ORIGINAL RESEARCH

Evaluating Pragmatism of Lung Cancer Screening Randomized Trials with the PRECIS-2 Tool

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Objective: **Lung cancer screening (LCS) implementation has been challenging for community and rural primary care settings. One contributing factor may be that the randomized clinical trials (RCTs) that form the evidence base are guided by explanatory methods not reflective of primary care settings. This study applied the PRagmatic Explanatory Continuum Indicator Summary (PRECIS - 2) tool to determine the pragmatism of LCS RCTs envisioned through a decentralized, primary care lens.**

Methods: **LCS RCTs were identified from efficacy meta-analyses, and the VA Demonstration Project was chosen as a nonrandomized multi-center comparator case. Two independent raters evaluated PRECIS-2 domains for each trial. Ratings were completed on a 5-point scale, where 1 indicated completely explanatory and 5 indicated completely pragmatic. Mean PRECIS-2 scores were calculated for each study and each domain. Descriptive information from raters' comments was used to describe differences between the most pragmatic and most explanatory RCTs.**

Results: **Eleven RCTs and the VA Demonstration Project were evaluated. Mean PRECIS-2 scores for each study ranged from 2.12 to 3.33, with the DLSCT rated the most explanatory and the Lung Screening Study and ITALUNG studies rated the most pragmatic. Six domains had a mean score <3, indicating more explanatory (eligibility, recruitment, setting, organization, staff flexibility, follow-up). The remaining 3 domains had mean scores >3, indicating more pragmatic (adherence, outcome, analysis).**

Discussion: **This approach of evaluating each study from a primary care lens demonstrated that LCS RCTs trended toward a more explanatory nature, incorporating considerable support and infrastructure that extend beyond the capacity of typical primary care settings in the US. (J Am Board Fam Med 2025;38:56–83.)**

Keywords: **Cancer Screening, Early Detection of Cancer, Implementation Science, Lung Cancer, Pragmatism, Preventive Health, Primary Health Care**

Introduction

Lung cancer screening (LCS) with low-dose CT (LDCT) has unparalleled potential to transform lung cancer outcomes and improve survival among high-risk individuals. When performed annually, LDCT reduced lung cancer specific mortality by approximately 20% relative to standard chest radiography.[1,2] Unfortunately, translation from clinical trial to real-world practice has been onerous and slow, hindered by multilevel barriers. Ten years

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after receiving a grade B recommendation by the US Preventive Services Task Force,[3] rates of LCS among eligible individuals have only reached 5.8% nationally[4] and sustained annual participation is extremely low at 22%,[5] starkly lower than >90% rates reported in large efficacy trials.[1,6]

The Centers for Medicare and Medicaid Services (CMS) mandated several LCS process requirements[7] that have impacted implementation in community, rural, and low-resource settings.[8,9] To meet these logistic requirements, organizational structures of LCS programs predominantly fall into 1 of 3 types: centralized, decentralized, or hybrid.[10] In a centralized model, the entire screening process, from identifying eligible individuals through a shared decision making visit, referral for LDCT, and results reporting and follow-up, is conducted by the program with limited primary care involvement. These types of programs typically have navigators or coordinators to facilitate the LCS process.[10] In a decentralized structure (the most common form of primary care in the US), the program only performs the LDCT and interpretation, with all other components completed by primary care/ordering clinician.[10] Hybrid programs use aspects of both centralized and decentralized programs.[10] Centralized program structure has been associated with improved adherence to LDCT follow-up recommendations and may help minimize racial disparities.[11,12] Unfortunately, centralization may be unrealistic for rural and low-resource settings with limited personnel and financial means.

Often the first-point of contact in the health care system, primary care has an important and increasing role in cancer screening and early detection.[13] Specific to LCS, the role of primary care is vitally important because clinicians must refer patients for LCS, and clinician recommendation is a leading factor for why individuals undergo LCS.[14] Common barriers for LCS in primary care include difficulty identifying eligible individuals, uncertainty of eligibility guidelines, and time constraints with competing health priorities.[15,16] Given both USPSTF and CMS guidelines are largely based on efficacy results of large randomized controlled trials (RCTs),[3,7] it is no surprise that processes required to received reimbursement for services are not particularly pragmatic in nature, leading to challenges with real-world application for primary care. To strengthen this evolving role, more emphasis must be placed on understanding how to support primary care's role in LCS.[17]

While it was vitally important to test the efficacy of LCS under ideal circumstances with RCTs, it is also essential to test the effects of LCS in usual care settings. Pragmatic clinical trials test interventions under real-world conditions to determine whether results generalize to a broader range of delivery settings and populations, emphasizing external validity.[18,19] This contrasts with efficacy-focused trials, also termed explanatory trials, that exert greater control over trial variables, delivery settings, and populations to test whether an intervention works under ideal conditions, placing a greater emphasis on internal validity.[18,19] The design of the clinical trial is determined by the desired outcome, although clinical trials are rarely exclusively explanatory or pragmatic.[19] The Pragmatic Explanatory Continuum Indicator Summary (PRECIS-2) tool was developed by multiple invested partners, including clinical trialists, clinicians, policy makers and the public, to guide trial planning and use appropriate procedures and measures.[19] For example, if the research question asks whether the intervention studied will be effective across a breadth of settings and populations, then it should choose a study design that is more pragmatic than explanatory.[19]

Given the challenges implementing LCS in primary care to date,[15,16] the study goal was to determine whether existing LCS RCTs were more explanatory or pragmatic for primary care clinics, according to the PRECIS-2 tool. The premise was that identifying elements of trials that are more pragmatic may yield lessons for improving LCS implementation in primary care. Although the PRECIS and PRECIS-2 tools were initially developed for planning trials, they have also been used to assess the level of pragmatism of published trials.[20–22] Our specific aim was to use the PRECIS-2 tool to rate LCS RCTs that compared LDCT to a control arm, as envisioned through a decentralized, primary care lens. This perspective is important because this is a common model of LCS

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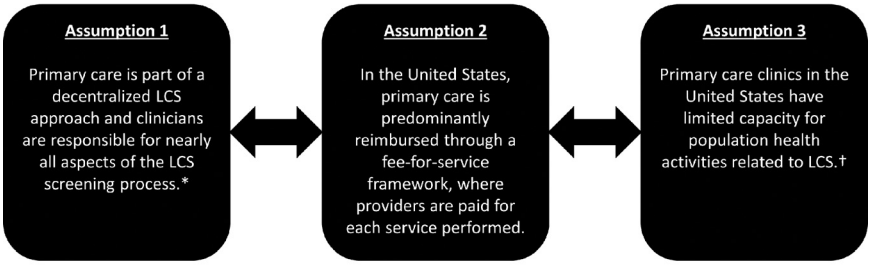
Figure 1. Assumptions of "usual care setting" for a decentralized, primary care perspective: Assumptions are based on the prevailing primary care infrastructure at the time of the rating process in 2022.[27,28] *Abbreviations:* LDCT, low-dose CT; LCS, Lung cancer screening; CMS, Centers for Medicare and Medicaid Services.



Notes: *Primary care is responsible for finding eligible candidates, performing shared-decision making and tobacco cessation counseling, and facilitating all necessary follow-up after the LDCT procedure, including the differential tracking/referral processes needed for individuals with no nodules, low-risk nodules and high-risk nodules. †Population health related activities includes identifying eligible patients for LCS apart from point-of-care visits,as well as challenges to complete the other CMS-specified steps of the LCS screening process in a systematic and timely manner.

delivery in the United States, particularly in rural areas, and primary care has reported the most challenges and barriers to LCS implementation.[8,9,15,16]

Methods

Selection of Studies Chosen for Rating

RCTs included in this study were identified from recent meta-analyses focused on evaluating the efficacy of LDCT screening on lung cancer and/or all-cause mortality,[23–25] including studies that offered a detailed randomization process and study procedures. Excluded studies lacked published data for the commonly reported PRECIS-2 domains of population, setting, outcomes, and analysis. Given the population health focus, the VA Demonstration Project (VADP) was selected as a non-RCT multi-center comparator case that initiated screening following the publication of National Lung Screening Trial (NLST) results.[26]

Assumptions of LCS within Primary Care

PRECIS-2 was developed as a rating scale to assess the degree to which a trial is more explanatory or pragmatic across 9 domains: 1) eligibility, 2) recruitment, 3) setting, 4) organization, 5) flexibility of delivery, 6) flexibility of adherence, 7) follow-up, 8) primary outcome, and 9) primary analysis.[19] Each domain has relevance and contributes to the overall PRECIS-2 score. To rate the PRECIS-2 domains in a standardized fashion, raters need clarification of what a "usual-care setting" is able to accomplish, as described by Luoma et al[20] Based on our decentralized primary care perspective, the research team of primary care clinicians, LCS experts, and health services researchers reached consensus on the assumptions, shown in Figure 1, of usual primary care capacity to guide PRECIS-2 ratings.[27,28]

Development of Rating Checklist and Data Collection

Each RCT meeting eligibility criteria was rated across all 9 PRECIS-2 domains on a 5-point Likert scale, where 1 indicated completely explanatory, 3 indicated equally explanatory and pragmatic, and 5 indicated completely pragmatic. A complete description of the PRECIS-2 tool and domains are available elsewhere.[19] We adapted a rating tool used to evaluate PRECIS-2 in a prior review.[20] This tool included relevant LCS information for each PRECIS-2 domain to consider about a decentralized primary care approach, according to the 3 assumptions of LCS within primary care (Figure 1). The aspects of each PRECIS-2 domain that make it more pragmatic or explanatory are briefly described in Table 1, with the complete rating tool included as Appendix 1.

The PRECIS-2 tool has been shown to have good interrater reliability and face validity,[29] and consistent with prior use of PRECIS-2 for retrospective RCT analysis, 2 raters independently rated each included RCT and a third rater was used for arbitration, if necessary.[20–22] Raters had expertise in

Table 1. Description and Rating Anchors for Each PRECIS-2 Domain*

PRECIS-2 Domain	Domain Description*	Completely Explanatory (PRECIS-2 anchor = 1)	Equally Explanatory/ Pragmatic (PRECIS-2 anchor = 3)	Completely Pragmatic (PRECIS-2 anchor = 5)
1) Eligibility Criteria	Who is selected to participate in the trial?	Sample much more narrow than representative population (meets USPSTF or CMS guidelines)	Most "typical" participants included some exclusions that limit study population	Sample representative of population expected to receive intervention in usual care setting (meets USPSTF or CMS guidelines)
2) Recruitment Path	How are participants recruited in the trial?	General advertising without relevance to usual care population, recruitment requires extra effort	Some extra effort/ resources used to recruit beyond usual care	Participants recruited unobtrusively during clinic visits
3) Setting	Where is the trial being done?	Few or one clinical sites that are not at all representative of usual care site	More than one clinical sites that is partially representative of usual care	Multiple sites nearly identical to usual care
4) Organization	What expertise and resources are needed to deliver the intervention?	Intervention requires many extra hours of staff time or infrastructure	Intervention requires some extra time of infrastructure	Intervention integrated into usual care and requires no extra time or resources
5) Flexibility (delivery by staff)	How should the intervention be delivered?	Intervention is protocol-driven with extensive oversight from clinicians	Intervention allows flexibility at discretion of clinician	Intervention oversight and follow-up managed by clinician
6) Flexibility (adherence)	What measures are in place to make sure participants adhere to the intervention?	Close monitoring to maximize participant adherence	Few strategies to monitor and increase adherence	Methods to maximize adherence within realm of usual care (i.e., send reminders)
6) Follow-up	How closely are participants followed-up?	Frequent visits for data collection during intervention period	Some added visits for data collection during intervention	No additional visits than what would be completed in usual care
7) Primary Outcome	How relevant is it to participants?	Measures/terms collected not relatable to participants/society and requires additional training to measure	Measures/terms somewhat understandable to participants/society and can be assessed in usual care	Measures/terms understood by participants/society and easy to assess
8) Primary Analysis	To what extent are all data included?	Analysis excludes data from individuals with poor adherence or missing data ("per protocol analysis")	Data from all study participants included but rigor slightly reduced	Data from all participants included with imputation if needed

Abbreviations: CMS, Centers for medicare and medicaid services; PRECIS, PRagmatic Explanatory Continuum Indicator Summary.
*Domain descriptions are from Loudon, et al. *BMJ*, 2015.[19]

implementation science, primary care practice, and lung cancer screening. To standardize PRECIS-2 ratings, an initial rater calibration phase was used, as described by others.[20,21] During calibration, the tool was tested with 2 randomly selected RCTs by 2 raters that subsequently rated all trials (SZ and MM), and scores were then discussed and clarified with the greater study team before rating additional studies. Two raters (SZ and MM) then independently rated 2 or 3 studies at a time and participated in routine consensus meetings to discuss ratings and agree on a single score for each PRECIS-2 domain for each study. A third rater (EAH) arbitrated ratings as necessary through additional consensus meetings to discuss ratings and supporting text.

Data Analysis

Characteristics of trials included in this investigation were analyzed descriptively to provide information on each RCT study design, eligibility criteria, and descriptions of LDCT and control arms. For each study, the mean PRECIS-2 composite and a mean

Table 2. Characteristics of the Studies Included in the PRECIS-2 Ratings

Study	Country	Study Design	Eligibility Criteria Based on Smoking History	LDCT Arm Characteristics	Control Arm Characteristics	Number of Study Sites	Overall PRECIS-2 Score*
AME Thoracic Surgery Collaborative Group (AME)[31]	China	• 1:1 randomization • Control: No screening • LDCT frequency: Baseline and one biennial scan	• Ages: 45–70 • Smoking history: Minimum 20 pack years, current or quit within past 10 years. • Other: also enrolled based on additional risk factors, did not necessarily need smoking history	• n = 3,512 • Mean age (±SD): 59.9 (±5.8) • Female: 54% • Currently smoke: 21%	• n = 3,145 • Mean age (±SD): 59.7 (±5.8) • Female: 53% • Currently smoke: 22%	1 screening site	2.83 (±0.41)
DANTE[32]	Italy	• 1:1 randomization • Control: No additional follow-up • LDCT frequency: Baseline and four annual	• Age: 60–74 • Smoking history: Minimum 20 pack years, current or quit within past 10 years • Other: Only males included	• n = 1,264 • Mean age: 64.6 (SEM 0.14) • Female: 0% • Non-white: NR • Currently smoke: 56%	• n = 1,186 • Mean age: 64.6 (SEM 0.12) • Female: 0% • Non-white: NR • Currently smoke: 57%	3 cancer centers within same network	3.00 (±1.00)
DESPISCAN[33]	France	• 1:1 randomization • Control: Chest radiograph • LDCT frequency: Baseline and two annual	• Ages: 50 to 75 • Smoking history: ≥ 15 cigarettes per day for 20 years, current or quit within 15 years	• n = 385 • Median age (range): 56 (47 to 75) • Female: 29% • Non-white: NR • Currently smoke: 65%	• n = 380 • Median age (range): 56 (47 to 76) • Female: 30% • Non-white: NR • Currently smoke: 64%	14 centers	3.11 (±0.78)
Danish Lung Cancer Screening Trial (DLCST)[34]	Denmark	• 1:1 randomization • Control: No screening • LDCT frequency: Baseline and four annual	• Ages: 50–70 • Smoking history: Minimum 20 pack years, current or quit after age of 50 and less than 10 years prior	• n = 2,052 • Age over 65: 9% • Female: 45% • Non-White: NR • Currently smoke: 77%	• n = 2,052 • Age over 65: 9% • Female: 44% • Non-White: NR • Currently smoke: 75%	1 medical center	2.12 (±0.83)
ITALUNG[35]	Italy	• 1:1 randomization • Control: No screening • LDCT frequency: Baseline and three annual	• Ages: 55–69 • Smoking history: Minimum 20 pack years, current or quit within past 10 years	• n = 1,613 • Age over 65: 18% • Female: 36% • Currently smoke: 66%	• n = 1,593 • Age over 65: 19% • Female: 35% • Currently smoke: 64%	3 screening centers in same region	3.33 (±0.87)

Continued

Table 2. Continued

Study	Country	Study Design	Eligibility Criteria Based on Smoking History	LDCT Arm Characteristics	Control Arm Characteristics	Number of Study Sites	Overall PRECIS-2 Score*
Lung Screening Study (LSS)[36]	United States	• 1:1 randomization • Control: Chest radiograph • LDCT frequency: Baseline and one annual	• Ages: 55 to 74 • Smoking history: 30 pack-years and currently smoke or quit within past 10 years	• n = 1,660 • Age > 65: 32% • Female: 42% • Non-White: NR • Currently smoke: 58%	• n = 1,658 • Age ≥ 65: 32% • Female: 41%: • Non-White: NR • Currently smoke: 57%	6 cancer/medical centers	3.33 (±0.50)
German Lung Cancer Screening Intervention Trial (LUSI)[37]	Germany	• 1:1 randomization • Control: No screening • LDCT frequency: Baseline and four annual	• Age: 50–69 • Smoking history: 1) 25 cigarettes for 15 years or 2) 10 cigarettes for 30 years, must have quit within past 10 years	• n = 2,029 • Age over 65: 11% • Female: 35% • Non-White: NR • Currently smoke: 38%	• n = 2,023 • Age over 65: 11% • Female: 35% • Non-White: NR • Currently smoke: 38%	1 cancer research Center	2.86 (±1.07)
Multicentric Italian Lung Detection (MILD)[38]	Italy	• 1:1:1 randomization (biennial, annual, control) • Control: No screening • LDCT frequency: Baseline and five annual or baseline and three biennial	• Ages: 49–75 • Smoking history: Minimum 20 pack years, current or quit within past 10 years	• n (annual) = 1190 • n (biennial) = 1186 • Age >65 (annual): 15% • Age >65 (biennial): 15% • Female (annual): 32% • Female (biennial): 31% • Currently smoke (annual): 69% • Currently smoke (biennial): 68%	• n = 1,723 • Age >65: 13% • Female: 37% • Currently smoke: 90%	1 cancer institution	3.00 (±1.15)
Dutch-Belgian Randomized Lung Cancer Screening Trial (NELSON)[2]	Netherlands/ Belgium	• 1:1 randomization • Control: No screening • LDCT frequency: Baseline and follow-up at year 1, year 3. And year 5.5 (1 year, 2 years, and 2.5 year intervals	• Ages: Adult (not specified) • Smoking history: 1) 15 cigarettes/day for 25 years or 2) 10 cigarettes/day for 30 years, current or quit within past 10 years	• n = 7,900 • Age ≥ 65: 17% • Female: 17% • Currently smoke: 56%	• n = 7,892 • Age ≥ 65: 17% • Female: 16% • Currently smoke: 55%	4 screening centers	2.78 (±0.44)
National Lung Screening Trial (NLST)[1]	United States	• 1:1 randomization • Control: Chest radiograph • LDCT frequency: Baseline and two annual	• Age: 55 to 74 • Smoking history: Minimum 30 pack years, current or quit within past 15 years	• n = 26,722 • Age ≥ 65: 27% • Female: 41% • Currently smoke: 48%	• n = 26,732 • Age ≥ 65: 27% • Female: 41% • Currently smoke: 52%	33 screening centers	3.11 (±0.78)

Continued

Table 2. Continued

Study	Country	Study Design	Eligibility Criteria Based on Smoking History	LDCT Arm Characteristics	Control Arm Characteristics	Number of Study Sites	Overall PRECIS-2 Score*
UK Lung Cancer Screening (UKLS)[39]	United Kingdom	• 1:1 randomization • Control: No screening • LDCT frequency: based on work-up protocol	• Ages: 50 to 75 • Other: 5-year lung cancer risk of ≥5%, calculated by Liverpool Lung Project	• n = 2,028 • Mean age (S.D.): 67.1 (4.1) • Female: 25% • Currently smoke: 38%	• n = 2,027 • Mean age (SD): 66.9 (4.1) • Female: 26% • Currently smoke: 39%	2 hospitals	2.55 (±0.53)
VA Demonstration Project[26]	United States	N/A†	• Age: 55 to 80 • Smoking history: Minimum 30 pack year, current or quit within 15 years	• n = 2,106 • Mean Age (SD): 64.9 (5.1) • Female: 4% • Currently smoke: 57%	N/A†	8 sites affiliated with academic medical centers	3.00 (±1.19)

*PRECIS-2 ratings are presented as mean (±standard deviation). Each rating anchor was developed for the decentralized primary care lens.
†Study design and control arm characteristics are not available for the VA Demonstration Project because it is not a randomized controlled trial.
Abbreviations: LDCT, low-dose computed tomography; PRECIS, PRagmatic Explanatory Continuum Indicator Summary; SD, standard deviation; SEM, standard error mean.

PRECIS-2 domain score average was calculated. We qualitatively compared characteristics of trials with composite scores and domain scores that were highly pragmatic and highly explanatory. Descriptive information from raters' comments was used to describe differences between the most pragmatic and most explanatory RCTs. This study is IRB exempt since it uses data available in published manuscripts.

Results

Selection of Studies

Recent meta-analyses identified 12 LCS RCTs that met the eligibility criterion of comparing LDCT to a comparator arm.[23–25] Of these 12 RCTs, 1 was excluded[30] due to insufficient published data to complete the PRECIS-2 ratings. Inclusion of the non-RCT comparator case (VADP[26]) left 12 studies available for review.[1,2,26,31–39] To better inform PRECIS-2 ratings, additional manuscripts containing information about study procedures were used when available (e-Table 1).

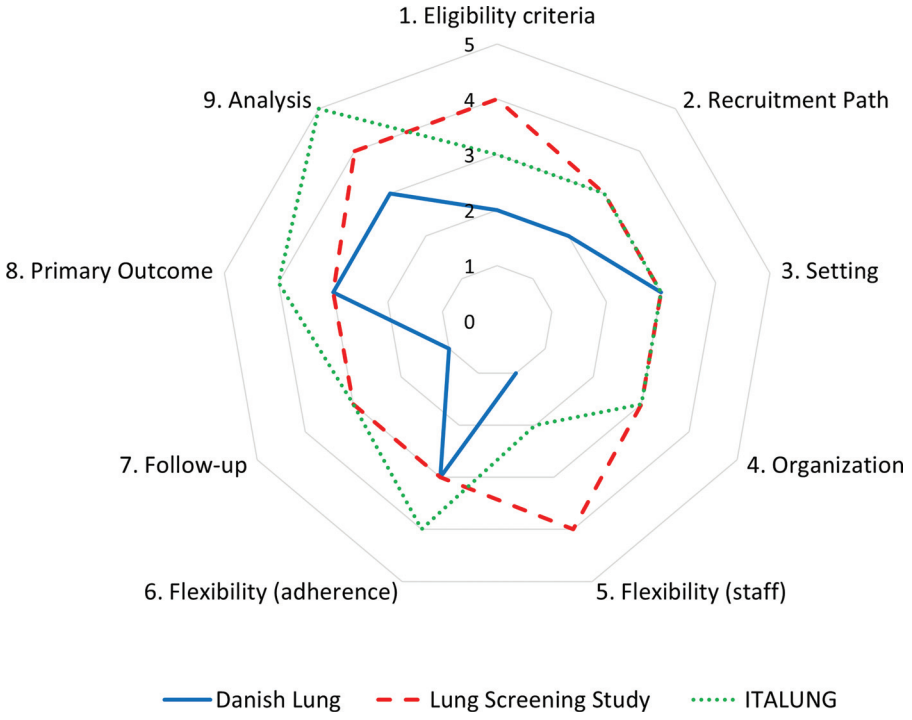
Characteristics of Included Studies

Characteristics of each study are presented in Table 2. Most studies (67%) were conducted in Europe, compared LDCT screening to no screening in the comparator arm, and completed screenings at multiple locations. Study procedures were predominantly completed at specialized hospitals affiliated with academic, research, or cancer centers. All studies included a minimum baseline and 1 annual LDCT screening in the comparator arm, except for the Chinese AME Thoracic Surgery Collaborative Group[31] that incorporated a baseline and 1 biennial LDCT. The Multicentric Italian Lung Detection (MILD)[38] study randomized to 2 separate intervention arms, 1 annual screening and 1 biennial screening. In addition, the Dutch-Belgian Randomized Lung Cancer Screening Trial (NELSON)[2] lengthened the frequency of screening over the study to intervals of 1 year, 2 years, and 2 and a half years (LDCTs performed at baseline, years 1, 3, and 5.5).

PRECIS-2 Ratings

The composite PRECIS-2 score for each study ranged from 2.12 to 3.33 (Table 2). The VADP[26] was rated as 3.00, similar in its ratings to other RCTs, despite its aim to enroll a more geographically diverse

Figure 2. Comparison of least and most pragmatic trials illustrated on the PRECIS-2 wheel: The Lung Screening Study and the ITALUNG trial were the most pragmatic studies, while the Danish Lung trial was the least pragmatic. The organization domain was unratable for the Danish Lung trial due to inadequate information available in manuscripts to complete a rating. *Abbreviation:* PRECIS, PRagmatic Explanatory Continuum Indicator Summary.



set of hospitals. Figure 2 illustrates the differences in each PRECIS-2 domain between the most explanatory trial, the Danish Lung Cancer Screening Trial (DLCST)[34] (mean PRECIS-2 score 2.12 (Standard Deviation (SD) ±0.83)) and the 2 most pragmatic trials, the Lung Screening Study (LSS)[36] (mean PRECIS-2 score 3.33 (±0.50)) and the ITALUNG study[35] (mean PRECIS-2 score 3.33 (±0.87)). Descriptive information and rationale for each domain of these 3 studies are presented in Table 3. The Danish Lung trial was rated as highly explanatory for several PRECIS-2 domains, including stricter exclusion criteria, infeasible primary care recruitment strategies, screening completion at a single center, and diagnostic follow-up that was highly protocol-driven. The LSS was rated as highly pragmatic in several PRECIS-2 domains, due to broader eligibility criteria that resembles current CMS guidelines, recruitment and study procedures completed across several sites, and primary care discretion for diagnostic follow-up of positive results. ITALUNG also had broader inclusion criteria, utilized multiple screening centers, and involved primary care in the recruitment and support for study participants, increasing adherence, as would be the case in clinical practice.

Composite mean PRECIS-2 scores for each domain for all eleven RCTs are illustrated on the PRECIS-2 wheel in Figure 3 (as a non-RCT the VADP[26] was excluded). Six domains had a mean score <3, indicating more explanatory, including eligibility (mean score = 2.91 (±0.83)), recruitment (mean score = 2.54 (±0.69)), setting (mean score = 2.50 (±0.97)), organization (mean score = 2.86 (±0.69)), staff flexibility (mean score = 2.62 (±2.92)), and follow-up (mean score = 2.72 (±0.65)). The remaining 3 domains had mean scores >3, indicating they were more pragmatic in nature, including adherence (mean score = 3.18 (±0.40)), outcome (mean score = 3.27 (±0.79)), and analysis (mean score = 3.54 (±0.9)). The spread of PRECIS-2 for each domain across the 12 studies are included in e-Figure 1; a 5 rating (completely pragmatic) was specified only 4 times across all 12 studies, once for primary outcome (DANTE study[32]) and 3 times for analysis (ITALUNG,[35] NLST,[1] and VADP[26] studies). Similarly, a 1 rating

Table 3. Comparison and Rationale for PRECIS-2 Ratings of Least and Most Pragmatic Randomized Controlled Trials

	Most Explanatory Trial (Danish Lung)		First Most Pragmatic Trial (Lung Screening Study)	
PRECIS-2 Domain	PRECIS-2 Rating	Description and Rationale for Domain Rating	PRECIS-2 Rating	Description and Rationale for Domain Rating
Eligibility criteria	2	• Age/Smoking History Inclusion: 50–70 years and minimum 20 pack year smoking history, currently smoke or quit within past 10 years. • Important exclusion: If formerly smokes, must have quit after age 50. • Rationale: Only including individuals through 70 years, having quit smoking within past 10 years, and must have quit smoking after age 50 excludes some typical LCS-eligible individuals.	4	• Age/Smoking History Inclusion: 55–74 and minimum of 30 pack year smoking history, currently smoke or quit within past 10 years. • Important exclusion: Participation in another cancer prevention trial • Rationale: Eligibility is slightly less inclusive of current LCS-eligible individuals by CMS guidelines, with added exclusion that does not match current eligibility.
Recruitment path	2	• Interested individuals responded to advertisements in regional newspaper and weeklies. • Rationale: Recruitment completed without relevance to LCS population, but didn't appear to utilize a lot of extra effort or incentive.	3	• Participants recruited from sites participating in the Prostate, Lung, Colon, and Ovarian screening trials. Recruitment through flyers and clinician recommendation. • Rationale: Recruitment completed at research centers with existing staff and partially recruited through clinician recommendation.
Setting	2	• Screening completed at one medical center. • Rationale: Only one screening site, however, appeared partially representative of usual care sites.	3	• Study completed at six academic or cancer centers with specialized resources. • Rationale: Most study sites are academic medical centers and not completely representative of usual care.
Organization	Not ratable	Adequate information not available in manuscripts to rate organization domain.	3	• Primary care involved in specialist referral for high-risk nodules. No tobacco cessation was incorporated in study. • Rationale: Primary care had discretion to follow and work-up positive, high-risk nodules, however, annual screening was considered a study procedure.
Flexibility (staff)	1	• Diagnostic follow-up was very specialized and protocol driven with no discretion for clinicians. • Rationale: No discretion for clinicians, especially primary care, for LDCT results follow-up and work-up	4	• Work up of positive results left to participants' medical team, although referrals and suggested diagnostic algorithms were provided if asked. • Rationale: Primary care had flexibility for work-up of positive LDCT results with suggested diagnostic algorithms available if needed.
Flexibility (adherence)	3	• Tobacco cessation was offered and annual visits with high adherence across all screening rounds. • Rationale: Annual study visits are not too burdensome and the same frequency as annual screening although study visits are more involved than a yearly LDCT.	3	• Yearly screening for negative scans, positive scans worked-up outside of study but research called to make sure at 4 and 8 weeks to make sure participants were being evaluated. • Rationale: Study personnel made a maximum of two phone calls to follow-up on individuals with positive results.
Follow-up	1	• Annual study visits with pulmonary function tests and additional data collection.	3	• Results were mailed to participants within 3 weeks of scan. Positive results were referred to primary care for diagnostic follow-up

Continued

Table 3. Continued

PRECIS-2 Domain	Most Explanatory Trial (Danish Lung)		First Most Pragmatic Trial (Lung Screening Study)	
	PRECIS-2 Rating	Description and Rationale for Domain Rating	PRECIS-2 Rating	Description and Rationale for Domain Rating
		• Rationale: Annual pulmonary function tests and data collection viewed as much more extensive compared to an annual LDCT.		although study teams made calls at 4 and 8 weeks to urge participants to receive follow-up. Study evaluated work-ups from medical record abstraction. • Rationale: Minimum follow-up on positive results as work-up was completed outside study. Additional data collection from medical record abstraction may require extra time and training for abstractors.
Primary outcome	3	• Primary outcome included a reduction of lung cancer specific mortality by 25% in the LDCT arm. • Rationale: While mortality reduction is easily understandable by participants and policy makers, this outcome is population health focused and hard to assess in usual care.	3	• Feasibility trial for the National Lung Screening Trial with primary goal of determining feasibility for accrual for larger LDCT trials. • Rationale: Primary outcome as a feasibility trial not completely understandable by LCS participants/society, however, is very relevant as this trial led to the much larger National Lung Screening Trial.
Analysis	3	• Study procedures appeared to include all data from all participants in the analysis, but it remained unclear how data from participants that were lost to follow-up was handled. • Rationale: Analysis rigor reduced slightly due to lack of clarity around how participants lost to follow-up were treated in analysis.	4	• NCI responsible for scientific oversight and data analysis. Ran analyses with and without individuals that were later found to be ineligible (many due to participation in the PLCO trial). • Rationale: Primary analyses excluded individuals that were found to be ineligible after study enrollment and randomization, but included a secondary analysis with all enrolled participants and did not find any differences in results.

PRECIS-2 Domain	Second Most Pragmatic Trial (ITALUNG Study)	
	PRECIS-2 Rating	Description and Rationale for Domain Rating
Eligibility criteria	3	• Age/Smoking History Inclusion: 55–69 and minimum of 20 pack year smoking history, currently smoke or quit within past 10 years. • Important Exclusion: Quit smoking >10 years prior (if formerly smoked), prior cancer history (except non-melanoma skin), general conditions precluding thoracic surgery. • Rationale: Eligibility is less inclusive of current LCS-eligible individuals by CMS guidelines, but includes most typical LCS eligible individuals.
Recruitment path	3	• Participants recruited through letters sent to residents aged 55–69 and lived in three regions where the screening centers were located and were registered with general practitioners involved with the trial. • Rationale: Recruitment matched age eligibility and linked with primary care, however, was completed by mass mailing that required extra personnel time.
Setting	3	• Study completed at three screening centers in the Tuscany region of Italy with a single coordinating center. • Rationale: Study sites affiliated with a Cancer Prevention Research center and not completely representative of usual care.
Organization	3	• Primary care counseled and enrolled participants in study and supported them to follow the study protocol. Tobacco cessation incorporated in study.

Continued

Table 3. Continued

PRECIS-2 Domain		Second Most Pragmatic Trial (ITALUNG Study)
		• Rationale: Primary care involved through direct contact with study participants and required some additional staff time beyond usual care.
Flexibility (staff)	2	• Although primary care was involved for support, LDCT diagnostic follow-up was protocol-driven. • Rationale: Explanatory because follow-up of positive and negative LDCT results was protocol driven with minimum discretion for primary care.
Flexibility (adherence)	4	• Study participants with negative results "invited" to three additional rounds of screening and participants with positive results followed work-up protocol with assumed support from primary care. • Rationale: "Inviting" participants to follow-up rounds and procedures with support from primary care was considered as encouragement for participants to comply.
Follow-up	3	• Negative results were mailed to participants within 3 weeks of LDCT. Positive results conveyed by phone call from screening center with follow-up from a pulmonologist. Sputum collected at baseline and after positive result. Information on control arm collected with annual interviews of participant/primary care clinician and cancer registry matches. • Rationale: LDCT follow-up was completed by protocol that was considered standard of care. Sputum collection and control arm interviews require additional time.
Primary outcome	4	• Primary outcome was to contribute to the evaluation of LDCT efficacy to lower lung cancer specific and all-cause mortality as part of the larger European Initiative. • Rationale: Primary outcome is relevant for participants and policy makers and was intended to be pooled with additional European studies for a population health level mortality reduction.
Analysis	5	• All analyses performed with intention-to-treat principle, study 'drop-outs' were included in the active (LDCT) arm. • Rationale: Data from all individuals were included in all analyses and manuscripts included information about how exclusions were included.

Abbreviations: CMS, Centers for medicare and medicaid services; LCS, lung cancer screening; LDCT, low-dose computed tomography; NCI, National Cancer Institute; PRECIS, PRagmatic Explanatory Continuum Indicator Summary.

Figure 3. Composite ratings of PRECIS-2 domains: Composite ratings were calculated by averaging the domain score for each randomized controlled trial. If a domain was unratable the score was averaged over the number of studies with available rating data. *Abbreviation:* PRECIS, PRagmatic Explanatory Continuum Indicator Summary.

Table 4. Mean Scores, Number of un-Ratable Domains, Number of Domains Requiring Consensus and Arbitration*

PRECIS-2 Domain	Mean Score* (± SD)	Number of Studies with Domains Not Ratable	Number of Studies Where Scoring Required a Consensus between an Explanatory (<3) or Pragmatic (>3) or If un-Ratable†	Number of Studies Where Scoring Required Arbitration by a Third Reviewer (EAH)
Eligibility criteria	2.91 (±0.83)	0/12 (0%)	2/12 (17%)	1/12 (8%)
Recruitment path	2.54 (±0.69)	0/12 (0%)	1/12 (8%)	0/12 (0%)
Setting	2.50 (±0.97)	1/12 (8%)	2/12 (17%)	0/11 (0%)
Organization	2.86 (±0.69)	4/12 (33%)	4/12 (33%)	0/12 (0%)
Flexibility (staff)	2.62 (±0.92)	3/12 (25%)	4/12 (33%)	2/12 (17%)
Flexibility (adherence)	3.18 (±0.40)	0/12 (0%)	4/12 (33%)	0/12 (0%)
Follow-up	2.73 (±0.65)	1/12 (8%)	3/12 (25%)	1/12 (8%)
Primary outcome	3.27 (±0.79)	0/12 (0%)	4/12 (33%)	0/12 (0%)
Analysis	3.54 (±0.93)	0/12 (0%)	1/12 (8%)	1/12 (8%)

Abbreviation: PRECIS, PRagmatic Explanatory Continuum Indicator Summary.
*Mean ratings were calculated by averaging the domain score for each randomized controlled trial. If a domain was un-ratable the score was averaged over the number of studies with available rating data.
*PRECIS-2 ratings are presented as mean (±standard deviation).
†Consensus was reached between two primary raters (SZ and MM).

(completely explanatory) was given 5 times, twice each in the setting (German Lung Cancer Screening Intervention Trial[37] and MILD[38] studies) and flexibility for delivery by staff (DLCST[34] and VA[26] studies) domains and once in the follow-up domain (DLCST[34]). Four PRECIS-2 domains (setting, organization, flexibility (adherence), and follow-up) could not be rated for several studies due to limited information available in study manuscripts (Table 4). Disagreements between pragmatic score (>3) and explanatory scores (<3) or determining if at least 1 domain was unratable occurred for 33% of studies, and consensus was generally achieved between SZ and MM; arbitration by a third reviewer (EAH) was needed for 17% of domains across all 12 studies (Table 4).

Discussion

The PRECIS-2 tool[19] facilitated retrospective evaluation of eleven LCS RCTs and the VADP to evaluate trials on the explanatory to pragmatic continuum, with the goal of identifying pragmatic aspects that could help improve and sustain future primary care implementation. Through this assessment, results revealed the overall mean PRECIS-2 score for each published RCT and the VADP tended to be middle of the road at approximately 2.0 to 3.0 but leaned more toward explanatory than pragmatic. This approach of evaluating each study from a primary care lens demonstrated that these studies included considerable supports and infrastructure that were not very pragmatic – and thus likely go beyond the capacity of typical primary care teams in the US.

These findings broaden the body of knowledge that provide insight on how best to support and guide collaborative partnerships between primary care and LCS programs. Similar to the domains that our analysis scored as most "explanatory" (and less pragmatic/real-world) in this study (eg, recruitment, setting, organization, staff flexibility, and follow-up), relate to others' work (qualitative interview studies) that found primary care clinician or physician lack adequate workflows for candidate identification, referrals, shared decision making, ordering, results follow-up, and providing educational and outreach opportunities.[40,41] Importantly, primary care clinicians are at the forefront of LCS adoption,[15] and using implementation frameworks and cocreation approaches[42] where primary care champions and practices can work with LCS programs in different contexts to develop and test alternate clinic workflows and other implementation strategies to support clinician teams will serve to improve screening in diverse health care settings.

Certain PRECIS-2 domains tended to be more explanatory and less "real-world" than others. This sheds light on areas that future trials could

consider to enhance external validity and inform implementation. For example, the DLCST[34] was rated completely explanatory in the flexibility (delivery by staff) and follow-up domains due to the rigidity of the study protocol for diagnostic pulmonary nodule work-up and the lack of primary care involvement. On the contrary, both the LSS[36] and ITALUNG[35] involved primary care for recruitment and support of study procedures and were rated as more pragmatic. Another notable reason Danish Lung[34] was rated more explanatory was restricted study eligibility by excluding individuals that had quit smoking before the age of 50, making the study population much narrower than current CMS eligibility.[7]

Evidence prompting the US to move LCS into clinical practice was primarily based on the NLST and subsequently adjusted following publication of the NELSON trial, that detected a 20% and 24% (for men) relative reduction in lung cancer mortality, respectively.[1,2] Thus, it is particularly important to consider areas that were more explanatory for these trials, as they highlight discrepancies between approach in the trial, the general populations served, and the supports available in primary care settings. Specifically, study clinicians often managed the diagnostic referral and work-up process for high-risk nodules. The NLST had a mean PRECIS-2 rating of 3.11 and NELSON was slightly more explanatory with a mean rating of 2.78. NLST has been the largest RCT to date with the highest number of screening centers (53,454 individuals participated at 33 centers)[1] contributing to the pragmatism and generalizability of the study; however, NLST enrolled a population that is younger, healthier, and less racially/ethnically diverse than the greater LCS-eligible population.[43] Other explanatory elements of the NLST included a set protocol for pulmonary nodule management with limited primary care involvement across the organization, flexibility (staff), and flexibility (adherence) domains. The second largest study (NELSON; n = 15,792) included individuals screened at 4 centers; however, only 17% of the enrolled population were women,[2] highlighting one study weakness since the incidence of lung cancer is increasing in women across Europe.[44] NELSON also had minimal primary care involvement for the diagnostic referral process for high-risk nodules.

Across all RCTs, the 2 least pragmatic PRECIS-2 domains were setting (mean score = 2.50) and recruitment path (mean score = 2.54), while the 2 most pragmatic domains were primary outcome and analysis, with mean scores of 3.27 and 3.54, respectively. Most (9/11 RCTs[1,2,32,34–39] and the VADP[26]) conducted study procedures at specialized centers affiliated with academic, research, or cancer centers and limited the involvement of primary care, decreasing the pragmatism of the setting domain. Recruitment for European studies was completed primarily through broad advertising, which bypassed the need to identify eligible individuals in a primary care setting. The majority (8/11) of RCT primary outcomes were focused on the efficacy of LDCT to detect early-stage cancer and reduce mortality,[1,2,31,32,34,35,37,38] while the remaining RCTs focused on outcomes relevant for feasibility of a larger trial,[33,36,39] such as ease of recruitment and cost-effectiveness. Primary analysis was the most pragmatic domain; none of the studies excluded data from analyses due to poor adherence and all identified missing data. Importantly, the 2 most pragmatic domains are not components of contextual factors that influence implementation and sustainability for primary care.[45]

It is also informative to consider how determinants of implementation relate to these findings. The Practical, Robust Implementation and Sustainability Model (PRISM) specifies key contextual factors that influence implementation outcomes, such as reach to patients and adoption/sustainment by clinics, as specified in the RE-AIM framework.[45] This approach is relevant to current endeavors to scale LCS, as shown by the efforts of the American College of Chest Physicians and the American Thoracic Society to develop a collaborative implementation guide for high-quality lung cancer screening based on the RE-AIM implementation framework.[46] Aligning these findings with PRISM allows researchers to consider how domains rated more explanatory by PRECIS-2 associate with known implementation challenges.[45] PRISM determinants of implementation success include: perceptions of LCS by staff/patients, characteristics of staff/patients; policy/funding environment, and the clinic implementation and sustainability infrastructure which may be considered as the supports needed to deliver LCS from patient identification to follow-up of LDCT findings. In this PRECIS-2 analysis, the least pragmatic domain (setting) reflects the *characteristics of clinics* in PRISM and reveals a large gap between the setting of trials (academic and research) and the variety of settings represented by primary care. The eligibility domain reflects the

characteristics of LCS participants from PRISM, also revealing the difference between trial participants and individuals eligible per recommended guidelines, with particular underrepresentation of women and nonwhite participants.[2,32] PRISM also posits that intervention implementation and sustainability is influenced by organizational infrastructure as reflected by recruitment, organization, and both flexibility domains in this analysis. With limited primary care involvement across many RCTs, these domains had mean PRECIS-2 ratings between 2.54 – 3.18, indicating trials are not wholly representative of usual primary care.

This PRECIS-2 analysis provided an innovative approach to describe the pragmatism of RCTs that form the LCS evidence base, and to the best of our knowledge, is the first application of an implementation framework to rate generalizability. This is important because these critical trials that have directly contributed to policy formation in the US and worldwide[1,2] were planned and defined as efficacy trials, emphasizing internal validity with limited priority allocated external validity and pragmatic outcomes. Despite this important perspective, assumptions and perspectives regarding fee-for-service primary care settings for these ratings is also a limitation, as it does not wholly encompass LCS implementation completed through centralized or hybrid program structures in the US or implementation of LCS in other countries. PRECIS-2 ratings from a centralized structure lens in the US would likely be rated as more pragmatic, particularly for organizational infrastructure elements. Importantly, only 3 of the studies included in this analysis were conducted in the US, and differences in country health care infrastructure, workforce, and data systems will affect how other countries implement LCS. Differences in contextual factors could also result in how PRECIS-2 domains would be rated in diverse implementation environments. Another study limitation involved the modest number of trials available for evaluation; and of these, all were feasibility and efficacy trials, limiting the breadth of data available for this analysis. Finally, this analysis used 2 raters to independently rate each RCT; while this is consistent with others' use of PRECIS-2 to retrospectively rate studies,[20–22] additional raters may have limited the need for arbitration across some domains.

In summary, this analysis found components of LCS RCTs and the VADP have a balance of explanatory and pragmatic elements when evaluated through a decentralized, primary care lens. Aspects of the trials that were rated most pragmatic, the primary outcome and analysis domains, are not directly related to intervention characteristics or strategies that influence implementation.[45] These findings suggest a need to further study feasible implementation strategies to build capacity within primary care clinics to implement LCS, with attention to the PRECIS-2 domains that were more explanatory, particularly the recruitment and organization aspects that align with components of PRISM that influence successful implementation and sustainment of interventions in clinical settings. This is particularly important for low-resource and community LCS programs that often have even more limited staff/system supports than "typical" primary care.[15,16] Future research and funding should prioritize pragmatic clinical trials to develop and test implementation strategies developed in partnership with primary care clinicians, teams, and communities. Cocreation of implementation approaches[42] with primary care may enhance the overall LCS adoption and reach, ultimately increasing participation and transforming survivorship.

E.A.H. is the guarantor of the paper and assumes full responsibility for the integrity of the submission, from inception to published article. E.A.H. takes responsibility for the integrity of the data and the accuracy of the data analysis. A.G.H and J.L.S. made substantial contributions to study conception, design, data interpretation, and writing of the manuscript. S.Z. and M.M. made substantial contributions to the study design, data collection, and writing of the manuscript. All authors read and approved the final manuscript.

To see this article online, please go to: http://jabfm.org/content/38/1/56.full.

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e-Table 1. Complete List of Manuscripts Provided to Raters for Each Included Study

Study	Manuscripts Provided for PRECIS-2 Ratings
AME Thoracic Surgery Collaborative Group (AME)	1. Yang W, Qian F, Teng J, et al. Community-based lung cancer screening with low-dose CT in China: Results of the baseline screening. Lung Cancer. 2018;117:20 to 26. doi:10.1016/j.lungcan.2018.01.003
DANTE	1. Infante M, Lutman FR, Cavuto S, et al. Lung cancer screening with spiral CT: baseline results of the randomized DANTE trial. Lung Cancer. 2008;59(3):355 to 363. doi:10.1016/j.lungcan.2007.08.040. 2. Infante M, Cavuto S, Lutman FR, et al. A randomized study of lung cancer screening with spiral computed tomography: three-year results from the DANTE trial. Am J Respir Crit Care Med. 2009;180(5):445 to 453. doi:10.1164/rccm.200901-0076°C. 3. Infante M, Cavuto S, Lutman FR, et al. Long-Term Follow-up Results of the DANTE Trial, a Randomized Study of Lung Cancer Screening with Spiral Computed Tomography. Am J Respir Crit Care Med. 2015;191(10):1166 to 1175. doi:10.1164/rccm.201408-1475°C.
DEPISCAN	1. Blanchon T, Bréchot JM, Grenier PA, et al. Baseline results of the Depiscan study: a French randomized pilot trial of lung cancer screening comparing low dose CT scan (LDCT) and chest Radiograph (CXR). Lung Cancer. 2007;58 (1):50 to 58. doi:10.1016/j.lungcan.2007.05.009.
Danish Lung Cancer Screening Trial (DLCST)	1. Pedersen JH, Ashraf H, Dirksen A, et al. The Danish randomized lung cancer CT screening trial–overall design and results of the prevalence round. J Thorac Oncol. 2009;4(5):608 to 614. doi:10.1097/JTO.0b013e3181a0d98f. 2. Saghir Z, Dirksen A, Ashraf H, et al. CT screening for lung cancer brings forward early disease. The randomized Danish Lung Cancer Screening Trial: status after five annual screening rounds with low-dose CT. Thorax. 2012;67 (4):296 to 301. doi:10.1136/thoraxjnl-2011 to 200736. 3. Wille MM, Dirksen A, Ashraf H, et al. Results of the Randomized Danish Lung Cancer Screening Trial with Focus on High-Risk Profiling. Am J Respir Crit Care Med. 2016;193(5):542 to 551. doi:10.1164/rccm.201505-1040°C
ITALUNG	1. Wille MM, Dirksen A, Ashraf H, et al. Results of the Randomized Danish Lung Cancer Screening Trial with Focus on High-Risk Profiling. Am J Respir Crit Care Med. 2016;193(5):542 to 551. doi:10.1164/rccm.201505-1040°C. 2. Lopes Pegna A, Picozzi G, Falaschi F, et al. Four-year results of low-dose CT screening and nodule management in the ITALUNG trial. J Thorac Oncol. 2013;8(7):866 to 875. doi:10.1097/JTO.0b013e31828f68d6. 3. Paci E, Puliti D, Lopes Pegna A, et al. Mortality, survival and incidence rates in the ITALUNG randomized lung cancer screening trial. Thorax. 2017;72 (9):825 to 831. doi:10.1136/thoraxjnl-2016 to 209825.
Lung Screening Study (LSS)	1. Gohagan J, Marcus P, Fagerstrom R, et al. Baseline findings of a randomized feasibility trial of lung cancer screening with spiral CT scan vs chest radiograph: the Lung Screening Study of the National Cancer Institute. Chest. 2004;126(1):114 to 121. doi:10.1378/chest.126.1.114. 2. Gohagan JK, Marcus PM, Fagerstrom RM, et al. Final results of the Lung Screening Study, a randomized feasibility study of spiral CT versus chest Radiograph screening for lung cancer. Lung Cancer. 2005;47(1):9 to 15. doi:10.1016/j.lungcan.2004.06.007. 3. Doroudi M, Pinsky PF, Marcus PM. Lung Cancer Mortality in the Lung Screening Study Feasibility Trial. JNCI Cancer Spectr. 2018;2(3):pky042. Published 2018 Sep 18. doi:10.1093/jncics/pky042.
German Lung Cancer Screening Intervention Trial (LUSI)	1. Becker N, Motsch E, Gross ML, et al. Randomized study on early detection of lung cancer with MSCT in Germany: study design and results of the first screening round. J Cancer Res Clin Oncol. 2012;138(9):1475 to 1486. doi:10.1007/s00432-012-1228-9. 2. Becker N, Motsch E, Gross ML, et al. Randomized Study on Early Detection of Lung Cancer with MSCT in Germany: Results of the First 3 Years of Follow-up After Randomization. J Thorac Oncol. 2015;10(6):890 to 896. doi:10.1097/JTO.0000000000000530. 3. Becker N, Motsch E, Trotter A, et al. Lung cancer mortality reduction by LDCT screening-Results from the randomized German LUSI trial. Int J Cancer. 2020;146(6):1503 to 1513. doi:10.1002/ijc.32486.
Multicentric Italian Lung Detection (MILD)	1. Pastorino U, Rossi M, Rosato V, et al. Annual or biennial CT screening versus observation in heavy smokers: 5-year results of the MILD trial. Eur J Cancer Prev. 2012;21(3):308 to 315. doi:10.1097/CEJ.0b013e328351e1b6. 2. Pastorino U, Silva M, Sestini S, et al. Prolonged lung cancer screening reduced 10-year mortality in the MILD trial: new confirmation of lung cancer screening efficacy. Ann Oncol. 2019;30(10):1672. doi:10.1093/annonc/mdz169.

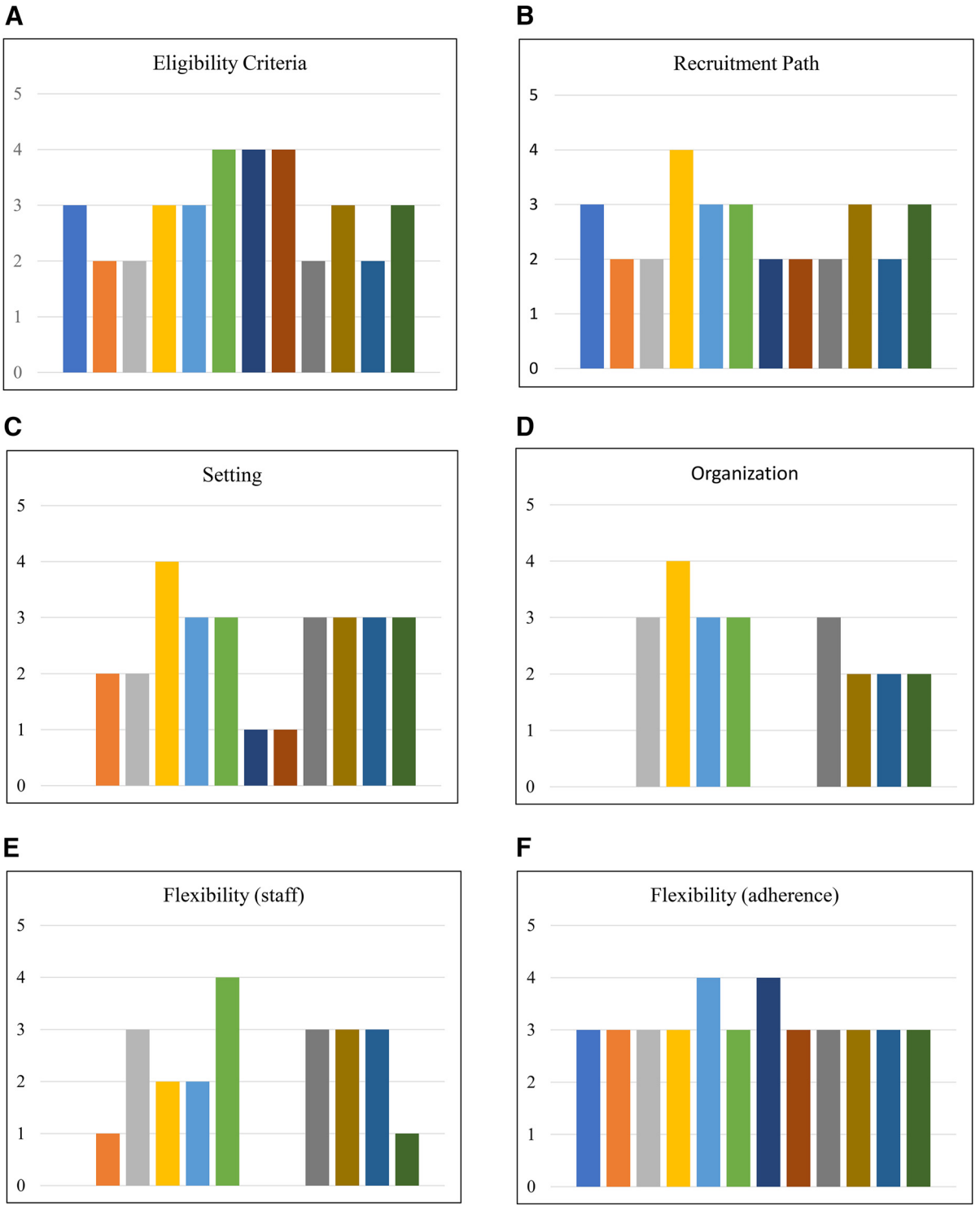
Continued

e-Table 1. Continued

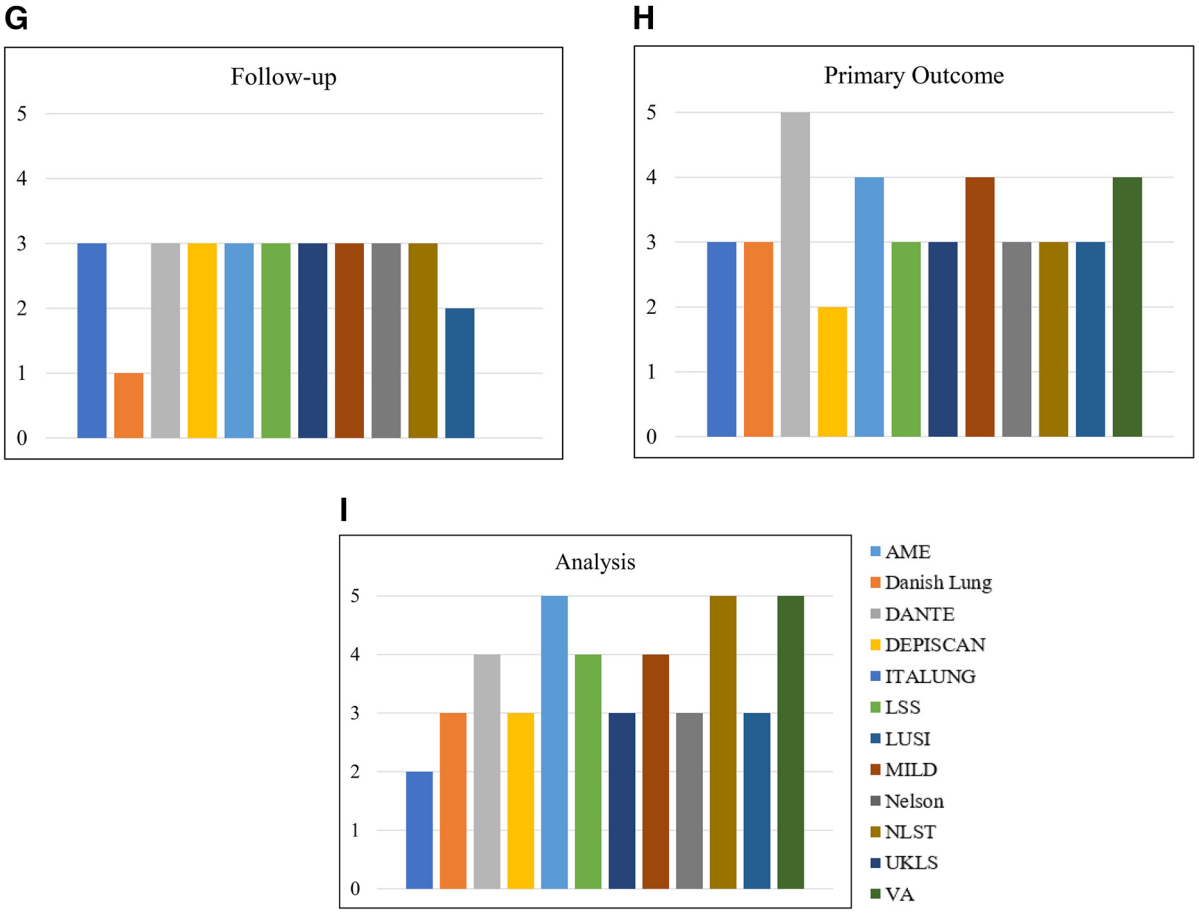
Study	Manuscripts Provided for PRECIS-2 Ratings
Dutch-Belgian Randomized Lung Cancer Screening Trial (NELSON)	1. van Iersel CA, de Koning HJ, Draisma G, et al. Risk-based selection from the general population in a screening trial: selection criteria, recruitment and power for the Dutch-Belgian randomized lung cancer multi-slice CT screening trial (NELSON). Int J Cancer. 2007;120(4):868 to 874. doi:10.1002/ijc.22134. 2. Ru Zhao Y, Xie X, de Koning HJ, Mali WP, Vliegenthart R, Oudkerk M. NELSON lung cancer screening study. Cancer Imaging. 2011;11 Spec No A (1A):S79-S84. Published 2011 Oct 3. doi:10.1102/1470 to 7330.2011.9020. 3. Yousaf-Khan U, van der Aalst C, de Jong PA, et al. Final screening round of the NELSON lung cancer screening trial: the effect of a 2.5-year screening interval. Thorax. 2017;72(1):48 to 56. doi:10.1136/thoraxjnl-2016 to 208655. 4. de Koning HJ, van der Aalst CM, de Jong PA, et al. Reduced Lung-Cancer Mortality with Volume CT Screening in a Randomized Trial. N Engl J Med. 2020;382(6):503 to 513. doi:10.1056/NEJMoa1911793
National Lung Screening Trial (NLST)	1. National Lung Screening Trial Research Team, Aberle DR, Adams AM, et al. Baseline characteristics of participants in the randomized national lung screening trial [published correction appears in J Natl Cancer Inst. 2011 Oct 19;103(20):1560]. J Natl Cancer Inst. 2010;102(23):1771 to 1779. doi:10.1093/jnci/djq434. 2. National Lung Screening Trial Research Team, Aberle DR, Berg CD, et al. The National Lung Screening Trial: overview and study design. Radiology. 2011;258(1):243 to 253. doi:10.1148/radiol.10091808. 3. National Lung Screening Trial Research Team, Aberle DR, Adams AM, et al. Reduced lung-cancer mortality with low-dose computed tomographic screening. N Engl J Med. 2011;365(5):395 to 409. doi:10.1056/NEJMoa1102873. 4. Aberle DR, DeMello S, Berg CD, et al. Results of the two incidence screenings in the National Lung Screening Trial. N Engl J Med. 2013;369(10):920 to 931. doi:10.1056/NEJMoa1208962.
UK Lung Cancer Screening (UKLS)	1. Field JK, Duffy SW, Baldwin DR, et al. UK Lung Cancer RCT Pilot Screening Trial: baseline findings from the screening arm provide evidence for the potential implementation of lung cancer screening. Thorax. 2016;71(2):161 to 170. doi:10.1136/thoraxjnl-2015 to 207140. 2. Field JK, Duffy SW, Baldwin DR, et al. The UK Lung Cancer Screening Trial: a pilot randomized controlled trial of low-dose computed tomography screening for the early detection of lung cancer. Health Technol Assess. 2016;20(40):1 to 146. doi:10.3310/hta20400. 3. Brain K, Lifford KJ, Carter B, et al. Long-term psychosocial outcomes of low-dose CT screening: results of the UK Lung Cancer Screening randomized controlled trial. Thorax. 2016;71(11):996 to 1005. doi:10.1136/thoraxjnl-2016 to 208283.
VA Demonstration Project	1. Kinsinger LS, Anderson C, Kim J, et al. Implementation of Lung Cancer Screening in the Veterans Health Administration. JAMA Intern Med. 2017;177(3):399 to 406. doi:10.1001/jamainternmed.2016.9022.

Abbreviation: PRECIS, PRagmatic Explanatory Continuum Indicator Summary.

e-Figure 1. *Spread of PRECIS-2 ratings over each domain. a) eligibility criteria, b) recruitment path, c) setting, d) organization, e) flexibility (delivery by staff), f) flexibility (adherence), g) follow-up, h) primary outcome, g) analysis. *If a domain was classified as unratable the study column is left empty on each chart. *Abbreviation:* PRECIS, PRagmatic Explanatory Continuum Indicator Summary.



e-Figure 1. Continued



Appendix 1

PRECIS-2 REVIEW OF LUNG CANCER SCREENING RANDOMIZED CONTROLLED TRIALS -- ABSTRACTION FORM, Version 9

REVIEWER NAME: _____ **DATE:** _____

Main Article PubMed ID: _____ **Lead Author** _____

Title: _____

Instructions:

1) Read "The PRECIS-2 tool: designing trials that are fit for purpose" by Loudon, et al (2015), and use it for reference while rating articles.

2) Have PRECIS-2 table in front of you, and use the PRECIS-2 website as a guide: https://www.precis-2.org/.
   5 = Completely pragmatic
   3 = Equally pragmatic and explanatory
   1 = Completely explanatory

3) Read the informational descriptions of the lung cancer screening process and rating exercise assumptions on page 2. For this rating checklist please assume that the lung cancer screening program is decentralized and primary care is responsible for all aspects of the screening process outside of performing and interpreting the CT scan.

4) Consider the information provided about real-world context regarding a primary care decentralized program when you are rating each PRECIS-2 domain.

5) Rate only on items reported in the provided items; please do not assume.

6) Use "NA" rating *only* when truly necessary, meaning truly "not applicable" (information for domain not included in rating materials).

7) If methods differ between intervention and control arm focus on rating the intervention arm as guided by the description of usual population and setting provided.

8) Use Comment section for any issues, concerns, or items worth highlighting.

The Lung Cancer Screening Process

The lung cancer screening (LCS) process is composed of several steps that are required for reimbursement by the Centers for Medicare and Medicaid Services (CMS). All steps are also highly recommended by the US Preventive Services Task Force.

1) Appropriate, high-risk candidates must be selected to maximize the effectiveness of screening.
2) LCS candidates should take part in a shared decision-making conversation prior to the baseline low dose CT to verify eligibility of the individual and to discuss the harms and benefits of screening. Additionally, tobacco cessation services or resources should be discussed and provided to screening eligible individuals that currently smoke cigarettes.
3) The CT scan is performed with a low radiation dose protocol and is ideally completed after shared decision-making is complete.
4) Appropriate follow-up procedures and timing will depend on the results of the CT scan.

Lung Cancer Screening PRECIS-2 Rating Exercise

For this PRECIS-2 rating please assume that the lung cancer screening program is decentralized and primary care is responsible for all aspects of the screening process outside of performing and interpreting the CT scan.

Assumptions:

1) **Primary care is part of a decentralized lung cancer screening program**. In a decentralized program, the program only performs the low dose CT and interpretation. Primary care is responsible for all other aspects of the screening process (finding eligible candidates, performing shared decision-making and tobacco cessation, and facilitating all necessary follow-up and next steps).[1]

    a. **Under this assumption, primary care refers all individuals that need further diagnostic work-up (positive CT results), however are responsible for following individuals that have recommended annual follow-up (negative CT results).**

2) **Primary care is predominantly reimbursed through a fee-for-service framework.** Fee-for-service is a payment model where providers are paid for each service performed; it is currently the most common payment model in the United States.[2]

3) **Primary care has limited capacity for population health activities.** In the primary care lung cancer screening context, this may mean that there are likely limited resources and staff available to complete the CMS specified steps in a systematic and timely manner.

[1] Lung cancer screening programs usually fit within one of three general categories: centralized, decentralized, or a hybrid structure. The structure of the program will depend on available resources, the type of institution and practice, and the skills and interests of the individual providers. More information is available from the American Thoracic Society and the American Lung Association: https://www.lungcancerscreeningguide.org/about-this-guide/program-structure/

[2] Thomas R. Health Insurance Systems An International Comparison, Academic Press, 2021.

1. **Eligibility Criteria** (exclusions, only include motivated) – the extent to which participants in the trial are similar to those who would potentially receive the intervention in the usual care setting.

Usual LCS eligible population for decentralized primary care:

- LCS programs should screen high-risk individuals as recommended by the US Preventive Services Task Force and/or the Centers for Medicare and Medicaid Services.
    - 50 – 77 years of age (USPSTF recommends screening through age 80). Prior to 2022 both CMS and USPSTF recommended starting screening at age 55.
    - Currently smoke cigarettes or have quit within the past 15 years.
    - Have a minimum of a 20-pack year cigarette smoking history. Prior to 2022, guidelines recommended a minimum of 30 pack years.

    Other criteria important for representative screening:

    - Represent variability in age, sex, gender, race, ethnicity, residence (urban/rural).
    - Ideally, limited co-morbidities that could limit life expectancy.
    - Individuals eligible for screening should not have symptoms suggestive of lung cancer.

5	4	3	2	1
Completely Pragmatic				Completely Explanatory
→Selection criteria highly inclusive of usual LCS population. →Systematic effort made to recruit sample representative of population setting expected to receive intervention in usual care setting		→Some exclusions →Selection criteria limit study population to an extent →Most "typical" participants included		→Stepwise selection criteria. →Restricted to participants highly responsive to experimental intervention. →Sample much more narrow than expected representative population.

Comments:

EXAMPLE: Early treatment with prednisolone or acyclovir in Bell's Palsy (Sullivan FM, Swan IR, Donnan PT, et al., 2009)

- Inclusion criteria – Patients with confirmed diagnosis: ≥ 16 years of age with unilateral facial nerve weakness of no identifiable cause who presented to primary care or an emergency department and could be referred to a collaborating otorhinolaryngologist <72 hours after the onset of symptoms.
- Exclusion criteria – Pregnancy, breast feeding, uncontrolled diabetes, peptic ulcer disease, suppurative otitis media, herpes zoster, multiple sclerosis, systematic infection, sarcoidosis and other rare conditions, and an inability to provide informed consent.
- Extra test – Randomised controlled trial of Bell's palsy treatment requited senior otorhinolaryngologist in hospitals to confirm a patient's eligibility to participate. Bell's palsy is usually diagnosed by a general practitioner in primary care.
- Suggested PRECIS score – 2, rather explanatory

2. **Recruitment Path** (effort made to recruit participants) – how much extra effort is made to recruit participants over and above what would be used in the usual care setting to engage with patients.

Usual identification of LCS eligible candidates for decentralized primary care:

- Identification of potential LCS candidates occurs primarily through visits to primary care appointments of clinics.
- Less frequently, primary care may employ electronic health records to help identify eligible individuals, however cigarette smoking history is often not accurate.

5	4	3	2	1
Completely Pragmatic				Completely Explanatory
→Participants recruited unobtrusively during clinic visits or through standard patient outreach (e.g., use typical usual care processes of outreach: letters, automated calls or emails generated by EMR)		→Some extra effort and/or resources used, above and beyond what would be used to recruit participants in usual LCS care (e.g., staff time needed to contact people from EMR search)		→General advertising without relevance to clinic population →Recruitment requiring extra effort →High level of incentive offered

Comments:

EXAMPLE: Leukotriene antagonists for asthma treatment (Price D, Musgrave SD, Shepstone L, et al., 2011)

- Initially extra resources were used to recruit patients at 53 primary care practices. Patients were recruited via a postal questionnaire to identify symptoms and trial eligibility, not just to invite to participate. This would push the recruitment path of this domain towards the explanatory end. By using this method of recruitment, which requires administration not normally present in primary care, it is possible that responders may be healthier than those at the clinic being invited to the trial and also more highly motivate and compliant as they have come through a different route than those invited during a clinic attendance.
- In this trial, recruitment was inadequate using a postal questionnaire, so participants were then recruited through clinic attendances changing the recruitment towards a more pragmatic trial design, creating results which are more applicable to users of the results in a primary care setting.
- Suggested PRECIS score – 2, rather explanatory; but, as trial continued, a PRECIS score of 3 (equally pragmatic and explanatory) since trial now more a mix of recruitment methods, some of which are feasible in usual care.

3. **Setting** (how different are settings of trial from usual care?) – the difference in the settings of the trial from the usual care setting where the results are likely to be applied.

Usual LCS setting for decentralized primary care

- LCS is completed in a wide-variety of primary care settings (urban/rural, academic/community).
- Ideally has resources for tracking and follow-up of participants for next steps after low dose CT results.

5	4	3	2	1
Completely Pragmatic				Completely Explanatory
→Setting nearly identical to location where results are intended to be applied (usual care) →Multiple centers selected for variation		→Setting is partially representative of usual care sites →More than one center involved		→Study not at all representative of usual care site (i.e., all sites highly specialized centers or tertiary-care academic centers) →Few or one clinical center involved

Comments:

EXAMPLE: Manual physical therapy versus corticosteroid injection to treat shoulder impingement (Rhon DI, Boyles RE, Cleland JA, et al., 2011)

- Single centre and specialised centre (Madigan Army Medical Center, USA), unlikely to be the usual setting for most individuals receiving physiotherapy for shoulder impingement.
- Suggested PRECIS score – 2, rather explanatory, dependent on how different raters think the treatment centre is similar from usual setting in the country they live in.

4. **Organization** (resources, provider expertise, and organization of care delivery) – the difference between the resources, provider expertise, and the organization of care delivery employed in the intervention arm of the trial and those available in usual care

Usual LCS organization for decentralized primary care

- Primary care practices generally have limited capacity for population health activities that may limit their ability to complete the LCS process as outlined by CMS. Below is a list of ideal resources and activities primary care has available for lung cancer screening.
    - Available workflows and resources to integrate shared decision-making into routine practice.
    - Availability of tobacco cessation resources and/or referral partners.
    - Able to refer to a radiology partner to perform the screening CT scan based on technical standards as specified by the American College of Radiology and uses a structured reporting system to report results of the CT.
    - Able to refer to a multidisciplinary team with expertise in the management of lung nodules and treatment of lung cancer.

When rating this domain for lung cancer screening for a decentralized primary care perspective, remember that primary care is referring eligible individuals for the CT scan and for any additional diagnostic work-up. Do not consider the detailed radiology and pulmonary nodule work-up procedures in your rating assessment as these are not applicable for primary care.

5	4	3	2	1
Completely Pragmatic				Completely Explanatory
→Intervention integrated into structure of usual care setting. →No extra staff time or resources required beyond what would be expected in usual care.		→Intervention requires some extra staff time and additional infrastructure.		→Intervention requires many extra hours of staff time and additional infrastructure.

Comments:

EXAMPLE: Establishment of Acute Respiratory Distress Syndrome (ARDS) Network in 1994 (NEJM, 2000)

- Multicenter clinical trials of ARDS treatments, but there was difficulty translating results from a trial involving low tidal volume (Vt) into usual clinical practice
- Ten academic centers with 75 intensive care units
- Extra staff, and very labor intensive
- Used additional equipment beyond usual care, none of which was planned for at the trial design stage
- Suggested PRECIS score – 1, very explanatory

5. **Flexibility (delivery by intervention staff)** – the difference in flexibility of intervention delivery compared to the flexibility anticipated in usual care.

Usual delivery of LCS by decentralized primary care

- Primary care should provide shared decision-making to each screening participant prior to the baseline CT scan and tobacco cessation services to individuals that currently smoke on an ongoing basis.
- Primary care should follow the frequency and duration of screening as recommended by the US Preventive Services Task Force and/or the Centers for Medicare and Medicaid Services.
    - Continued annual screening for individuals with negative results (no nodules or benign appearance) until no longer eligible.
    - Shorter term follow-up for individuals with positive results (nodules worrisome for malignancy). Work-up timing and procedures will depend on nodule characteristics and provider and patient preference.

5	4	3	2	1
Completely Pragmatic				Completely Explanatory
→No extra measures employed to increase practitioner adherence (but OK to just monitor practitioner delivery). →Program outline/M.O.P. may be provided, but the specifics of intervention delivery (e.g., dose schedule, description of educational program) are left to interpretation by practitioner.		→Some strategies to monitor and increase practitioner adherence. →Intervention delivery somewhat pre-specified but with some flexibility (e.g., dose schedule, work-up of nodules left to discretion of practitioner).		→Extensive actions made to enhance provider adherence attention to details. →Intervention highly specified and protocol-driven (e.g., Highly specific Manual of Procedures (M.O.P.) in place)

Comments:

EXAMPLE: Elective caesarean section syntocinon infusion trial (Murphy DJ, Carey M, Montgomery AA, et al., 2009)

- Protocol drive – Much detail give, with protocol violations recorded in self reported case form. Investigators accept this may occur due to clinical needs (such as anaesthesia).
- Co-interventions – Specific direction
- Complications – Specific directions for managing complications or side effects
- Improving adherence – No measures in place
- Suggested PRECIS score – 2, rather explanatory

6. **Flexibility (adherence)** – the difference in the flexibility in how participants engage with the intervention compared to the flexibility anticipated in usual care

Usual engagement of LCS by participants screened through decentralized primary care

- Participants should participate in shared decision-making prior to the baseline CT scan and receive tobacco cessation resources (applicable for individuals that currently smoke) on an ongoing basis.
- Participants should follow the frequency and duration of screening as recommended by the US Preventive Services Task Force and/or the Centers for Medicare and Medicaid Services.
    - Continued annual screening for individuals with negative results (no nodules or benign appearance) until no longer eligible.
    - Shorter term follow-up for individuals with positive results (nodules worrisome for malignancy). Work-up timing and procedures will depend on nodule characteristics and provider and patient preference.

5	4	3	2	1
Completely Pragmatic				Completely Explanatory
→Encouragement to comply with intervention is acceptable (only if within the realm of what would be seen in usual care) (i.e., send reminders)		→A few strategies to measure and increase participant adherence		→Close monitoring →Actions to maximize participant adherence
Comments:				

EXAMPLE: Music therapy to support communication in autistic children (Geretsegger M, Holck U, Gold C., 2012)

- The sessions were all individual based on interaction with child and allowed for range of responses to the intervention
- Suggested PRECIS score – 5, very pragmatic

7. **Follow-up** (how closely are patients followed up) – the difference in the intensity of follow-up of participants (including data requiring interaction) during the trial compared to the typical follow-up expected in usual care

Usual LCS follow-up for decentralized primary care

- Primary care should develop strategies to maximize compliance with annual screening exams and evaluation of screen-detected findings

5	4	3	2	1
Completely Pragmatic				Completely Explanatory
→No more than annual additional visits of study individuals during intervention phase where may influence efficacy. →Infrequent follow-up by practitioner		→Some added visits during intervention phase →Some data collected during intervention (but not much beyond what would be expected in usual care) →Occasional practitioner follow-up		→Much more frequent visits for data collection **during** intervention period. →Extensive data collected ***during*** intervention. →Frequent practitioner follow-up

Comments:

EXAMPLE: Perioperative β blockade for patients undergoing infra-renal vascular surgery (Brady AR, Gibbs JSR, Greenhalgh RM, et al., 2005)

- Clinical follow-up until patient left hospital (discharge or death) or until 30 days after surgery, whichever was the longer, so more than usual care.
- Monitoring intensity involved more extensive data collection than usual:
  - Pre-operation – three-lead electrocardiogram (ECG) Holter monitor (Flashcard with 2x48 hour recording) set up on each patient and maintained for 72 hours.
  - Troponin values at 1, 3, and 7 days after surgery (more usual for only 1 and 3 days after surgery)
  - ECG after randomization and at 7 and 30 days after surgery.
- Unscheduled follow-up visits triggered by primary outcome a cardiovascular event (such as angina, myocardial infarction, stroke)
- Suggested PRECIS score – 1, very explanatory

8. **Primary Outcome** (how clinically meaningful and understandable is the PRIMARY OUTCOME to patients, healthcare providers, society, and policy makers; outcome could practically be assessed with resources available in usual care setting) – the extent to which the trial's primary outcome is directly relevant to participants and other stakeholders.

Primary LCS outcome for decentralized primary care

- The primary LCS outcome for both primary care and participants is to diagnosis and treat lung cancers at each early stage to improve survival and lower mortality rates.

5	4	3	2	1
Completely Pragmatic				Completely Explanatory
→Primary outcome is relevant, understandable and important to LCS participants as well as to society, policy-makers and healthcare providers →Could be assessed with resources available in in usual care setting		→Clinical measures that are somewhat relevant and understandable to LCS participants, society, policy-makers and healthcare providers →Could be assessed in usual care with some additional training/expertise		→Only uses measures/terms that are not relatable to LCS participants, society, policy-makers and healthcare providers. →Requires specialized training to collect and not feasible to measure in usual care.

Comments:

EXAMPLE: Early treatment with prednisolone or acyclovir in Bell's palsy (Sullivan FM, Swan IR, Donnan PT, et al., 2009)

- Primary outcome – Recovery of facial function as rated on the House-Brackmann scale.
- Test not routinely used in primary care and requires training. It is, however, an easy clinical test widely used in secondary care for grading recovery from facial nerve paralysis caused by damage to lower motor neurons.
- Central adjudication – Photographs taken of patients were assessed and graded independently by a panel of three experts (not general practitioners, who usually assess).
- Suggested PRECIS score – 1, very explanatory

9. **Analysis** Extent to which all data is included in analysis of the primary outcomes

Not specifically applicable to LCS processes or outcomes

When rating this domain, primarily consider how missing data was treated and whether it is included in the analysis. Additionally consider how data from individuals that were later found to be ineligible for the study were handled and/or included in analyses.

5	4	3	2	1
Completely Pragmatic				Completely Explanatory
→Data from all participants under usual conditions included in the analysis, with multiple imputation of missing data →No exclusion of data from non-compliant participants from analysis →No exclusion of data from trial sites with lower than expected recruitment →Various missing data analytic procedures are OK as long as not excluding due to poor adherence.		→Data from all participants included in analysis but analysis rigor reduced slightly in some way →Various missing data analytic procedures are OK as long as not excluding due to poor adherence		→Data analyzed excludes individuals who violated/deviated from protocol ("per protocol analysis"), →Excludes data from trial sites or providers who recruited below expectations or had poor adherence →Various missing data analytic procedures are OK as long as not excluding due to poor adherence

Comments:

EXAMPLE: Effects of Rosuvastatin versus atorvastatin on LDL and HDL cholesterol in patients with type IIa or IIb hypercholesterolemia (Davidson M, Ma P, Stein EA, et al., 2002)

- Dietary lead in to screen and exclude non-compliers, then post-randomization excluded non-compliers who did not take medication, so "per protocol analysis." The trial did, however, include those who violated protocol, deviated from protocol, or withdrew (mainly due to adverse events)
- Suggested PRECIS score – 2, rather explanatory

General Comments: