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CT screening for lung cancer: comparison of three baseline screening protocols

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Abstract

Purpose Clinical management decisions arising from the baseline round for lung cancer screening are the most challenging, as findings have accumulated over a lifetime and may be of no clinical concern. To minimize unnecessary harms and costs of workup prior to the first, annual repeat screening, workup should be limited to participants with the highest suspicion of lung cancer while still aiming to identify small, early lung cancers.

Methods We compared recommendations for immediate, delayed (by 3 or 6 months) workup to assess growth at a malignant rate, and the resulting overall and potential biopsies of three baseline screening protocols: I-ELCAP, the two scenarios of ACR-LungRADS, and the European Consortium. For each protocol, the efficiency ratio (ER) of each recommendation was calculated by dividing the number of participants recommended for that workup by the number of resulting lung cancer diagnoses. The ER for potential biopsies was calculated, assuming that biopsies were performed on all participants recommended for immediate workup as well as those diagnosed with lung cancer after delayed workup.

Results For I-ELCAP, ACR-LungRADS Scenario 1, ACR-LungRADS Scenario 2, and the European consortium, the overall ER was 13.9, 18.3, 18.3, and 31.9, respectively, and for potential biopsies, it was 2.2, 8.1, 3.2, and 4.4, respectively. ER for immediate workup was 2.9, 8.6, 3.9, and 5.6, respectively, and for delayed workup was 36.1, 160.3, 57.8, and 111.9, respectively.

Conclusions I-ELCAP recommendations had the lowest ER values for overall, immediate, and delayed workup, and for potential biopsies.

Key Points

- *Small differences in protocol thresholds can lead to many unnecessary diagnostic workups.*
- *I-ELCAP recommendations were the most efficient for immediate and overall workup, and potential biopsies.*
- *Definition of a "positive result" and recommendations for further workup in the baseline round needs to be continually reevaluated and updated.*

Keywords Tomography · Spiral computed · Lung neoplasms · Cancer screening · Clinical protocols

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Abbreviations

AAPM	American Association of Physicists in Medicine
ACR	American College of Radiology
CMS	Centers for Medicare and Medicaid Services
ER	Efficiency ratio
I-ELCAP	International Early Lung Cancer Action Program
LDCT	Low-dose computed tomography
LungRADS	Lung Imaging Reporting and Data System
NCN	Noncalcified nodules

NELSON	The Dutch-Belgian Lung Cancer Screening Trial
PET	Positron emission tomography

Introduction

Clinical management decisions arising from the first, baseline round of screening for lung cancer are most challenging, as nodules that are seen for the first time may have accumulated over a lifetime and thus may be of no clinical concern. In contrast, new or changing findings on subsequent annual repeat low-dose CTs (LDCTs) have greater clinical significance, and cancers diagnosed in these rounds are also more aggressive than cancers identified in the baseline round [1–3]. To minimize unnecessary harms, workup within 12 months after the baseline low-dose CT (LDCT) scan should be limited to those with a high suspicion of lung cancer while still identifying as many small, early lung cancers as possible. Knowledge has increased about nodule subtypes, their probabilities of malignancy, and frequency of different cancer cell types in the baseline round [3–20], and this knowledge has been incorporated into updated guidelines [21–27].

Centers for Medicare and Medicaid Services (CMS) provided coverage for an estimated eight million smokers in the USA [28, 29]. Despite these strong endorsements, only some 4% of eligible people have been screened [30]. Many reasons have been suggested [31–38], but potential harms of follow-up tests and procedures have been cited as a key concern, and these depend on the management protocol which determines the frequency of workup and biopsy recommendations. As diagnostic tests requiring intravenous injection (e.g., PET scans and contrast CT), biopsies, and surgery have greater risks than LDCT, management protocols should aim to minimize these higher risk procedures as much as possible.

Our goal was to compare the frequency, type, and efficiency for the recommended workup in the baseline round by three different published screening protocols, the I-ELCAP [21], American College of Radiology (ACR)-LungRADS [26], and the European Consortium protocols [27].

Materials and methods

This report is based on the 25,506 baseline screenings performed in the International Early Lung Cancer Action Program (I-ELCAP) according to an IRB-approved common protocol between January 2006 and December 2017 [21]. Participating sites were in large metropolitan hospitals, major academic centers, as well as smaller community medical centers. As criteria for screening eligibility vary by country, all participants 50 years of age or older with at least 20 pack-years of smoking were included (Table 1). All noncalcified nodules (NCNs) identified in the baseline LDCT in these participants were documented as to the consistency (solid, part-solid, nonsolid), length, and width in millimeters to the tenth of a decimal point. The diameter of the NCN was calculated as the average of the length and width rounded to the nearest tenth of a millimeter. For part-solid NCNs, however, the diameter of the solid component rather than the entire NCN was used as it has been shown that when lung cancer was diagnosed, the solid component typically represented the invasive component [15], and pathologists now also categorize cancers according to the invasive component [3, 20]. Table 2 shows how each of the 25,506 participants was categorized according to the consistency and diameter of their largest NCN for solid and nonsolid NCNs and by the average diameter of the solid component of part-solid NCNs. The diagnosed lung cancers by NCN consistency are also given.

Three published protocols, I-ELCAP [21], ACR-LungRADS [26], and European Consortium [27] were compared as to their workup recommendations and resulting diagnoses of lung cancer. All three use the diameter of the entire solid and nonsolid NCN, but differ for part-solid NCNs. For part-solid NCNs, I-ELCAP uses the diameter of the solid component, while ACR-LungRADS uses both the entire diameter of the part-solid NCN as well as the diameter of its solid component. The European Consortium protocol determines the volume of a solid NCN using their software [5], but also specifies the equivalent diameter values for the entire part-solid and nonsolid NCNs as volumetric measurements for these are problematic [27].

Each protocol provides threshold values for its workup recommendations. Threshold values for I-ELCAP are 6.0 mm and 15.0 mm; for ACR-LungRADS, 6 mm, 8 mm, and 15 mm; and for the European Consortium, 50 mm^3 (5 mm) and 300 mm^3 (10 mm) for solid NCNs, and 5 mm for part-solid and nonsolid NCNs. As volume measurements are not available in the database, the published nodule diameter thresholds of the European Consortium protocol are used.

I-ELCAP [21] specifies its threshold values to tenth of a decimal, while ACR-LungRADS [26] and European Consortium [27] protocols round each measurement to nearest whole number. The consequences of rounding measurements to whole numbers have been shown by Li et al [39] as rounding significantly affects the workup recommendations close to the threshold values, especially for smaller NCNs which are most frequent. For example, measurements between 4.5 mm and 4.9 mm are rounded to 5, 5.5 mm and 5.9 mm are rounded to 6, 9.5 mm to 9.9 are rounded to 10, and 14.5 to 14.9 are rounded to 15 [39]. Both the length and width are rounded to whole numbers, and then calculated average diameter is again rounded [39]. Thus, these measurements meet the threshold criteria of 5, 6, 10, and 15, triggering workup that may be unnecessary.

The protocol recommendations are summarized in Table 3. All three protocols provide recommendations for immediate workup or noncontrast LDCT 3 months later. Immediate

Table 1 Gender, age, and ethnic group of participants

	All		At least one noncalcified nodule (NCN)	
	N = 25,506		*N* = 13,938	
	n (%)		*n* (%)	
Gender				
Female	10,505	(41.2%)	6169	(44.3%)
Male	15,001	(58.8%)	7769	(55.7%)
Median age (IQR)	60	(55–66)	61	(56–67)
Ethnicity				
White	23,490	(92.1%)	12,844	(92.2%)
Asia	438	(1.7%)	202	(1.4%)
African American	918	(3.6%)	534	(3.8%)
Hispanic	292	(1.1%)	169	(1.2%)
Other	368	(1.4%)	189	(1.4%)
Median pack-years (IQR)	37.5	(29.5–50.0)	39.0	(30.0–50.0)

IQR interquartile range

workup typically includes PET scans and biopsies. The ACR-LungRADS protocol provides two options for solid NCNs ≥ 8 mm but < 15 mm: one is an immediate PET/CT and the other, a 3-month LDCT. As either option can be chosen, each needs to be considered separately. ACR-LungRADS scenario 1 assumes that all these cases will have PET scans, and ACR-LungRADS scenario 2 assumes that all will have a 3-month LDCT. The actual decision as to which scenario is chosen is left to each radiologist and thus the actual frequency cannot be determined, but it would be some combination of the two scenarios for each radiologist.

To determine the frequency of participants for ACR-LungRADS and European Consortium protocol recommendations, some participants need to be re-categorized when they have more than one NCN, as it is possible that the NCN that triggers the workup for one protocol may be different from the NCN that triggers workup for another protocol. This occurs, for example, for a participant with two NCNs, a 14.3-mm solid NCN and a 11.0-mm part-solid NCN with a 9.0-mm solid component. For this participant, I-ELCAP recommends 3-month LDCT because of the 14.3-mm solid NCN and the 9.0-mm solid component of the part-solid NCN while the European Consortium recommends immediate workup as the solid NCN ≥ 10 mm. However, the ACR-LungRADS scenario 1 recommends immediate PET scan because of the 14.3-mm solid NCN and the 9.0-mm solid component of the part-solid NCN while scenario 2 recommends immediate workup only because of the 9.0-mm solid component of the 11.0-mm part-solid NCN.

As the goal of each management protocol is to minimize unnecessary workups while diagnosing as many early lung

Table 2 The frequency of the largest noncalcified nodule (NCN) in the baseline low-dose CT scan of 25,506 participants, by average diameter (to the nearest tenth of a decimal) and consistency

Average diameter of largest NCN (mm)	Solid NCN (Dx Ca)		Solid component of part-solid (Dx Ca)		Nonsolid (Dx Ca)		Total (Dx Ca)	
None							11,568	(0)
< 5.0	8460	(0)	520	(0)	406	(0)	9386	(0)
5.0–5.4	779	(0)	35	(2)	89	(0)	903	(2)
5.5–5.9	574	(1)	43	(0)	59	(0)	676	(1)
6.0–7.4	983	(7)	68	(1)	157	(0)	1208	(8)
7.5–9.4	522	(12)	73	(1)	104	(0)	699	(13)
9.5–14.4	455	(32)	82	(12)	99	(1)	636	(45)
14.5–14.9	26	(3)	3	(0)	6	(1)	35	(4)
15.0–19.5	115	(27)	28	(6)	26	(0)	169	(33)
≥ 19.5	180	(78)	22	(5)	24	(1)	226	(84)
Total	12,094	(160)	874	(27)	970	(3)	25,506	(190)

The average diameter of each part-solid NCN is tabulated according to the diameter of its solid component. Lung cancers diagnosed before or by the first annual repeat screening are given in the parentheses

Dx Ca diagnosed lung cancer

Table 3 Recommendations for each protocol by NCN subtype and size on the baseline LDCT for (a) immediate workup, (b) 3-month follow-up LDCT, and (c) 6-month follow-up LDCT

	I-ELCAP	ACR-scenario 1	ACR-scenario 2	European
a. Immediate workup PET, biopsy, follow-up CT				
Solid NCN, largest	≥ 15.0 mm	≥ 8 mm	≥ 15 mm	≥ 10 mm
Part-solid NCN, largest	Solid component ≥ 15.0 mm	Solid component ≥ 8 mm	Solid component ≥ 8 mm	None
b. 3-month LDCT				
Solid NCN, largest	≥ 6.0 mm but < 15.0 mm	–	≥ 8 mm but < 15 mm	≥ 5 mm but < 10 mm
Part-solid NCN, largest	Solid component of NCN ≥ 6.0 mm but < 15.0 mm	Entire size of NCN ≥ 6 mm with solid component ≥ 6 mm but < 8 mm	Entire size of NCN ≥ 6 mm with solid component ≥ 6 mm but < 8 mm	Entire size of NCN ≥ 5 mm
Nonsolid NCN, largest[a]				≥ 5 mm
c. 6-month LDCT				
Solid NCN, largest	None	≥ 6 mm to < 8 mm	≥ 6 mm to < 8 mm	None
Part-solid NCN, largest	None	Entire size of NCN ≥ 6 mm with solid component < 6 mm	Entire size of NCN ≥ 6 mm with solid component < 6 mm	None
Nonsolid NCN, largest[b]		≥ 20 mm	≥ 20 mm	

The recommendations for part-solid NCN are based on either the size of the entire NCN or on the size of solid component as specified by each protocol

[a] The I-ELCAP protocol and ACR-LungRADS do not recommend 3-month follow-up for nonsolid NCNs

[b] The I-ELCAP protocol does not recommend 6-month follow-up for nonsolid NCNs, only annual repeat follow-up

cancers as possible, the efficiency of each recommendation, designated as ER, was defined as the number of participants recommended for a particular workup divided by the resulting number of participants diagnosed with lung cancer. An optimum value for ER would be ER = 1, which would mean that a lung cancer would be diagnosed for each recommended workup. Increasing ER values indicate decreasing efficiency.

Biopsies, whether surgical or nonsurgical, are the most invasive tests and thus present the greatest risk to participants. I-ELCAP specifies malignant growth for NCNs in the baseline round which incorporates both actual growth and measurement error [21]. The ACR-LungRADS specified malignant growth as an increase of 1.5 mm in the size of the NCN without specifying the time interval between the two scans [25]. The European Consortium protocol uses volume doubling time as an indicator of malignant growth without specification of measurement error. As these considerations make comparison difficult, we defined the ER for potential biopsies by summing all participants recommended for immediate workup and the participants diagnosed with lung cancer after each follow-up LDCT, assuming that the follow-up LDCT demonstrated growth at a malignant rate. Realistically, more participants are biopsied, but these assumptions provide a common ground for comparison.

All statistical analyses were performed using SAS 9.4 software (SAS Institute, Cary, NC).

Results

Among the 25,506 participants, one or more NCN were identified in 54.6% (13,938); thus, 45.4% (11,568) had no NCNs (Table 2). The largest NCN was solid in 86.8% (12,094/13,938) and nonsolid in 6.9% (970/13,938). The solid component of the part-solid NCN was the largest in 6.3% (874/13,938). Of the diagnosed cancers, 84.2% (160/190), 14.2% (27/190), and 1.6% (3/190) manifested as solid, part-solid, and nonsolid NCNs, respectively.

Recommendations for immediate workup

I-ELCAP recommends immediate workup for 1.4% (352/25506) of the participants (Tables 3 and 4a). Included are participants whose largest solid NCN ≥ 15.0 mm ($n = 295$), largest solid component of part-solid NCN ≥ 15.0 mm ($n = 50$), and those with other findings suggestive of malignancy (mediastinal masses, enlarged mediastinal lymph nodes, pleural effusions, and other highly significant findings) ($n = 7$). Thus, immediate workup recommended for 352 participants of which 123 are diagnosed with lung cancer, yielding an ER = 352/123 = 2.9.

ACR-LungRADS (scenario 1) recommends immediate workup for 5.9% (1507/25506) of the participants (Tables 3 and 4a). Included are participants whose largest solid NCN ≥ 15 mm (with round-off ≥ 14.5) ($n = 327$), whose largest part-solid NCN with a solid component ≥ 8 mm (with round-off ≥ 7.5) ($n = 209$), and those with other findings suggestive of malignancy (e.g., mediastinal masses, enlarged lymph nodes, and pleural effusions) ($n = 7$). Immediate PET/CT is recommended for another 3.8% (964/25506) (scenario 1) for participants with solid NCN ≥ 8 mm but < 15 mm (with round-off 7.5–14.4) ($n = 964$), leading to the diagnosis of lung cancer in 38. Thus, under scenario 1, immediate workup and PET would be recommended for 5.9% (1507/25506) of the participants of whom 176 are diagnosed with lung cancer, yielding ER = 1507/176 = 8.6.

Under scenario 2 of the ACR-LungRADS protocol, immediate workup is recommended for 2.1% (543/25506) of which

Table 4 For each baseline protocol, the ER values for overall protocol and for the recommendations for (a) immediate, (b) 3-month follow-up LDCT, and (c) 6-month follow-up LDCT are given. The potential biopsy recommendations are also provided

	I-ELCAP	ACR-scenario 1	ACR-scenario 2	European
Summary				
Total no. of workups (sum a–c)	2557	3431	3431	6052
Total no. of lung Ca Dx	184	188	188	190
ER (no. of workups/Ca Dx)	13.9	18.3	18.3	31.9
a. Immediate workup (% participants)	1.4	5.9	2.1	3.1
No. of participants	352	1507	543	794
No. of lung Ca Dx	123	176	138	143
ER (no. of participants/Ca Dx)	2.9	8.6	3.9	5.6
b. 3-month LDCT (% participants)	8.6	0.5	4.4	20.6
No. of participants	2205	153	1117	5258
No. of lung Ca Dx	61	2	40	47
ER (no. of participants/Ca Dx)	36.1	76.5	27.9	111.9
c. 6-month LDCT (% participants)		6.9	6.9	
No. of participants		1771	1771	
No. of lung Ca Dx		10	10	
ER (no. of participants/Ca Dx)		177.1	177.1	
Potential biopsies (%)	1.6	6.0	2.3	3.3
No. of biopsies	413	1519	593	841
No. of lung Ca Dx	184	188	188	190
ER (no. of biopsies/Ca Dx)	2.2	8.1	3.2	4.4

Ca Dx cancer diagnosis

138 are diagnosed with lung cancer, yielding an ER = 543/138 = 3.9 (Tables 3 and 4a).

The European Consortium protocol recommends immediate referral to pulmonologist for 3.1% (794/25506) of the participants (Table 4a). Included are participants whose largest solid NCN ≥ 10 mm (with round-off ≥ 9.5) ($n = 781$), whose part-solid NCN was larger in size of solid component than their solid NCN ≥ 9.5 mm ($n = 6$), and those with other findings suggestive of malignancy (e.g., mediastinal masses, enlarged lymph nodes, pleural effusions, and other significant findings) ($n = 7$). Thus, immediate workup would be recommended for 794 participants of which 143 are diagnosed with lung cancer, yielding an ER = 794/143 = 5.6.

Recommendations for 3-month follow-up LDCT to assess growth

I-ELCAP recommends 3-month LDCT for 8.6% (2205/25506) of the participants, those with solid NCNs 6.0–14.9 mm ($n = 1980$) and part-solid NCNs with solid component 6.0–14.9 mm ($n = 225$) (Tables 3, and 4b). Therefore, 3-month LDCT was recommended for 2205 participants of which 61 are diagnosed with lung cancer, yielding an ER = 2205/61 = 36.1.

ACR-LungRADS scenario 1 recommends far fewer participants for 3-month LDCT, 0.6% ($n = 153$) of the participants (Tables 3 and 4b). Included are participants whose largest solid component of a part-solid NCN ≥ 6 mm to < 8 mm (with round-off 5.5–7.4 mm) ($n = 110$) as long as the overall size of the part-solid NCN is > = 6 mm (with round-off 5.5 mm), and whose solid NCNs larger than their part-solid NCN that met the above criteria ($n = 43$). Therefore, 3-month LDCT is recommended for 153 participants of which two are diagnosed with lung cancer, yielding an ER = 153/2 = 76.5.

Using the recommendations of ACR-LungRADS scenario 2, 3-month LDCT is recommended for 4.4% (1117/25506) participants which includes the 964 participants that under scenario 1 were recommended for immediate PET/CT (Tables 3 and 4b). Thus, scenario 2 would lead to a diagnosis of lung cancer in 40, an ER = (1117/40) = 27.9.

The European Consortium recommends 3-month follow-up CT for 20.6% (5258/25506) participants (Tables 3 and 4b). Included are participants with largest solid NCN ≥ 5 (100 mm^3) but < 10 mm (300 mm^3) (with round-off 4.5–9.4 mm) ($n = 4068$), whose part-solid NCN with overall average diameter ≥ 5 mm ($n = 526$), whose nonsolid NCN ≥ 5 mm ($n = 664$). Thus, 3-month LDCT was recommended for 5258 participants of which 47 are diagnosed with lung cancer, an ER = 5258/47 = 111.9.

Recommendations for 6-month follow-up LDCT to assess growth

Both ACR-LungRADS scenarios recommend 6-month LDCT for 6.9% (1771/25506) participants (Tables 3 and 4c). Included participants whose solid NCN ≥ 6 mm but < 8 mm (rounded off

5.5–7.4 mm) ($n = 1622$), participants whose part-solid NCN ≥ 6 mm in overall average diameter (rounded off ≥ 5.5 mm) with solid component < 6 mm (rounded to < = 5.4 mm) ($n = 118$), participants whose nonsolid NCNs ≥ 20 mm (rounded off 19.5 mm) ($n = 24$), and participants whose solid NCN was larger than the solid component of their part-solid NCN ($n = 7$). Thus, both ACR-LungRADS scenarios 1 and 2 would recommend 6-month LDCT for 1771 participants of whom ten are diagnosed with lung cancer, yielding an ER = 1771/10 = 177.1.

Comparison of the three protocols

The overall frequency and percentage of participants requiring (a) immediate workup or PET, (b) 3-month LDCT, and (c) 6-month LDCT and the corresponding diagnoses of lung cancer is summarized in Table 4.

The overall ER for I-ELCAP, ACR-LungRADS scenario 1, ACR-LungRADS scenario 2, and the European Consortium was 13.9, 18.3, 18.3, and 31.9, respectively (Table 4). For immediate workup, the ER was 2.9, 8.6, 3.9, and 5.6, respectively (Table 4a) and for delayed (3- or 6-month) LDCT, the ER was 36.1, 160.3, 57.8, and 111.9, respectively (Table 4b, c). The two ACR-LungRADS scenarios represent the extreme application of two scenario recommendations. In practice, the ER would vary for each radiologist according to the frequency with which each scenario was chosen by that radiologist. However, any combination of the two ACR-LungRADS scenarios would still yield a higher ER than I-ELCAP.

How many additional workups were recommended by the ACR-LungRADS and European Consortium as compared to I-ELCAP? An additional 1155 (1507–352) participants were recommended for immediate workup by ACR-LungRADS (scenario 1) to diagnose 53 (176–123) participants with lung cancer who would be diagnosed at 3 months in I-ELCAP. None in I-ELCAP had progressed beyond stage I when diagnosed after 3 months after showing growth at a malignant rate. Therefore, the tradeoff for using the ACR-LungRADS protocol would perform immediate workup, including possible biopsy in 1155 participants to diagnose the 53 participants with lung cancers 3 months earlier than I-ELCAP.

Comparing I-ELCAP with the European Consortium protocol, immediate workup was recommended by the European Consortium protocol for 490 participants for solid NCN ≥ 10 (rounded off ≥ 9.5), while 3-month LDCT was recommended by I-ELCAP for those ≥ 6.0 mm and < 15.0 mm. As a result of the 490 participants recommended for immediate workups by the European Consortium protocol, 30 participants would be diagnosed with lung cancer 3 months earlier than I-ELCAP, all were still in stage I when diagnosed in I-ELCAP. For another 48 participants with part-solid NCN with solid component ≥ 15.0 mm, the European Consortium protocol recommended 3-month LDCT, while immediate workup was recommended by I-ELCAP. As a result of the immediate workup of 48 by I-ELCAP, ten were diagnosed with lung cancer 3 months earlier than when recommended by the European Consortium protocol. While these ten cases were in stage I when diagnosed in I-ELCAP, it is not known whether these 10 cases with large solid components would have progressed beyond stage I when diagnosed 3 months later by the European Consortium protocol. As to the 6-month LDCT recommended by both ACR-LungRADS scenarios which would have led to the diagnosis of ten cases of lung cancer, these were diagnosed 3 months earlier in I-ELCAP and it is unknown whether there would have been stage progression in the interim.

In summary, of the 190 participants diagnosed with lung cancer within 12 months of the baseline LDCT, 184 were diagnosed either immediately or 3 months later according to the I-ELCAP protocol, 188 would have been diagnosed according to the ACR-LungRADS protocol (using either scenario), and 190 according to the European Consortium protocol. The ACR-LungRADS protocol would have diagnosed four additional participants compared to I-ELCAP (188–184), and the European Consortium protocol would have diagnosed an additional two participants beyond ACR-LungRADS (190–188). These six participants showed growth on the first annual repeat screening in I-ELCAP and were all still in stage I when diagnosed.

To examine the effect of rounding the final calculated diameter while not rounding the length and width, we re-calculated the overall ER. For ACR-LungRADS for both scenarios which would be 17.7 instead of 18.3 and for the European Consortium, the overall ER would be 30.8 instead of 31.9.

The ERs for potential biopsies for each protocol as shown in Table 4 were 2.2 for I-ELCAP, 8.1 for ACR-LungRADS scenario 1, 3.2 for ACR-LungRADS scenario 2, and 4.4 for the European Consortium (Fig. 1). For I-ELCAP, 352 participants were recommended for immediate workup, and 61 participants were diagnosed with lung cancer after 3-month follow-up, so that ER = (352 + 61)/184 = 2.2. For ACR-LungRADS (scenario 1), 1507 participants would be recommended for immediate workup or PET and two would be diagnosed with lung cancer after 3-month LDCT and ten after 6-month LDCT, so that ER = (1507 + 2 + 10)/188 = 8.1. Similarly, for ACR-LungRADS (scenario 2), ER = (543 + 40 + 10)/188 = 3.2. For the European consortium, the ER = (794 + 47)/190 = 4.4.

We also re-calculated the overall ER and the ER for potential biopsies for each of the three protocols if only participants meeting the CMS criteria for screening (age 55–77, at least 30 pack-years of smoking, and quit within the last 15 years) were considered. The overall ERs were 10.9, 14.3, 14.3, and 24.7, respectively, for I-ELCAP, ACR-LungRADS scenarios 1 and 2, and the European Consortium. The ER for potential biopsies was 1.9, 6.5, 2.6, and 3.7, respectively. As expected, the ERs were lower because of the higher risk of lung cancer, but the relative rank order of the protocols remained the same.

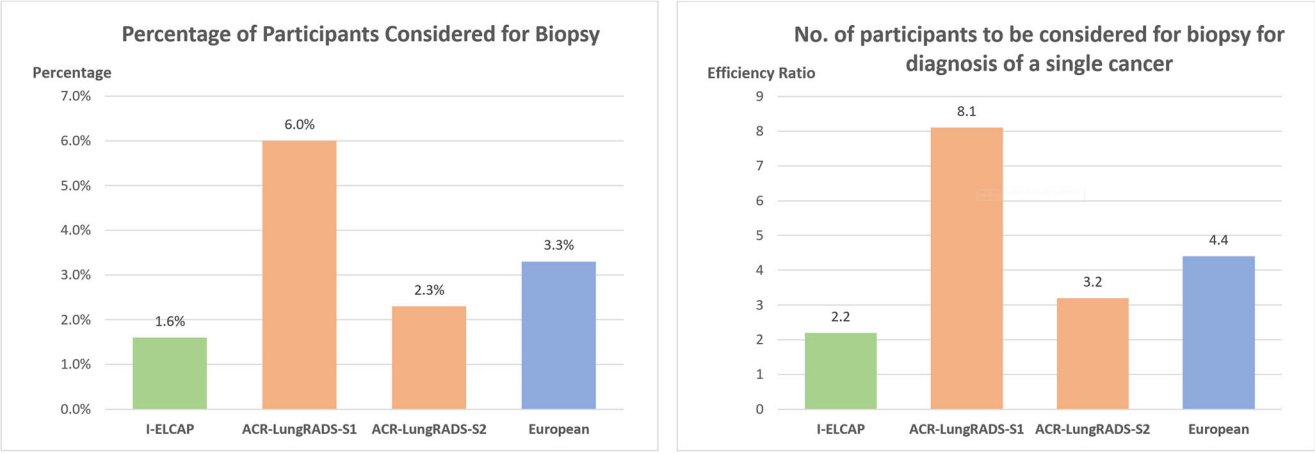

Fig. 1 Comparison of the biopsy recommendations of three baseline screening protocols: I-ELCAP, two possible scenarios of ACR-LungRADS, and the European Consortium by percentage of participants recommended and the efficiency ratio

Discussion

The frequency of identifying a NCN on LDCT scans in the baseline round has more than doubled, from 23% in the 1990s [1] to 54.6%, highlighting the need for constant reevaluation of the screening protocols. As shown in Table 4, immediate workup for large nodules or masses was very efficient when compared to the follow-up LDCTs for all three protocols as the ERs were lower. The 3-month LDCT was also efficient in identifying growth at a malignant rate, thus markedly limiting unnecessary biopsies of smaller NCNs (Table 4). I-ELCAP recommendations proved to have the most efficient recommendations, for immediate workup, overall workup, and biopsy recommendations. As criteria for screening eligibility of the three protocols vary, participants 50 years of age or older with at least 20 pack-years of smoking were included, but the conclusions did not change when the higher CMS eligibility criteria for participants were used.

Of note is that all three screening protocols use a stepwise process. The baseline LDCT was used to identify large cancers for immediate diagnosis and treatment, while the 3-month LDCT was used to identify smaller NCNs showing growth at a malignant rate. Thus, the baseline round of screening requires in reality two LDCTs for many participants. This suggests that the term "positive result" in the baseline round be confined to recommendations for immediate workup, biopsy, or expensive tests with injection of radioactive or contrast material rather than for all participants with NCNs. This definition of positive result has already been used by the NELSON investigators [5]. Using this definition, the positive results for the three protocols would be 1.4%, 5.9%, and 3.1% of the 25,506 participants according to the I-ELCAP, ACR-LungRADS (scenario 1), and the European Consortium protocols, respectively, while the use of scenario 2 of the ACR-LungRADS would reduce the percentage from 5.9 to 2.1%.

All three protocols used LDCT to guide evaluation of NCNs, particularly the smaller NCNs. LDCT is a very low risk test as it requires no injection of contrast, the radiation dose is deemed "small" and "hypothetical" by the American Association of Physicists in Medicine [38], and the charge for a LDCT is 10–20 times lower than for a PET scan. This underscores the recognition that LDCT is a very useful tool for identifying growth at a malignant rate prior to further invasive testing [40, 41].

When considering the costs and risks of unnecessary procedures, small percentage differences in the three protocols impact many participants. For example, among the eight million smokers who are eligible for lung screening according to CMS [26], even the use of a decimal point can make an important difference in the frequency of unnecessary diagnostic workup. The additional procedures recommended by ACR-LungRADS, using 6 mm rather than 6.0 mm, lead all participants with NCNs 5.5–5.9 mm to have a follow-up LDCT instead of the 12-month annual repeat screening, an additional (2.4% × 8 million) = 193,523 unnecessary LDCTs. Similarly, the use of 15 mm instead of 15.0 mm causes all with NCNs 14.5–14.9 mm to have immediate invasive workup, an additional 8155 participants (0.10% × 8 million). Considering the European Consortium protocol, an additional (4.6% × 8 million) = 367,286 unnecessary LDCTs would be performed and unnecessary immediate invasive workup for (0.29 × 8 million) = 23,524 participants. Thus, round-off considerations are important in protocol development [39].

The ACR-LungRADS also recommends that participants with NCNs 8 mm or larger solid component of part-solid NCNs to have PET scans (scenario 1), so that 5.4% eight million = 429,703 participants with solid NCNs between 7.5 and 14.9 mm with ≥ 8-mm solid component might have this very expensive test which gives additional radiation exposure instead of a 3-month follow-up LDCT as recommended by I-ELCAP.

A limitation of this report is that the comparisons are based on retrospective analysis of the I-ELCAP screening database and resulting diagnoses of lung cancer. However, analyses of large databases have been instrumental in continual updating of screening protocols and proven to be highly predictive of results that are achieved by the updated protocol when

prospectively implemented [10, 11]. Also, the current I-ELCAP protocol has been prospectively implemented, showing results as predicted by retrospective analyses. In estimating the frequency of biopsy, the most invasive procedure, it was assumed that all diagnoses of lung cancer would ultimately be biopsied and that, other than those recommended for immediate workup, no other benign LDCT finding was biopsied. Though limited and clearly an underestimate, these assumptions provide a common basis for comparison. Actual data on biopsies, of course, would be more compelling. Lastly, the reported ERs were based on 100% compliance of the workup recommendations suggested by these protocols, but in reality, the actual workup will ultimately be determined by the discussion between the patient and their referring physician.

The main point of this report is that the definition of a "positive result" needs to be continually reevaluated and updated in light of emerging evidence from ongoing screening programs with the goal of reducing unnecessary invasive procedures for non-malignant pulmonary NCNs, which will markedly reduce the concerns about potential harms and increase the benefit by early diagnosis and treatment of small, early *curable* lung cancers.

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Compliance with ethical standards

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Conflict of interest The authors of this manuscript declare relationships with the following companies:

Dr. Yankelevitz is a named inventor on a number of patents and patent applications relating to the evaluation of diseases of the chest including measurement of nodules. Some of these, which are owned by Cornell Research Foundation (CRF), are non-exclusively licensed to General Electric. As an inventor of these patents, Dr. Yankelevitz is entitled to a share of any compensation which CRF may receive from its commercialization of these patents. He is also an equity owner in Accumetra, a privately held technology company committed to improving the science and practice of image-based decision making. Dr. Yankelevitz also serves on the advisory board of GRAIL.

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Informed consent Written informed consent was obtained from all subjects (patients) in this study.

Ethical approval Institutional Review Board approval was obtained.

Study subjects or cohorts overlap Some study subjects have been previously reported for lung findings but comparison of the three protocols and recommendations for invasive workup and resulting diagnoses have never been reported.

Methodology
- Retrospective
- Observational (cohort)
- Multicenter study

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