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Intergroupe francophone de cancérologie thoracique, Société de pneumologie de langue française, and Société d'imagerie thoracique statement paper on lung cancer screening

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A B S T R A C T

Following the American National Lung Screening Trial results in 2011 a consortium of French experts met to edit a statement. Recent results of other randomized trials gave the opportunity for our group to meet again in order to edit updated guidelines. After literature review, we provide here a new update on lung cancer screening in France. Notably, in accordance with all international guidelines, the experts renew their recommendation in favor of individual screening for lung cancer in France as per the conditions laid out in this document. In addition, the experts recommend the very rapid organization and funding of prospective studies, which, if conclusive, will enable the deployment of lung cancer screening organized at the national level.

Abbreviation

^{18}F-FDG	^{18}F-Fluoro-desoxy-glucose
ACRIN	American College of Radiology Imaging Network
BTS	British Thoracic Society
CAD	computer-assisted decision
CI	Confidence interval
COPD	Chronic obstructive pulmonary disease
CT	Computed tomography
CTDI	CT dose index
DANTE	Detection And screening of early lung cancer with Novel imaging TEchnology and molecular assays
DEP KP80	Dépistage du Cancer du Poumon dans la Somme
DICOM	Digital Imaging and Communications in Medicine
DLCST	Danish Lung Cancer Screening Trial
DLP	Dose-length product; ERS: European Respiratory Society
ESR	European Society of Radiology
GOLF	Groupe d'oncologie de langue française
GGO	Ground-glass opacity
HAS	Haute Autorité de Santé

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IFCT Intergroupe Francophone de Cancérologie Thoracique
IRSN Institut de Radioprotection et de Sûreté Nucléaire
JECS Japanese randomized trial for evaluating the efficacy of low-dose thoracic CT Screening for lung cancer in non-smokers and smokers
LDCT Low-dose computed tomography
LLPv2 Liverpool Lung Project version 2
LungRADS Lung CT Screening Reporting & Data System
MDT Multidisciplinary team
MILD Multicentric Italian Lung Detection
NCCN National Cancer Centers Network
NELSON Nederlands–Leuvens Longkanker Screenings Onderzoek
NLST National Lung Screening Trial
PET-CT Positron emission tomography-computed tomography
PLCOm2012 Prostate Lung Colon Ovary model 2012
PPV Positive predictive value
PY Pack-year
SFR Société française de radiologie
SIT Société d'imagerie thoracique
SPLF Société de pneumologie de langue française
UKLS United Kingdom Lung Screening
VDT Volume doubling time

1. Introduction

Bronchopulmonary cancer (lung cancer hereafter) is the leading cause of cancer death worldwide, with no exception for France, where it was the cause of around 33,000 deaths in 2018 [1]. The disease's incidence has stabilized in men but it is rising rapidly in women (+5.3% per year). Lung cancers are usually detected at advanced stages (68% of newly-diagnosed patients) [2] and despite current advances in therapy, the pathology's five-year survival rate in those stages does not exceed 15% [3,4]. However, when diagnosed at stage I and with surgical resection possible, the ten-year survival rate of lung cancer exceeds 80% [5,6].

Chest X-ray, sputum cytology, bronchoscopy and ^{18}F-Fluoro-desoxy-glucose (^{18}F-FDG) positron emission tomography-computed tomography (PET-CT) are ineffective for lung cancer screening [7–10]. By contrast, low-dose computed tomography (LDCT) has been or is being studied in ten randomized trials [11] (Fig. 1). Among them however, only two have sufficiently large enrollments to detect a possible difference in lung cancer mortality with sufficient statistical power: the American National Lung Screening Trial (NLST) with 90% power to detect a > 20% difference in mortality, and the Dutch-Belgian NELSON trial, with 80% power to detect a 25% difference in male patients [12,13].

Following the positive results of the NLST published in 2011 [12], a French multidisciplinary group of specialists with members from the *Intergroupe francophone de cancérologie thoracique* (IFCT; French Cooperative Thoracic Intergroup), the *Société d'imagerie thoracique* (SIT; Thoracic Imaging Society) representing the *Société française de radiologie* (SFR; French Society of Radiology), and the *Groupe d'oncologie de langue française* (GOLF; Francophone Oncology Group) representing the *Société de pneumologie de langue française* (SPLF; Francophone Pulmonology Society) had made a number of propositions for individual (*i.e.*, physician-to-patient recommendation) lung cancer screening [14,15]. Six years later, this group decided to update the previous statement following the communication of the NELSON trial positive results [16].

2. Methods

A national group of experts has been established upon a call for expression of interest by IFCT, SIT and GOLF; as well as all experts who participated in the initial multidisciplinary taskforce were also systematically reconvened [14]. Upstream of the new meeting, a number of questions, presented as section headings below, were isolated and distributed to pairs of experts for consideration. Those expert pairs were supplied with the previous texts developed for the preceding recommendations [15]. Thereafter, all the contributors were gathered for a workshop held 7th–8th November, 2018. There, the expert pairs presented their propositions, which were directly discussed and corrected until obligatory consensus was reached. After the workshop, the rationales of certain passages were reworked, when needed and/or in the presence of new data, by the expert pairs. The final version of the text was fully approved by all authors then all contributors. The level of evidence of the group's recommendations was graded as per the scale of the *Haute Autorité de Santé* (HAS; French National Authority for Health) (Table 1).

3. Should lung cancer screening be proposed in France?

In 2012, the group of experts stated its support for individual lung cancer screening in precise settings and with particular eligibility criteria based on the results of the NLST [12,14]. This latter involved 53,454 high-risk patients aged 55 to 74 years with a ≥ 30 pack-year (PY) smoking history and who had not quit smoking more than 15 years prior. All were randomly assigned to three years of yearly screening by PA chest X-ray or LDCT [12]. The NLST's results showed a significant 20% reduction (95% confidence interval [CI]: 6.8–26.7; $P = 0.004$) in lung cancer-related mortality and a 6.7% reduction (95% CI: 1.2–13.6; $P = 0.020$) in all-cause mortality in the patients screened by LDCT, compared to those screened by chest X-ray. Results from other trials on LDCT screening have since been reported (Fig. 1). The randomized DLCST trial found no improvement in cancer-related death but it had several limits affecting that endpoint. First, the trial was not conceived to demonstrate a reduction in specific mortality, but to be grouped for analysis with the NELSON trial, an aspect that explains the relatively modest enrollment for DLCST. Also, it reported early results, with a median follow-up of only five years [17]. Similarly, the ten-year results reported from the ITALUNG trial were also negative but they too suffered from limited statistical power [18]. Pooled results from the Italian DANTE and MILD trials after a median eight years of follow-up were published in 2017 and showed no significant mortality benefit for LDCT at that amount of surveillance [19]. However, the authors of the MILD trial recently provided a new report on their results at ten years of follow-up for their cohort [20]. Although the MILD trial was not designed to detect a difference in mortality but to evaluate annual or biennial screening, its results did show a significant 39% reduction in lung cancer-related mortality in the patients who had LDCT screening (annual and biennial grouped) compared to those who had no intervention. Also recently, the results of the German LUSI trial were reported with a median follow-up of 8.8 years. Here too, the study cohort was too small to ensure sufficient power for the detection of a significant difference in specific mortality. Nonetheless, the authors did report a 26% reduction (0.74 [95% CI: 0.46–1.19]; $P = 0.21$) in cancer-related mortality for patients who had LDCT screening (*vs.* X-ray). Furthermore, that difference significantly benefited women (HR = 0.31 [95% CI: 0.10–0.96], $P = 0.04$) [21]. Finally and particularly, the eleven-year results of the NELSON trial were recently published [16]. These results were eagerly awaited, as their statistical power was sufficient for detecting a change in lung cancer mortality in men (initially planned in association with the Danish DLCST study). The inclusion criteria of the NELSON study [20] were different from those of the NLST (especially the lower age limit: 50 years). The NELSON study also had a different screening schedule, with CTs at baseline (detection of prevalent nodules), one year, three years and optionally five and a half years. It also

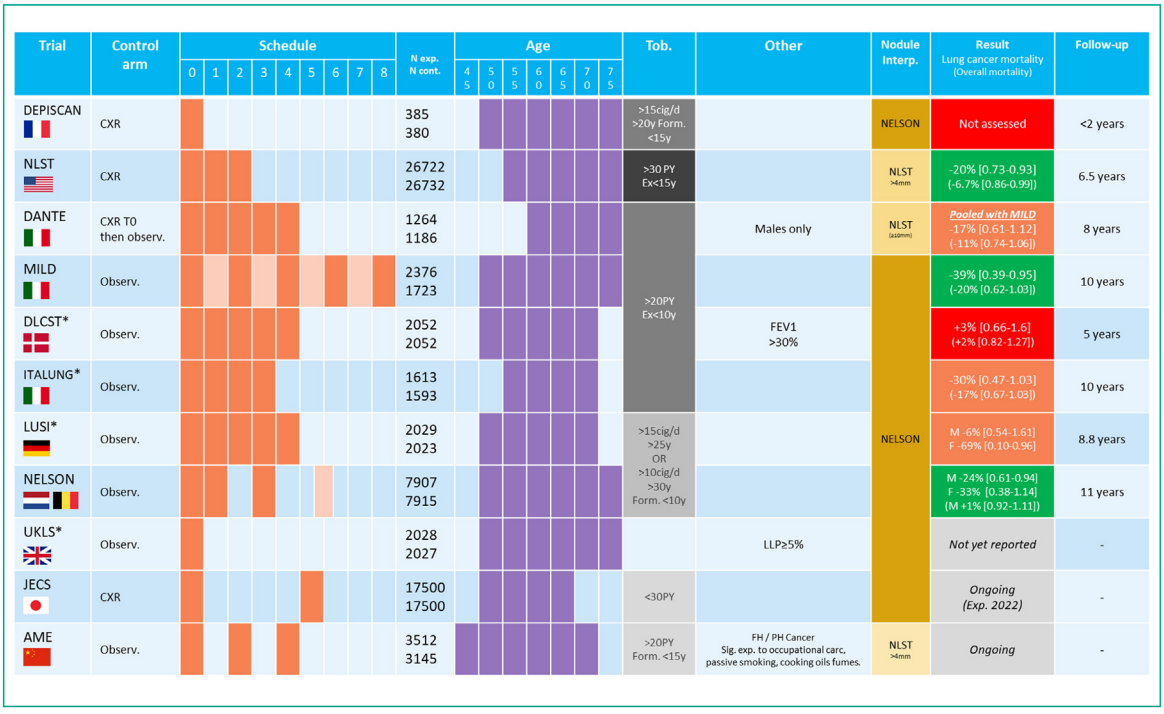

Fig. 1. Randomized trials on low-dose computed tomography for lung cancer screening.

Table 1
Employed recommendations grading (*Haute Autorité de santé* [HAS; French National Authority for Health]).

A	Established scientific evidence Founded on strong evidence (level 1): randomized controlled trials (RCTs) with high statistical power and no major biases or meta-analyses of RCTs, decision analysis based on well-designed studies
B	Scientific presumption Founded on intermediate evidence (level 2): RCTs with lesser statistical power, well-designed non-randomized studies, cohort studies
C	Low scientific evidence Founded on lower levels of evidence: case control studies (level 3), retrospective studies, case series studies, comparative studies with important biases (level 4)
AE	Expert agreement In the absence of studies, recommendations are founded on consensus among the expert work group members, after consultation with the reading group. The absence of grading does not imply a lack of pertinence or utility, but it must lead to a commitment for complementary studies

differed fundamentally from the NLST in positive screen management, based on nodule volume and evolution at three months in patients with 50 to 500 mm^3 nodules. The NELSON study provided positive results at 11 years of follow-up even without the initially-planned grouped analyses of data from other studies. Indeed, after eight years of follow-up, it showed significant reductions in lung cancer mortality of about 25% in men and about 40 to 60% in women [16]. As of this writing, the UKLS and JECS studies have not yet provided consolidated results.

There are also a number of French studies on the interest of lung cancer screening. One modeling study crossed demographic information on the French population with data published upstream of the NELSON study results. Using first the strict NLST criteria then those criteria with the NELSON's 50-year age threshold, the authors of that modeling study reported screening-eligible populations of respectively 1650 and 2283 people. According to that study, the cost of screening could be covered by a modest, 10-cent (€)/pack price increase for cigarettes [22]. A prospective cohort study (DEP KP80) was carried out in the French administrative department of the Somme [23]. Using the inclusion criteria of NLST and a decisional algorithm adapted from NELSON, its baseline results showed the feasibility and effectiveness of a yearly LDCT lung cancer screening program. DEP KP80 recruited 1307 patients in two and a half years and reported a participation rate of 73% and a positive screening rate of 5.7%. Of these positive screenings, 45% were confirmed cancer ($n = 24$) and of these latter, 75% were detected at early stages (0 to II).

The authors of DEP KP80 considered their results sufficient to justify the implementation of screening in France, the first step of which would be the deployment of large-scale testing in pilot regions.

#1 The two randomized studies with patient enrollments conferring sufficient statistical power satisfactorily demonstrated the ability of LDCT screening to significantly reduce lung cancer-specific mortality. Thus, in accordance with all international guidelines, the experts renew their recommendation in favor of individual screening for lung cancer in France as per the conditions laid out in this document (grade A). Here, we defined individual screening as the systematic proposal of screening, as described in this document, by a physician to an eligible patient, independent of any possible national programs.
#2 Considering the rarity of data on the feasibility of LDCT screening for lung cancer in France, the experts recommend the very rapid organization and funding of prospective studies, which, if conclusive, will enable the deployment of lung cancer screening organized at the national level (grade AE).
#3 Lung cancer screening should be carried out using low-dose non-contrast-enhanced computed tomography (grade A).

4. To whom should individual lung cancer screening be proposed?

The work group expressed their opinion that screening should be proposed only to patients whose characteristics would have made them eligible for the NLST or NELSON study (Fig. 1 and Table 2) [14,24]. Consequently, screening should be proposed to all patients aged 50 to 74 years with a history of current or former (quit ≤ 10 years prior) smoking counting > 15 cigarettes/day for ≥ 25 years or > 10 cigarettes/day for ≥ 30 years.

In the NLST and NELSON study, the upper age limit for screening was 74 years. The United States Preventive Services Task Force recommends screening up to the age of 80 years based on modeling studies using the NLST contributively and performed on cohorts of American smokers [25]. In the absence of prospective European data, the work group decided to maintain the upper limit of screening initiation to 74 years and proposed additional research on advanced age groups.

In the NLST, patients who had quit smoking within the preceding 15 years were eligible for enrollment. In the NELSON trial, that interval was limited to 10 years. The present expert group considers that patients eligible for screening on all other criteria and having quit smoking ≤ 10 prior or optionally ≤ 15 years prior may benefit from screening.

A number of teams have studied the contribution of risk modeling, which integrates novel variables to optimize the identification of screening candidates. Risk scores are conceived to improve screening performance, with such goals as, for example, reducing the number of individuals to screen to detect one cancer or prevent one death [26]. These scores, often built upon clinical and/or radiological data, do appear pertinent [27–29], but none have been compared in prospective randomized trials. In the UKLS trial, the LLPv2 (*Liverpool Lung Project*) score was not a randomization but an inclusion criterion. Of all the randomized trials, the UKLS trial identified the highest proportion of stage I or II lung cancers. The PLCOm2012 score was used to select eligible patients in the prospective PanCan trial. In its cohort, the cumulative incidence rate for cancer was significantly higher than that of NLST, with furthermore a higher proportion of stage I/II cancers (77% *vs.* 57%; $P < 0.001$). For other lung cancer risk factors (professional or environmental carcinogen exposure, rare hereditary predispositions, comorbidities), there are currently insufficient data in the literature to propose specific recommendations.

All patients who accept screening must do so voluntarily after having received complete information on the possible benefits and risks (see below). They may need time to reflect on whether to accept screening. Current smokers must be strongly encouraged to join a smoking cessation program and oriented toward professionals and/or institutions specialized in smoking cessation (in France: http://www.tabac-info-service.fr). Encouraging the patient to stop smoking must be systematically repeated at ever screening visit and smoking cessation counseling formally integrated in the process [30]. No particular cessation strategy has demonstrated its superiority over any other [31–33].

Patients who have developed symptoms or signs suggestive of lung cancer (hemoptysis, weight loss > 10% of normal weight and/or lung infection) in the preceding year must undergo immediate diagnostic work-ups; they are thus not candidates for screening. Also, screening should not be proposed to patients meeting NELSON and/or NLST exclusion criteria (Table 2), including severe comorbidities contraindicating invasive thoracic procedures and thus any surgical treatments. LDCT screening is not a substitute for diagnostic examination(s) when respiratory disease is suspected. Finally, patients with a history of cancer are to be placed under specific surveillance and thus the work group does not recommend including them in individual lung cancer screening procedures.

#4 Individual LDCT screening for lung cancer should be thoroughly explained (informed consent) and proposed to all patients aged > 50 years who have a current or recent past (cessation within the preceding 10 years) history of smoking > 15 cigarettes/day for > 25 years OR > 10 cigarettes/day for > 30 years and who do not meet exclusion criteria. Entry into a screening program may be proposed to patients up to 74 years of age (grade A).
#5 Ex-smokers who meet the above criteria but quit smoking > 10 but < 15 years prior may be proposed screening as an option (grade AE).
#6 Patients who have a history of cancer, present clinical signs suggesting cancer, recently underwent a thoracic CT for other reasons, or present one or several severe comorbidities contraindicating invasive thoracic procedures are ineligible for LDCT screening (grade A).

5. What is the optimal duration of screening?

There are few prospective data available on the optimal duration of lung cancer screening in at-risk patients. The cohort from the ELCAP study was compared to that of another study (CARET) not involving screening. The comparison clearly showed that interrupting screening was associated with an increase in the rate of lung cancer-related death [34]. Complementarily, Veronesi et al. showed that the rate of lung cancer detection remained stable across a long duration of yearly LDCT screening [35,36].

Other elements also argue in favor of regular screening for lung cancer, such as its comparability with other cancer screening programs, the theoretical need for continuous screening, or the consistent cancer detection rates observed in all three of the NLST's annual screenings, respectively 1%, 0.7% and 0.9% [12]. The persistence of the effectiveness of screening when maintained beyond three to five years was recently demonstrated in the NELSON study, wherein a fourth screening CT was done 5.5 years after inclusion and concerned thus 5279 patients (*i.e.*, 68% of the initially-included experimental group). That fourth screening was positive in 105 patients (*i.e.*, 2% of the 5279 participants) among which 43 (0.8%) were diagnosed with cancer for a positive predictive value (PPV) of 41%, which was similar to the mean PPV of all four of the NELSON study's screening rounds [37]. Thus, at five and a half years and even further up to eleven years, the cumulative number of detected lung cancers remained significantly higher in the experimental group vs. the control group. Finally, the relative risk of lung cancer-related death was significantly reduced from 24% by year at eight to ten years and by 22% at eleven years in men. In women lung cancer mortality was significantly reduced by 54%, 59%, and 48% at 7, 8 and 9 years, respectively [16].

More recently, the ten-year data of the randomized MILD trial were published. In MILD, either annual ($n = 1190$) or biennial ($n = 1186$) screening was maintained for ten years and the results compared to those of a control group [20]. The trial showed an overall reduction in cancer-related mortality, with that benefit being more pronounced after five years. Thus, at ten years, the sex, age and consumption (in PY)-adjusted overall death risk was significantly lowered by 32% and the lung cancer-related death risk was reduced by 68%. These data convincingly demonstrate that screening continues to reduce the risk of lung cancer-related death when continued for at least ten years.

#7 LDCT screening should be continued for at least 5.5 to 10 years (grade A).

Table 2
Eligibility, exclusion and exit criteria for individual lung cancer screening.

Eligibility criteria	Exclusion criteria	Exit criteria
Age between 50 and 74 years; AND smoking > 10 cigarettes/day for > 30 years OR > 15 cigarettes/day for > 25 years; AND current smoker or ex-smoker having quit in the preceding 10 years OR preceding 15 years (OPTION)	Inability to climb two floors by stairway without stopping	Cessation of smoking dating > 10 years (optionally > 15 years)
AND accepting screening after provision of informed consent	Weight ≥ 140 kg	Age > 74 years after 3 CT examinations (excluding studies)
AND willing to accept help for smoking cessation	History of thoracic CT within the preceding year (except screening CT)	Development of an exclusion criterion
	History of lung cancer within preceding five years or under treatment for lung cancer	
	History of cancer currently monitored by thoracic imaging studies	
	Severe comorbidity(ies) contraindicating therapeutic possibilities or invasive thoracic procedures	
	Current or recent respiratory symptomatology suggestive of cancer (hemoptysis, weight loss, recent pulmonary infection)	

6. How frequently should screening CT be performed?

The optimal interval between screening LDCT has not yet been clearly established. In a debated interim analysis within the MILD trial, an increase in the cumulative incidence of lung cancers was observed in the annual compared to the biennial screening group (excluding nonsolid nodules), but there was no sign of an increase in advanced-stage detections in the biennial group. Furthermore, there were no statistically significant differences between the annual and biennial screening groups in terms of mortality, test performance (sensitivity, specificity, predictive values) or number of interval lung cancers (those detected between screening CT) [38–40].

The NELSON trial performed a baseline screening (first round) and thereafter spaced their screenings incrementally, with first a one-year (second round), then a two-year (third round) and finally an optional two and a half-year (fourth round) interval. In comparison to the trial's second screening round, the fourth round detected significantly less stage IA cancers (75.9% *vs.* 60.9%) and more stage IIIB/IV cancers (6.8% *vs.* 17.3%; $P = 0.02$). In comparison to the third screening round, the fourth round again detected less stage IA cancers (72.7% *vs.* 60.9%) and more stage IIIB/IV cancers, but this time without statistical significance ($P = 0.10$). Nonetheless, the number of cancers detected in the fourth screening round (five and a half years after baseline) was only slightly and statistically insignificantly lower than those of the preceding rounds, suggesting a screening performance (rate of lung cancer detection) that is not inferior to other intervals. There was however the drawback of a greater number of interval cancers observed in that two and a half-year period between the trial's third and four screening rounds [37]. An analysis of the results from the one and two year intervals (second and third rounds) showed that there was no statistically significant difference between them in the number of cancers detected in later stages ($P = 0.09$) [41].

In the absence of personalized risk assessments, these results argue in favor of a screening interval of two years at the most. Based on a modeling study of the NELSON data, it does appear that shorter screening intervals do have a greater effect on reducing mortality, with one, two and three-year intervals between screenings reducing that endpoint respectively from 11 to 21%, 6.5 to 9.6%, and 4.6 to 6%. Annual screening does thus appear to be more cost-effective when considered in terms of life-years saved compared to saved costs [42,43]. Furthermore, another work derived from the NELSON trial demonstrated a significantly longer preclinical time (the time needed to progress from stage IA to stage II) for IA adenocarcinoma in women (2.44 years) compared to men (1.82 years), but no such difference was detected for other histopathological types between sexes [44].

Equally, the results of preceding screening rounds appear to be an important predictive element [45]. Indeed, *post-hoc* analyses of NLST data have shown that incidence and mortality are inversely related to a preceding negative screening and that the effect strengthens with a second preceding negative screening. Other variables significantly associated with the risk of cancer diagnosis were a known history of COPD and CT detection of emphysema [46].

These data were furthermore confirmed in the NELSON study. In its fourth round, the risk of lung cancer was 0.6% for patients with negative results from all the preceding three rounds, but 1.6% for those with at least one indeterminate round (but never a positive round) and 3.7% for those with an indeterminate third round (*vs.* 0.6% for those with a negative third round) [37]. Finally, the NELSON trial also showed that the risk of cancer was correlated to nodule size and nodule volume doubling time (VDT) [47].

Thus, several authors have suggested personalizing screening intervals after the second screening as a function of the patient's individual risk profile as determined by prediction scores such as $PLCO_{m2012}$ or the radiological data from the first (baseline) screening. Very recently, the team behind the PLCO cancer risk prediction model developed and validated a model wherein preceding screening results are considered in addition to the $PLCO_{m2012}$ variables [45]. Their results suggested that for at-risk patients (PLCO > 1.3% for the NCCN; > 2% risk in the *Cancer Care Ontario pilot study* cohort), the screening interval should be maintained at one year whereas for others, an interval of two years may be proposed. Setting a screening interval based on individual risk would of course reduce costs and furthermore lower exposure to radiation for people at low risk, who could be scheduled for screening once every two years. However, no prospective studies have been done on this strategy.

7. What technical procedures are necessary for screening?

Lung cancer screening is performed via a volumetric, unenhanced LDCT scan [48,49]. Scanners with ≥ 16 raws of detectors should be used for acquisitions, these latter taken with the patient in the supine position, arms extended behind the head, during a deep-inspiration breath-hold and covering the lung from its apex through to the inferior pleural recesses. Native slice thickness should be ≤ 1.25 mm with a 30%-overlap reconstruction to enable volumetric analysis of abnormalities.

#8 Considering the current state of knowledge and the absence of risk personalization, the expert group recommends a maximum interval of two years between LDCT screenings (grade B).
#9 Pending specific studies, it seems reasonable to initially propose two screenings with a one-year interval between them. When both are negative and the patient has no risk factors other than tobacco use (e.g., emphysema, history of COPD), biennial screening may be proposed. Screening must however remain annual in the presence of any additional risk factors and/or any indeterminate screening result (grade AE).

There is currently no consensus definition of "low-dose" CT. Considering the diverse range of employed CT equipment, radiation limits should not be expressed in terms of volts or milliamps but instead in volume CT dose index (CTDI), with a goal of achieving a volumetric CTDI (or CTDIvol) of no more than 3 mGy in a standard-size patient (height, 170 cm; weight, 70 kg) [50,51] and for instance ≤ 0.4 mGy for patients weighing < 50 kg; ≤ 0.8 mGy for patients weighing ≥ 50 to ≤ 80 kg; and ≤ 1.6 mGy for patients weighing > 80 kg. DLP and CTDI should be indicated on the imaging study report. Ultra-low-dose CT (dose close to that of a frontal + lateral chest X-ray) currently lacks sufficient validation for deployment in screening [50–52]. However, techniques to optimize image noise to irradiation ratios such as iterative reconstruction or *deep learning* are recommended.

Readings should be done at the workstation from axial slices no thicker than 1.5 mm reconstructed in lung (parenchyma) and mediastinal windows and furthermore in multiplanar reconstruction for detected abnormalities. Maximum intensity projections with slab thicknesses of 5 to 8 mm should be used to optimize the detection of peripheral solid nodules [53]. Second-reading computer-aided detection (CAD) has been shown to increase lung nodule detection sensitivity (76%) compared to results provided by single (50%) or double (63%) human readers [54]. Within a study involving 400 CT examinations randomly chosen from the NELSON trial (double radiologist reading), 22% of nodules ≥ 50 mm^3, including one cancer, were identified only by CAD [55]. That study reported detection rates of 78% and 97% respectively for double readings and CAD (*i.e.*, 19% more nodules using the latter compared to the former). It also reported that false-positives by CAD could be limited by excluding nodules measuring less than 50 mm^3 (equivalent to a mean diameter of 5 mm) [55]. Those results were confirmed in a study performed on anthropomorphic phantoms to compare various combinations of single or double readings and three different CAD programs for solid and nonsolid nodules measuring ≥ 5 mm. Combining one human reader with one CAD provided sensitivities constantly greater than those obtained by any combination of two CADs (97–99% *vs.* 85–88%) [56]. In the setting of organized screening, it appears more realistic to systematically deploy a second reading by CAD with a predefined detection threshold rather than double radiologist readings. Limitations to the use of CAD include an increase in reading time, the management of false-positives and a lower sensitivity for the detection of nonsolid nodules [57]. In the near future, the introduction of artificial intelligence should improve CAD performance and ultimately will find itself the subject of research, notably through "radio-banking" [58]. An advantage of CAD is that it can be paired with volumetric evaluation of detected nodules for immediate classification according to guidelines [59].

The interpretation of screening-derived CT images must be entrusted to radiologists specialized in thoracic imaging or thereto trained via specific, validated programs. Nodule volume measurements should be done with dedicated software on standard reconstructions. If that is not possible, measurements may be taken manually following the Fleischner Society's recommendations for fortuitously-discovered nodules [60]. Manual measurement of nodule diameter must be done on reconstructed sections with lung window settings. The average of the long and short axes should be used to express the size of nodules ≤ 10 mm. The maximum diameter is sufficient for nodules > 10 mm or with a round shape. All measurements are expressed in millimeters rounded to the nearest whole number. For part-solid nodules, the solid component and global diameters must be indicated.

The screening CT examination must be assessed first as a separate entity then in comparison with all available preceding CT (including the oldest ones) to evaluate lesion evolution. The CT report must include all observations necessary for determining the most pertinent course for clinical management [61]. A radiological report model will help to ensure inter-reader reproducibility (Table 3). Screening CT imaging files are to be stored on a centralized server in the Digital Imaging and Communications in Medicine format for quality control and research purposes.

Each patient should be encouraged to have all his/her iterative screenings performed in a single center. Should that recommendation not be followed by the patient, centralized file management may nonetheless enable access to CT histories and their indispensable comparison. All medical centers having the necessary technical/organizational capacities and pertinently specialized or trained radiologists may propose lung cancer LDCT screening.

Table 3
Minimal requirements for lung cancer CT screening structured report.

Type	Variable (unit)
Technical data	Dose-length product (mGY.cm) Delivered dose (Sv) CTDIvol (mGy)
Nodule characterization	Attenuation (solid/nonsolid/part-solid) Location (laterality and lobe) Number of slices at nodule center Findings suggesting benignity (calcification; fat density; typical lung lymph node aspects) Prevalent or incident Morphology (regular or spiculated borders, perifissural aspects) Involvement of neighboring structures (yes/no) Dimension: solid nodule: volume (in mm^3); nonsolid: average of the long and short axes; part-solid: volume of solid component and average of the long and short axes VDT (days) and comparison to preceding examinations
Emphysema	Yes/no (if yes, number of affected lobes)
Other abnormality(ies) justifying management: parenchymatous, mediastinal, abdominal	

CTDI: CT dose index; VDT: volume doubling time.

#10 Lung cancer screening should be done via unenhanced LDCT at a DLP < 100 mGy.cm and a CTDI consistent with patient weight, and includes volumetric measurement of any detected abnormalities (grade A).
#11 Second-reading computer-aided detection is recommended (grade AE).
#12 The use of a minimum radiological report model is recommended (grade AE).

8. How screening CT should be interpreted?

There are several formalized guidelines for screening-detected nodule management including those of the Fleischner Society [49,62] – which were edited for incidentally found nodules – or the LungRADS classification (updated to version 1.1 in 2019) of the American College of Radiology (The American College of Radiology's Lung CT Screening Reporting & Data System is available at https://www.acr.org/Clinical-Resources/Reporting-and-Data-Systems/Lung-Rads, accessed 05 July 2019). These guidelines define positive tests in different ways and have not been subjected to prospective comparative trials as of this writing. In addition to those formalized guidelines, there are also clinical trial protocols, including those for the NLST and NELSON study, that have been prospectively tested in the setting of a randomized trial with definitions for positive, indeterminate (for NELSON) or negative tests as well as associated decisional algorithms. The NELSON trial defined a positive screening via a combination of nodule presence and size (volume) with a later contribution of VDT. That approach yielded a PPV of 41%. Comparatively, the NLST, wherein all non-calcified nodules > 4 mm were considered positive, reported a PPV of 3.6% and a criticized false-positive rate of 96% [12,47,48,58]. Several *post-hoc* analyses were programmed as part of the NELSON trial with the goal of better identifying at-risk abnormalities by, for example, refining thresholds for nodule volume or VDT. On another point, those analyses showed notably that incident nodules (those not present in preceding screenings) carried a greater risk of malignancy [63,64]. The threshold refinements however, although interesting in theory, did not appear to demonstrate an interest. Indeed, such changes performed inferiorly to the initial protocol, notably in terms of PPV and specificity [47,65].

Nonetheless, a group of authors who participated in screening programs in eight European countries recently published an expert opinion recommending the use of the threshold refinements, developed in the above-mentioned *post-hoc* analyses, for solid nodules [58]. Those threshold refinements are also forwarded in recent recommendations by the European Society of Radiology (ESR) and the European Respiratory Society (ERS) [66]. The refined positivity thresholds vary for prevalent (nodules present at baseline: 100 to 300 mm^3 and VDT of 600 days) or incident (30 to 200 mm^3 and VDT of 600 days and remaining inferior to 200 mm^3 [or 8 mm]) nodules, these latter necessitating a greater level of attention. Notwithstanding the positioning of these other expert groups, the French expert group recommends the nodule interpretation rules defined in the initial NELSON protocol, whatever the type of nodule, considering that these rules only have been validated in a prospective randomized trial [16,48]. This recommendation necessitated votes among the work group members (20 votes cast) for solid (13 votes in favor of the NELSON trial rules [48], 5 votes in favor of the post-hoc-developed rules [47,58], 1 vote for neither, 1 no opinion vote) and subsolid (10 votes in favor of the NELSON trial rules [48], 5 votes in favor of the Fleischner Society rules [62], 2 votes in favor of the LungRADS v1.1 rules, 1 vote for neither, 2 no opinion votes) nodules.

The analysis of a CT screening will give one of three possible results: a "positive" screening, leading to management involving a multidisciplinary team (MDT) meeting due to a high probability of lung cancer [67]; a "negative" screening, finding no suspicious abnormalities and necessitating only the maintenance of the screening schedule; and finally an "indeterminate" screening, representing only a temporary result and necessitating a follow-up CT in three months. That follow-up imaging study remains an unenhanced LDCT. The probability of malignancy for a screening-detected nodule depends primarily on its density (solid, part-solid, nonsolid), volume (or diameter) and evolution. In the case of multiple nodules, the strategy to be deployed is that pertinent to the most suspicious nodule.

#13 The expert group recommends using the protocol deployed in the NELSON trial for the interpretation of all nodule types (solid, part-solid, nonsolid) detected in LDCT. This recommendation was subjected to votes by the work group members (20 votes cast): 13/20 voted for this recommendation in the setting of solid nodules and 10/20 voted for it in the setting of subsolid nodules (grade AE).

9. Decision-making strategy for solid nodules

The first step in the presence of a solid nodule is to determine if it meets benignity criteria. If the nodule is entirely calcified or if it has a central calcification on two orthogonal planes, the screening is considered negative regardless of nodule size. In this case, the established screening schedule may be maintained. Other benignity criteria include: an intranodular fat deposit (−40 to −120 Hounsfield units) or features suggesting an intrapulmonary lymph node (solid homogenous density, size < 10 mm, < 10 mm from a pleural surface, location inferior to the tracheal carina, triangular or oval shape, connection to adjacent pleura by a thin septum) [14].

For non-calcified solid nodules, the main feature to be considered is nodal volume, or, failing that, the mean of the long and short axes (Fig. 2). Because nodules are never perfectly spherical, there is no strict proportionality between volume and diameter measurements. As a simplification measure, the diameter thresholds given below have been rounded; consequently, they do not correlate strictly with the corresponding volume thresholds. It is also important to underline the need for identical acquisition parameters when calculating VDT from two volumetric evaluations.

Non-calcified nodules measuring < 50 mm^3 (or with a diameter < 5 mm) indicate a negative screening and the patient may maintain the established screening schedule. Non-calcified nodules measuring ≥ 500 mm^3 (or with a diameter ≥ 10 mm) indicate a positive screening and the patient must be referred to an MDT for the determination of complementary investigations. Non-calcified nodules measuring in between those thresholds indicate an indeterminate screening. A follow-up CT should be scheduled at three months (6–8 weeks for incidental nodules) for nodal volume (or mean diameter) comparisons and VDT calculations. A VDT ≥ 400 days indicates a negative test and the patient may return to the established screening schedule. Inversely, a VDT < 400 days indicates a positive test and the patient must be referred to a MDT (Fig. 2).

#14 For non-calcified solid nodules, the volume thresholds of < 50 mm^3 and ≥ 500 mm^3 indicate respectively negative and positive screenings. Patients with nodal volumes in between the above thresholds should be scheduled for a follow-up CT in three months (6–8 weeks for incidental nodules). Calculated upon that follow-up CT, VDTs ≥ 400 days and < 400 days indicate respectively negative and positive tests (grade A).

10. Decision-making strategy for subsolid nodules

Particularities in the management of subsolid nodules arise from, on one hand, their propensity to self-resolve (approximately 50% of nodules) but, on the other hand, their tendency to become adenocarcinomas—albeit generally non or minimally invasive—when they do not resolve [62,68]. It is these indolent lesions that are most likely to expose patients to overdiagnosis [69,70]. Thus, in the presence of subsolid nodules, surveillance should be given priority to avoid that risk [58]. Also, in this

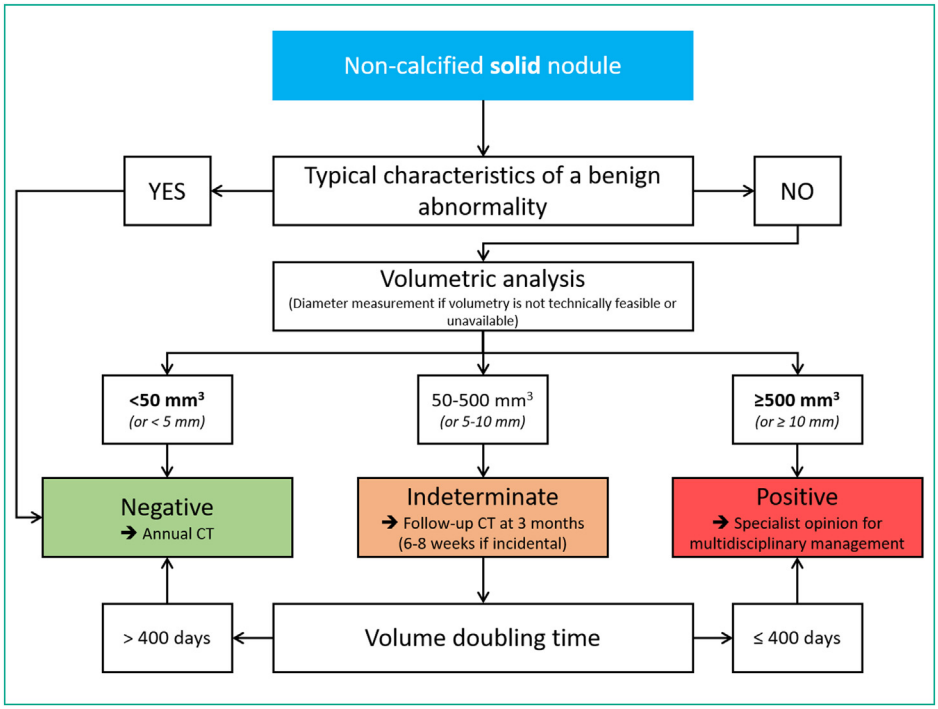

Fig. 2. Proposition for a non-calcified solid lung nodule decisional algorithm (adapted from [48]).

setting, the reproducibility of volumetric measurements is reduced. It is also important here to re-emphasize the irrelevance of ^{18}FDG PET-CT for nonsolid nodules.

In a position statement, some European experts recommended the deployment of the protocol proposed by the British Thoracic Society [58,71]. That protocol is however complex and unvalidated in prospective trials as of this writing. With the present document, the French expert group recommends the prospectively-validated NELSON trial protocol [48]. This latter distinguishes nonsolid and part-solid nodules. Nonsolid nodules are described using the mean of the long and short axes. When it is < 8 mm, the screening may be considered negative. When it is ≥ 8 mm, the screening should be considered indeterminate and the patient rescheduled for a follow-up CT in three months. If no solid component has appeared the screening is considered negative; otherwise, it is considered positive (Fig. 3). Specialist opinion should be however considered in case of ground-glass opacity extension (≥ 2 mm) only (with no solid component appearance). Part-solid nodules are described by the mean of the long and short axes and the volume of the solid component. The decisional algorithm proposes pathways as a function of those two variables (Fig. 4).

#15 In the presence of a nonsolid nodule, the screening is considered negative when the mean diameter is < 8 mm; indeterminate when the mean diameter is ≥ 8 mm; and positive if a solid component has developed at the time of the three-month follow-up CT (grade A).
#16 In the presence of a prevalent part-solid nodule, the screening is considered negative when the mean diameter of the nodule is < 8 mm and the volume of the solid component is < 50 mm^3; indeterminate when the mean diameter is ≥ 8 mm or when the volume of the solid component is ≥ 50 and < 500 mm^3; and positive when the volume of the solid component is ≥ 500 mm^3, or when the volume of the solid component is ≥ 50 and < 500 mm^3, and the nonsolid component evolves rapidly (VDT < 400 days at three-month follow-up scanner).

11. What information should be provided to eligible patients?

Cancer screening is of interest only if it reduces mortality from the cancer it targets. Screening for lung cancer does so, and in a statistically significant fashion, as shown by three studies, the American NLST (> 50,000 participants) and the European NELSON (> 15,000 participants) and MILD (> 4000 participants) studies. Thus, deploying lung cancer screening does appear to be advantageous, but doing so has consequences that must be communicated to screening-eligible patients (Appendix 1). Principally, these latter must be informed about the high-risk of discovering an abnormality—whatever the nature—that could necessitate further and sometimes invasive investigations. Considering the NELSON data, of every 1000 patients who underwent screening, 22 had positive results, and among them, 9 were ultimately diagnosed with lung cancer. That result implies 13 false-positives that would need complementary examinations, most being supplementary imaging studies rather than invasive procedures that could cause complications. Information provided to patients must emphasize that the risk of cancer discovery remains low at about 0.9 to 3.7% in the screening-eligible population [12,16]. The psychological impact resulting from the possible discovery of an abnormality must be discussed with patients, as must the sometimes large amount of time needed to determine benignity or malignancy. On those points however, several research teams have looked at the effects of LDCT cancer screening on patient anxiety and quality of life and reported relatively reassuring findings [72–77].

Also to be considered is the risk of overdiagnosis (*i.e.*, the discovery of indolent tumors that would have never manifested clinically nor caused the death of the patient). That said, this risk is likely globally infrequent in lung cancer, where VDT is usually short, about 180 days on average [78,79]. Evaluating overdiagnosis in this setting is complex. According to different studies and especially different employed methodologies, it may occur in 0 to 67% of cases [18,80,81]. The NLST reported an estimated 1.38 cases of overdiagnosis for every 320 patients who would need to

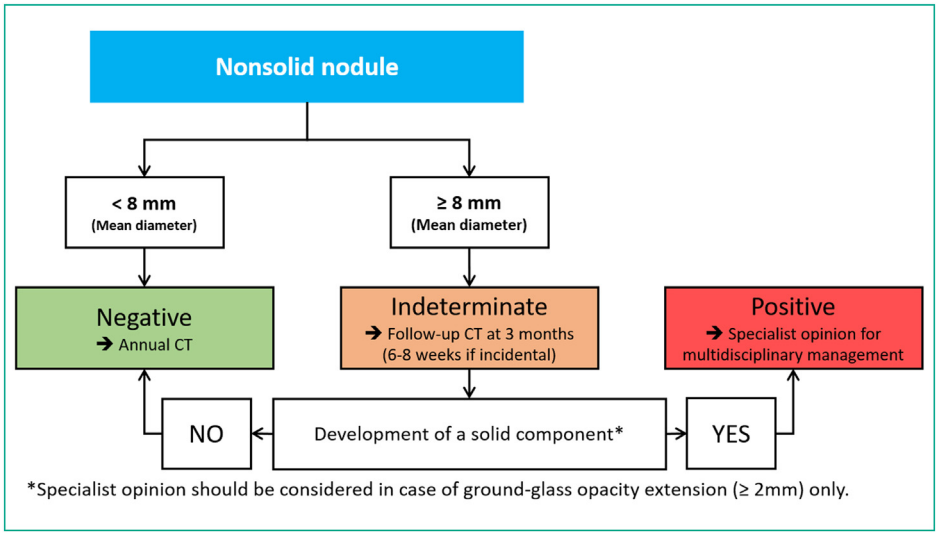

Fig. 3. Proposition for a nonsolid lung nodule decisional algorithm (adapted from [48]).

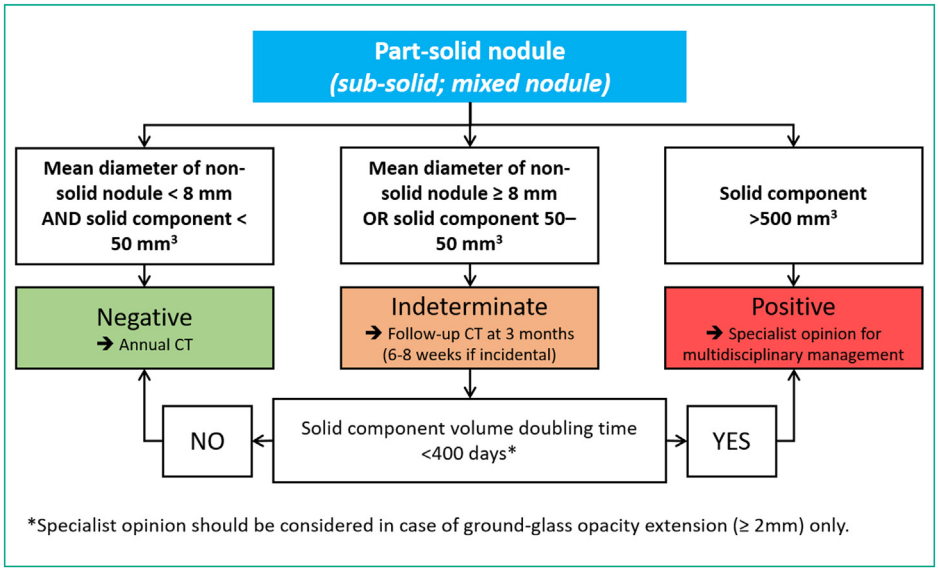

Fig. 4. Proposition for a part-solid (or sub-solid nodule) lung nodule decisional algorithm (adapted from ref. [48]).

be screened to avoid one lung cancer death [80]. Very recently, an article on extended follow-up results (12 years) for the NLST reported a reassuring 3% rate of overdiagnosis, noting however that this was after the exclusion of bronchioloalveolar/lepidic adenocarcinomas (corresponding morphologically to subsolid nodules), which carry a very high rate of overdiagnosis, approaching 80% [70]. Thus, the risk of overdiagnosis in lung cancer screening appears to be present mainly in subsolid nodules, which show longer VDTs, sometimes exceeding 400 days. Nonetheless, the degenerative potential of subsolid nodules must not be underestimated as they are able to evolve sometimes quite belatedly, into invasive and even metastatic cancer. Therefore, some of these nodules may, in reality, be slow-growing cancers [69,82], which leads less to a overdiagnosis bias than to a lead–time bias. These lesions thus do require long-term monitoring and may deserve MDT consideration.

Unneeded investigations and treatments can be avoided by following recommendations for the management of screening-detected nodules. In the NELSON trial, 264 subsolid nodules were detected in 234 patients, representing 3.3% of all detected nodules. It must be underlined that more than half of those nodules disappeared during follow-up, confirming their benignity and probable infectious etiology. Of the 33 subsolid nodules resected in the NELSON trial, 28 were confirmed as non-small cell lung cancers, among which nine were *in situ* adenocarcinomas. Of the 19 resected invasive cancers, 16 had VDTs > 400 days. The other nodules were assigned to monitoring [83]. Only 0.7% of the NELSON trial participants had incident subsolid nodules [84].

Also, an important isue is the radiation exposure resulting from repeat CT examination. In the NLST, the mean LDCT dose was 1.5 mSv. The mean natural irradiation in France is 2.9 mSv per year (Institut de Radioprotection et de Sûreté Nucléaire [IRSN]; French Institute for Radioprotection and Nuclear Safety, 2015). For comparison, frontal and frontal + lateral chest X-rays deliver respectively 0.05 and 0.2 mSv. LDCT screening-eligible patients should be informed that any one CT corresponds to six months of natural exposure at the most. Although the risk of developing radiation-induced cancer cannot be totally eliminated, it does appear to be extremely low, notably considering the age of patients eligible for screening [85]. Furthermore, the reduction in overall mortality observed in the NLST suggests an absence of

significant consequences on survival. In the Italian ITALUNG trial, in which 3206 patients were randomized to five years of annual LDCT screening or no screening for lung cancer, the mean, cumulated, individual irradiation dose in the patients concerned by it ranged from 6.2 to 6.8 mSv. The screening CT themselves were responsible for 77% of that exposure and complementary examinations for the remaining 23% [86]. Some authors have underlined the deleterious effects of overstating the risks of radiation to patients, including that of premature mortality caused by the non-detection of serious pathologies, whereas any theoretical risk caused by irradiation would appear many years after the examination, if at all [87]. However, the advent of ultra-low dose scanners that will provide comparable nodule-detection capacities for a radiation dose (0.25 mSv) close to that of a chest X-ray will probably change the game in the future [50–52].

Finally, the issue of smoking cessation must be discussed with screening candidates and the degree of nicotine dependency evaluated for them. The participants in the ACRIN arm of the NLST had provided particularly high amounts of smoking data. A recent study focusing on those NLST participants [88] confirmed increased rates of lung cancer and specific and all-cause mortality in patients with higher vs. lower dependency scores. Cessation is thus a major issue. The NLST counted 24,190 current and 26,073 former smokers. The control group's former smokers who had seven years of abstinence showed 20% less lung cancer-specific mortality (*i.e.*, a reduction equivalent to that obtained by the LDCT screening program). The experimental group's (*i.e.*, those who received LDCT screening) former smokers abstinent for seven years did even better with a 30% reduction in that same endpoint. However, the best result, −38% in specific mortality, was obtained in patients who were abstinent for 15 years and in the experimental group [89]. Participation in a screening program can however contribute to cessation. The NLST observed a reduction in the number of active smokers each year, and that reduction was stronger in patients for whom screening results were positive with features highly suggestive of cancer [90]. The patients who quit smoking in these conditions appeared to do so durably. For all of the above reasons, smoking cessation assistance must be systematically proposed to all patients undergoing LDCT for lung cancer screening. The work group recommends that information on smoking cessation be provided in both oral and written forms (Appendix 1).

#17 Precise information on the benefits of screening, the possible risks of screening (including overdiagnosis), and tobacco cessation must be provided to patients before they participate in an individual LDCT screening program for lung cancer (grade AE).

12. Conclusion

Although the effectiveness of LDCT for lung cancer screening has been clearly demonstrated, its optimization remains dependent on the clarification of numerous points. In the opinion of the work group, there are three topics that merit prioritized investigation. The first topic is favoring the adherence of the eligible population to the screening program in its entirety, including smoking cessation. The second topic is optimizing eligible population selection and identifying patients eligible for but not receiving screening. For these two points, pooled subgroups analysis may be helpful. The third topic is intensifying the study of radiomics (with artificial intelligence [91,92] and biomarkers) in the setting of lung cancer screening and the contributions they may make to it. Finally, cost–risk–benefits analysis, adapted to each healthcare system, are also essentials. Thus, the experts renew their recommendation in favor of individual screening for lung cancer in France as per the conditions laid out in this document (grade A); and recommend the very rapid organization and funding of prospective studies, which, if conclusive, will enable the deployment of lung cancer screening organized at the national level (grade AE).

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All authors attest that they meet the current International Committee of Medical Journal Editors (ICMJE) criteria for Authorship.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at https://doi.org/10.1016/j.diii.2021.01.012.

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