**). For screen-detected cancers, the model also simulates a new lung cancer survival time based on stage at diagnosis.

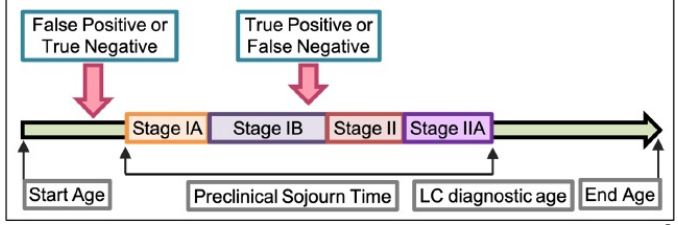
Figure 7. Natural history component of the UM-LCS model.



Model inputs consist of:

i) age- and sex-specific lung cancer risk by smoking history, ii) tumor stage distributions with/without undergoing LDCT screening exams[24, 26, 120] by histology and sex, iii) lung cancer specific survival time as a function of age at diagnosis, sex, stage, and comorbidity, iv) preclinical sojourn time in each stage[121] as a function of sex and comorbidity, v) screening sensitivities, specificities, false positive rates by sex, stage, and comorbidity, vi) adherence with Lung-RADS® recommendation as a function of comorbidity burden, vii) outcomes of LDCT screening, including biopsies and complications from screening and diagnostic procedures, and viii) other-cause mortality rates for the population being simulated.

Fig 8. Screening component of the UM-LCS model, example for an individual diagnosed with stage IIIA lung cancer in natural history component.



<u>For our proposed study, our refined model will also include as a model input more refined measures of</u>

comorbidity, functional limitations and pulmonary function status, which will allow us to simulate outcomes for real-world subpopulations with varying levels of multimorbidity. We will also be able to compare simulation results using our Aim 1 and 2 real-world data versus results generated by the original UM-LCS model using CISNET[121] data and other trial data (e.g., NLST, PCLO, etc.) **Table 3 below** summarizes the model inputs and data sources. ***Model outcomes include***: (i) screening eligible population, (ii) LDCT screens and follow-up scans, (iii) false-positive screens, (iv) biopsies, (v) lung cancer incidence, (vi) lung cancer mortality, (vii) life-years/quality-adjusted life-years gained compared to no screening, (viii) number needed to screen to prevent one lung cancer death, (ix) overdiagnosis, and (x) radiation-related lung cancer death.

Table 3: Model elements and data sources

Model Inputs	Possible Data Sources
Lung cancer incidence by age, sex and smoking history	NHS/HPFS, SEER
Tumor stage distribution by histology, and sex	SEER, PLCO, NLST
Lung cancer specific survival times by age, histology, stage and sex	SEER
Pre-clinical sojourn time in each stage	NLST, PLCO
Sensitivity and specificity of LDCT; False positive rates	NLST/LungRADS® & real-world LCSC
Adherence with Lung-RADS® recommendations by multimorbidity burden	Real-world LCSC
Outcomes of LDCT screening; biopsies, complications	Real-world LCSC
Competing other-cause mortality	CISNET,NLST,PLCO, real-world LCSC

NHS: Nurses' Health Study; **HPFS**: Health Professionals Follow-Up Study; **SEER**: Surveillance, Epidemiology, and End Results; **NLST**: National Lung Screening Trial; **PLCO**: Prostate, Lung, Colorectal and Ovarian Cancer Screening Trial; **real-world LCSC**: real-world lung cancer screening cohort data (Aims 1 & 2).

E.5.2.a. Model design and analyses. We propose to adapt the previous UM-LCS model to real-world clinical settings by re-calibrating some model elements using data generated in Aims 1 and 2. Then, informed by the findings from Aims 1 and 2, our refined model will evaluate various measures for the benefits and harms of LCS under diverse screening scenarios. Our reference scenario will be annual LDCT screening of individuals ages 55 through 80 years who have smoked 30 pack- years and either currently smoke or quit smoking within 15 years (i.e., the USPSTF criteria[11]). We will compare the benefits and harms in diverse screening scenarios by varying starting and stopping ages, frequencies, and eligibility criteria based on smoking pack-years, years since quit, COPD status, and level of comorbidity. We will also assess the comparative effectiveness of various LDCT screening strategies according to level of smoking exposure, overall comorbidity, functional limitations and pulmonary/COPD status. And we will extend the UM-LCS model to incorporate complications observed in screened individuals. We will also determine the threshold of multimorbidity (co-existing conditions, limited functioning and/or impaired pulmonary function) where the benefits and harms of LCS are comparable to those for a pre-defined subgroup having average health status for the population.

E.5.2.b. Individual preferences analysis. Using a modified version of the UM-LCS model, we evaluated the impact of patient's preferences on expected individual quality-adjusted life-year gains (net-benefit) from LCS.[122] We will apply the methods in Caverly et al[122] to assess jointly the impact of individual preferences and comorbidities on the net benefit of LCS with LDCT based on real-world clinical settings.

E.6. Study timeline: The team will have monthly calls conference calls to discuss analyses, findings and manuscripts in addition to the annual in-person team meetings. We expect to complete all 3 aims during the 5-year study. **(Table 4).** Specifically, we anticipate applying for regulatory approvals from all study sites in the first year of the grant. Cohort development will begin in the second quarter of Year 1. We will assemble the real-world LCSC cohort and generate data inputs (from Aims 1 and 2) for the simulation model during the first three years of the project. Years 4-5 will largely focus on refining the CISNET simulation model (Aim 3) with real-world LCS cohort data.

Table 4: Timeline

	2020		2021		2022		2023		2024	
IRB subcontracts and regulatory approvals	x									
Retrospective/prospective cohort data collection	x	x	x	x	x	x				
Database development, pooling of data & linkages, Aims 1 and 2 analyses	x	x	x	x	x	x	x	x		
Simulation model refinement, literature review, Aim 3 analyses		x	x	x	x	x	x	x	x	x
Manuscript preparation					x	x	x	x	x	x

*Based on June 2019 grant submission; earliest start date of January 2020

E.7. Future directions: To help advance a vision of precision LCS tailored to patient-specific characteristics, our proposed study will **generate direct and previously unavailable evidence** about LCS with LDCT in real-world populations and settings. The urgency of this research is reflected in the current controversy over the likely net benefit of LCS among patients with chronic co-existing illness.[20] Our investigative team, with input from

patient advocates, will disseminate study findings to key stakeholders, which will lead to more informed decision-making for this vulnerable, yet sizable, LCS subpopulation. The CISNET model we propose to use has already informed the USPSTF guidelines in 2015.[60] By refining this model with the use of real-world data, we expect to extend our track record of helping to inform guideline development. Moreover, by **identifying subgroups of LCS candidates most and least likely to benefit from LCS**, our proposal speaks directly to the NCI's precision cancer screening initiative.[21]

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