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Lung CAncer SCreening in french women using low-dose computed tomography and Artificial intelligence for DEtection: the CASCADE pilot study

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Keywords: Lung cancer ; Early Detection of Cancer; Multidetector Computed Tomography; Artificial Intelligence

Abstract

Introduction

Lung cancer screening (LCS) using low-dose computed tomography (CT) has been demonstrated to reduce lung cancer-related mortality in large randomized controlled trials. Moving from trials to practice requires answering practical questions about the level of expertise of CT readers, the need for double reading as in trials, and the potential role of artificial intelligence (AI). (AI)Additionally, most LCS studies have predominantly included male participants with women being under-represented, even though the benefit of screening is greater for them. Thus, the aim of this study is to compare the performance of a single CT reading by general radiologists trained in LCS using artificial intelligence as a second reader to that of a double reading by expert thoracic radiologists, in a campaign for low-dose CT screening in high-risk women

Methods and analysis This observational cohort study will recruit 2400 asymptomatic women aged between 50-74 years, current or former smokers with at least a 20 pack-year smoking history, in 4 different French district areas. Assistance with smoking cessation will be offered to current smokers. An initial low-dose CT scan will be performed, with subsequent follow-ups at 1 year and 2 years. The primary objective is to compare CT scan readings by a single LCS-trained, AI-assisted radiologist to that of an expert double reading. The secondary objectives are: to evaluate the performance of AI as a stand-alone reader; the

adherence to screening of female participants; the influence on smoking cessation; the psychological consequences of screening; the detection of COPD, coronary artery disease and osteoporosis on low-dose CT scans and the costs incurred by screening.

Ethics and dissemination Ethics approval was obtained from the Comité de Protection des Personnes (CPP) Sud-Est 1 (ethics approval number: 2021-A02265-36 with an amendment on 15 July 2022). Trial results will be disseminated at conferences, through relevant patient groups and published in peer-reviewed journals.

Strengths and limitations of this study

- The CASCADE study will answer important preliminary questions by exploring practical methods for CT readings before an organized large-scale lung cancer screening is implemented
- The study will validate the single reading of low-dose CT scans by non-expert radiologists trained in lung cancer screening.
- The study will provide a prospective evaluation of artificial intelligence in lung cancer screening based on current low-dose CT technology.
- The results of this study regarding adherence to screening, its psychological consequences and its effect on smoking cessation will be based only on French participants, with the limitation that the results may not be generalizable to other countries.
- Due to the nature of the study design, missing data is expected in some patients

Introduction

Background and rationale

Lung cancer is the leading cause of cancer death worldwide [1]. Less common than breast cancer, it has been the main cause of cancer death in women in the United States since 1987. This was not observed in France, where the incidence of smoking started later in the female population. However, the epidemiology of female lung cancer is extremely worrying in France as in Spain [2]. Lung cancer incidence and mortality in French women showed an average increase of 5% and 3% per year respectively during the period from 2010 to 2018 [3]. With an equivalent smoking history, the risk of developing lung cancer is 1.2 to 1.7 times higher in women than in men [4]. The results of the French KBP 2020 study [5] conducted in 82 general hospitals and including 8,999 patients, were presented in early 2022. The

proportion of women among lung cancer patients increased from 16% in 2000 to 34.6% in 2020, and to 41% for patients younger than 50 years. When diagnosed on the basis of symptoms, 80% of patients have advanced lung cancer and are not eligible for surgical treatment, resulting in poor long-term survival [6]. Screening with low-dose computed tomography (CT) can detect lung cancer at earlier stages, thereby reducing lung cancer-related mortality in the screened population. In 2011, the National Lung Cancer Screening Trial (NLST) reported a 20% reduction in lung cancer- related mortality in the screened arm, at the cost of a high false positive rate [7]. In 2020, the NELSON study, reported a 26% and 33% reduction of lung cancer deaths at 10 years in male and female participants, respectively, as compared to controls [8]. The overall referral rate for suspicious nodules was only 2.1% in this study, which adopted an efficient nodule management strategy based on volumetry and volumetric estimation of growth for indeterminate nodules. The Multicentric Italian Lung Detection (MILD) study also reported a reduction in lung cancer-related mortality of 39% in the screened arm [9]. The UKLS and LUSI trials also demonstrated a reduction in lung cancer mortality through screening, despite this being significant only for women in the LUSI trial [10,11].

While the medical benefit of screening is well established, the practicalities of its implementation still need to be evaluated, hence the need for implementation research programs [12,13].

Most lung cancer screening studies are based on double reading [8,11,13–18], with the exception of the NLST which involved only one expert for the reading. It is estimated that the number of individuals eligible for lung cancer screening in France varies between 2.5 and 3.7 million, depending on the inclusion criteria. Training radiographers is not an option as their performance is lower than that of experienced radiologists [19]. There are not enough expert thoracic radiologists for this task, especially if double reading is required, thus making it necessary to train generalist radiologists in lung cancer screening. Moreover, none of the lung cancer screening studies mentioned above evaluated the role of artificial intelligence in screening. An ancillary study of 400 randomly selected CT exams in the NELSON trial reported a superior performance of computer-assisted detection of lung nodules compared to double reading by radiologists, at the cost of 3.7 false positives per exam [20]. The development of modern algorithms based on deep learning could solve this problem [21–24]. Google engineers claimed to have developed a program capable of diagnosing lung cancer with a performance superior to that of human doctors [21]. However, their algorithm was trained on NLST data, not on current CT technology, which uses iterative image

reconstruction or deep learning. Finally, most studies of lung cancer screening have primarily included male participants, with women being under-represented, leading the authors of the NELSON trial to conclude that further research is needed in this subgroup [8].

Objectives

Main objective: The main objective of the CASCADE study is to compare the performance of a single generalist radiologist trained in LCS using artificial intelligence as a second reader with that of the reference standard (a double reading by expert thoracic radiologists), in a campaign for low-dose CT screening in high-risk women.

Hypothesis: a single reading of the CT scans by a generalist radiologist, trained in screening, and assisted by an artificial intelligence algorithm which plays the role of a second reader, should have a performance comparable to that of a double reading by experts.

Secondary objectives: to evaluate:

- The performance of AI as a stand-alone reader
- The screening adherence according to the different modes of invitation
- The influence of screening on smoking cessation
- The detection of three comorbidities with smoking as the causative or additional risk factor: chronic obstructive pulmonary disease (COPD), coronary artery disease and osteoporosis
- The psychological consequences of screening
- The costs incurred by screening

Trial design: prospective cohort study

The study protocol is consistent with the recommendations of the European position statement on lung cancer screening, which states that individuals participating in screening programs should be informed about the benefits and harms of screening, smoking cessation should be offered to all current smokers, and the management of solid nodules should involve semi-automatically measured volume and volume doubling time [25].

Methods: Participants, interventions, and outcomes

We used the SPIRIT reporting guidelines for clinical trials protocols [26]

Study setting

The study will be conducted in four French cities, namely Paris, Rennes, Béthune and Grenoble, which represent different socio-economic profiles and will be disseminated in neighbouring areas. The recruitment centers will be a university hospital in Paris and community clinics for the other three cities.

Inclusion and exclusion criteria for participants.

Inclusion criteria

- Women aged 50 to 74 years
- Current or former smokers
- Having smoked at least 20 pack-years and quit for less than 15 years
- Having given their consent and understood the need for a 2-year follow-up
- Affiliated to social security

Exclusion criteria

- Presence of clinical symptoms suggestive of malignancy (weight loss, hemoptysis) or ongoing infection (febrile cough, expectoration)
- Cancer within the last 2 years
- History of lung cancer
- Follow-up at 2 years is impossible
- Chest CT scan in the previous 2 years

Eligibility criteria for individuals/study centers who will perform the interventions

- Pulmonologists: trained in the "5 As" strategy for quitting smoking
- Onsite general radiologists (first readers): trained in lung cancer screening according to the European Society of Thoracic Imaging (ESTI) lung cancer screening certification programme, available at https://www.myesti.org/lungcancerscreeningcertificationproject/
- Study centers: equipped with an artificial solution for lung nodule detection (Veye Lung Nodules, **version 3.9.2**, Aidence, Amsterdam, the Netherlands) and fulfilling the technical requirements by performing a test CT scan on a phantom

Interventions

- Low-dose CT scans performed at inclusion then at 1 year and 2 year follow-ups.

An additional CT scan if one of the three previously listed CT scan results is indeterminate.

All CT examinations will be performed according to the technical recommendations of the European Society of Thoracic Imaging (ESTI), available at https://www.myesti.org/content-esti/uploads/ESTI-LCS-technical-standards_2019-06-14.pdf

- CT scan reading modalities: general radiologist firstly without the use of AI, then with the use of AI as well as two independent experts.
- Consultation with a pulmonologist at inclusion and then at the end of the study participation, as well as in the event of an indeterminate CT scan result, after the additional CT scan.

The inclusion visit will be carried out by a pulmonologist who will:

- Provide information on the methods, risks and benefits of screening presented in an information note
- Check eligibility
- Offer help with smoking cessation via a tobacco dependence questionnaire (CDS, cigarette dependence scale) followed by a discussion on the benefits of cessation and its methods. A prescription for nicotine substitutes will be offered. The follow-up of this care will be conducted by telephone interviews with a nurse specialized in smoking cessation. Participants who request this will be referred to a specialized smoking cessation consultation.
- Look for signs suggestive of COPD according to the 6-question COPD test available on the French national social health insurance (CNAM) website (https://www.ameli.fr/assure/sante/themes/bpco/symptomes-diagnosticcomplications). In the event of a positive score, the result will be communicated to the participant and her attending physician, for further evaluation using spirometry.
- Explain that a visual quantification of the coronary artery calcium score and a search for thoracic vertebral fractures related to osteoporosis will be performed during the CT reading. The results will be communicated to the participant and her attending physician for management

- Questionnaires: The Hospital Anxiety and Depression Scale (HADS) questionnaire completed after each CT scan. The Cancer worry scale and Satisfaction with Decision scale questionnaires completed at the inclusion and end of study visits. The CDS questionnaire for current smokers completed at the inclusion visit.

Management of study participants

Management of study participants will be based on the consensus of the double expert reading. The criteria for positive, negative and indeterminate screen results can be found in the appendix. In summary, solid nodules with a volume of less than 100 mm^3 at baseline are considered a negative screen result, according to Horeweg et al [27]. For a positive screen

result, the CASCADE scientific committee considered and adopted the initial threshold volume of 500 mm^3 used in the NELSON trial in order to avoid increasing the recall rate.

Outcomes

Main outcome: to demonstrate that the reading of CT scans by a radiologist trained in screening, assisted by detection software, has a similar performance to that of expert double reading, taking the NELSON study as a reference.

Main outcome measure: diagnostic performance (sensitivity, specificity, predictive values and likelihood ratios) of initial readings aided by detection software. The reference standard will be the pathological report for the positive screen results and for the negative screen results, a 2-year follow-up stability or absence of nodules on CT.

Secondary outcomes:

1- Effectiveness of screening

2- Diagnostic performance of reading without AI as second reader, in order to assess its additional value

3- Diagnostic performance of AI as stand-alone reader

4- Agreement of the different readings

5- Adherence to screening

6- Impact of screening on smoking cessation

7- Psychological impact of screening

8- Number of comorbidities (COPD, coronary heart disease) diagnosed

9- Evaluation of the costs incurred by screening

10- Prevalence of osteoporosis by opportunistic screening

Secondary outcome measures:

1- Proportion of participants with a positive screen result and proportion of cancers confirmed

2- Sensitivity, specificity, predictive values and likelihood ratios of reading without AI.

3- Sensitivity, specificity, predictive values and likelihood ratios of AI as stand-alone reader.

4- Kappa coefficient between the different readings

5- Number of participants compared to the number of eligible women, having all three CT scans, time needed to include the target number of participants

6- Proportion who quit smoking at the end of the study

7- Cancer worry scale, Satisfaction with Decision scale, HADS questionnaires translated into French

8- Number of participants in relation to the number of women included, in whom treatment is started

9- Total cost, average cost per woman, cost per case detected

10- Presence of at least one thoracic vertebral fracture and a trabecular attenuation of the T8 vertebral body of less than 100 Hounsfield unit

Participant timeline

A timeline of the enrolment process, study visits, interventions, and assessments performed on participants is presented in Figure 1.

Sample size

The objective is to confirm a diagnostic performance comparable to that of the Nelson study after three scans. The recruitment of 2400 women over two years will allow us to estimate a positive predictive value of 43.5% with a 95% confidence interval of [29.5% - 56.7%] as well as a rate of positive scans (true and false positives) of 2.1% (51/2400 women) with a 95% confidence interval of [1.6% - 2.7%]. The expected cancer rate at 2 years (0.9%, i.e. 22/2400 women) can be estimated with a 95% confidence interval of [0.5% - 1.3%].

Recruitment

The participants will be recruited through social networks (facebook, twitter ...), as well as through communications via town halls, regional print and television media, with the following announcement approved by the ethics committee:

"You are a female smoker or ex-smoker between 50 and 74 years old. You can participate in a lung cancer screening study in women by calling the following number: 06 15 06 58 35 Monday to Friday between 9 a.m. and 5 p.m. You can also contact us by email: cascade.cch@aphp.fr. Your eligibility criteria will be checked during the first telephone contact. If you are eligible, you will then be offered a consultation appointment with a pulmonologist to screen for the various tobacco-related pathologies".

The same note will be included in the invitation letter for breast cancer screening in the 4 participating French regions.

A web page is accessible for participants, containing a summary of the study, the information note, as well as a short video presentation of the study (https://www.aphp.fr/actualite/depistage-du-cancer-du-poumon-par-scanner-faible-dose-lap-hp-lance-letude-pilote-cascade)

The total number of eligible women in the 4 participating French regions is 39,094. The inclusion target of 2,400 women corresponds to 6% of the eligible population.

Patient and Public Involvement

The project is motivated by previous experiences with patients and discussions with patient associations. Lung Cancer Europe (LuCE) an umbrella lung cancer patient organization expressed its support, estimating that the study will evaluate essential preliminary questions before considering large-scale lung screening. The project places the patient at the center of the research process, by evaluating at several occasions the satisfaction with the decision and the psychological impact of the screening.

Methods: Data collection, management, and analysis

Data collection methods

Clinical data will be collected in each center during the inclusion and end visits by the investigator or by a clinical research technician, supervised by the investigator. De-identified data will be collected on an electronic form, using the cleanweb software.

Reminders by telephone, postal and electronic mail will be used to schedule appointments and collect data from all participants. If the participant is lost to follow-up, the contact details of the participants' GPs will be used to collect the information of cancer diagnosis at 2 years.

Anonymized CT images and AI reports will be transferred via secure connections to a dedicated Picture Archiving and Communicating System (PACS SPHERE CASCADE), developed for the study. Expert readers will access CT images, but not AI reports via a secure encrypted connection, using a CE marked DICOM viewer allowing nodule segmentation and volume doubling time measurement (Veolity Lung Screening 1.7, MeVis Medical Solutions AG, Bremen, Germany).

Data management

The coordinating center (URC Cochin) will be responsible for the development of the electronic file, and will ensure that the data is well collected

Statistical analysis.

The statistical analyzes will be carried out at Cochin Hospital Clinical Research Unit using R and/or SAS software version 9.3. A statistical analysis plan will be produced and validated by the study steering committee before freezing and analyzing the data. Data analysis and reporting will follow the recommendations of the STARD statement (http://www.equator-network.org).

The analysis will be carried out on all the participants included in the protocol.

Quantitative variables will be described as mean and standard deviation or median and interquartile ranges depending on the data distribution. Qualitative variables will be described as numbers and percentages.

Diagnostic performance (sensitivity, specificity, negative and positive predictive values, positive and negative likelihood ratios) will be calculated as usual. The proportion of women with a positive CT scan and the two-year cancer rate for the entire screened population will be estimated with their 95% confidence intervals using the exact binomial law.

The definition used for the presence or absence of cancer is as follows:

- lung cancer: positive histology
- Absence of cancer: absence of nodule, or stability at 2 years, or negative histology

In case of persistent missing data regarding the main outcome (the information of cancer diagnosis at 2 years), multiple imputations with chained equations will be applied using the MICE package of the R statistical software.

Agreement between the different readings will be analyzed using the Kappa coefficient, provided with its 95% confidence interval.

The false positives and false negatives for each reading will be calculated using the above definition of lung cancer. The analysis of other endpoints will be mainly based on descriptive statistical methods.

Cost analysis

The cost analysis is based on a non-comparative study undertaken from a health system and payer perspective over a 2-year time timeframe. One expected outcome of the cost analysis is to advice at national level the need for the use of AI for lung cancer screening. The other reported cost data include the average screening costs with scenario analyses on the uptake of screening, the costs per cancer detected and the costs associated with the workup of thoracic lesions detected by screening. These will be collected prospectively at the participant level via the study case report form. Screening program costs include:

- The fixed costs of invitation to screening such as those involved if the program is implemented (printing invitation letters and additional postage costs), retrieved from the billing systems of the regional cancer screening organizations.
- The costs of the CT scan: we will use the social health insurance tariffs for the most recent type of equipment, to which the radiologist fees are added.
- The cost of the AI solution is the purchase price, annual volume estimates are subjected to scenario analyses.

In the event of a positive or indeterminate result, or an incidental finding, we will estimate the healthcare costs for the following 2 years. Consultations and examinations (additional CT scan, biopsies, coronary angiography, bone densitometry and generally any assessment directly attributable to the results of the initial scan) will be valued by taking into account the social health insurance tariffs, hospital admissions (in- and outpatient) from the most recent national cost study.

The total fixed and variable cost of the 2-year screening program will be estimated with and without AI, including all downstream healthcare costs. We will calculate the average cost per participating woman, the average cost per lung cancer detected and the average cost per any relevant finding.

Methods: Monitoring

Steering committee

The CASCADE study steering committee will have the overall responsibility for trial oversight, monitoring trial progress and protocol adherence.

Data monitoring

Data monitoring will be performed by research technicians who will alert the investigators by email in case of missing data on the electronic report file.

A data monitoring committee comprising of a statistician and two methodologists will perform an interim analysis halfway through the inclusions. They will review the initial statistical assumptions, regarding the prevalence of lung cancer and the performance of initial readings, especially the rates of positive and indeterminate CT scans, in order to have low confidence intervals when calculating positive predictive values.

Harms

Screening can be anxiety-provoking, especially since the participants will not have immediate results, due to a double reading being necessary. Anxiety will be evaluated at each CT scan using the HADS questionnaire. Performing an additional CT scan in the event of an indeterminate result is also a potential source of stress, and the participants will be forewarned of this possibility, as this concerned 9% of the NELSON trial participants [8].

Auditing

An audit may be carried out at any time by persons appointed by the sponsor and independent of the investigators. Its objective is to ensure the quality of research, the validity of its results and compliance with the law and regulations in force.

Ethics and dissemination

Research ethics approval

The study protocol and the informed consent form template contained in the appendices have been approved by the Comité de Protection des Personnes (CPP) Sud-Est 1. Any modifications to the protocol which may impact on the conduct of the study will be submitted to this committee for its approval and subsequently communicated to the relevant parties.

Consent

Informed consent will be obtained from the trial participants during the inclusion visit with the pulmonologist. The sponsor will ensure that each person who takes part in the research has given their written consent for access to their individual data.

Confidentiality

During the research and at its end, the data collected on the participants will be de-identified/anonymized. Only the initials of the family name and first name will be recorded, accompanied by a coded number specific to the research indicating the order of inclusion of the subjects.

Declaration of interests

The investigators have no financial and other competing interests

Access to data

The data will be kept within the clinical research unit (URC) of Cochin Hospital.

Data access requests must be approved by the ethics committee, the CASCADE scientific committee and the sponsor APHP

Dissemination

The study results will be disseminated at relevant conferences and societies, published in peer-reviewed journals without intervention of professional writers and disseminated through relevant patient groups. Authorship will be according to the International Committee of Medical Journal Editors (ICMJE) guidelines.

Trial status

Recruitment started on April 8, 2022 and is expected to end in April 2024

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Figure legend

Figure 1: Participant timeline

Authors' contributions:

Contributors MPR, HA, MW and IDZ constructed the protocol and design. MPR made the first draft of this manuscript. HA contributed with statistical advice and study design. MPR, HA, MW, GC and IDZ contributed with a thorough evaluation of the design, method and manuscript. All authors accepted the final manuscript version.

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Competing interests: None declared

Patient and public involvement: Patients were involved in the design and dissemination plans of this research. Refer to the Methods section for further details.

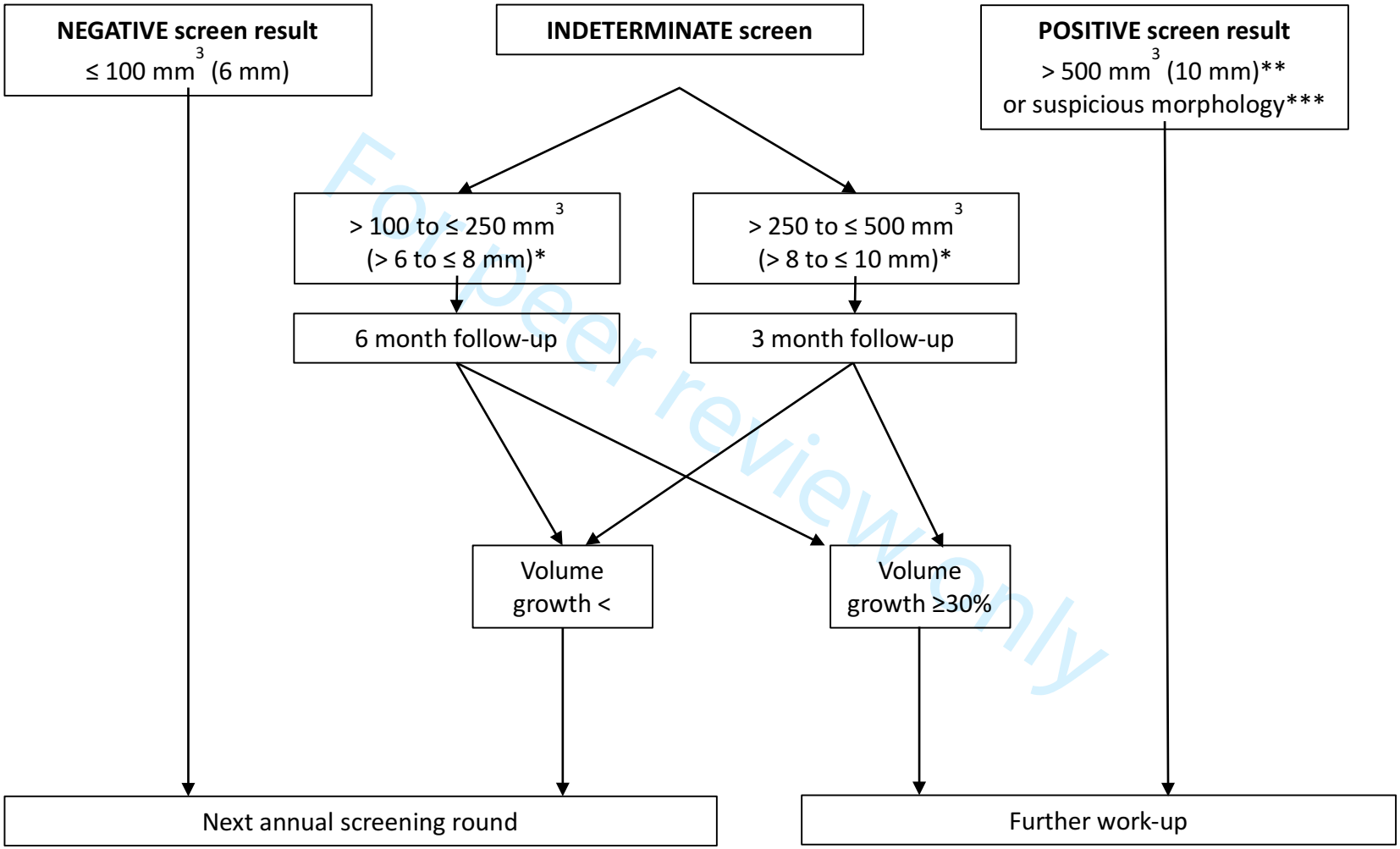
Word count: 4347

	Pre enrolment	Inclusion visit	Baseline visit (CT)	3 first weeks after baseline visit	1-year visit (CT)	2-year visit (CT)	End visit
Informed consent		X					
Eligibility screen	X	X					
ASSESSMENTS							
Baseline variables*		X					
Outcome variables**							X
INTERVENTIONS							
Five As' strategy prescription of nicotin substitutes for current smokers		X					
Telephone consultation for follow-up of smoking cessation				X			
Low-dose CT			X		X	X	
Questionnaires							
Cancer worry scale		X					X
Satisfaction with Decision scale		X					X
Hospital Anxiety and Depression scale			X		X	X	
Cigarette dependance scale		X					

* List of collected baseline variables: *Age of smoking onset, date of cessation, number of cigarettes per day, study level, family history of lung cancer, previously diagnosed coronary artery disease or osteoporosis, status in relation to other cancer screenings: breast, cervix, colon, How information about the study reached them*

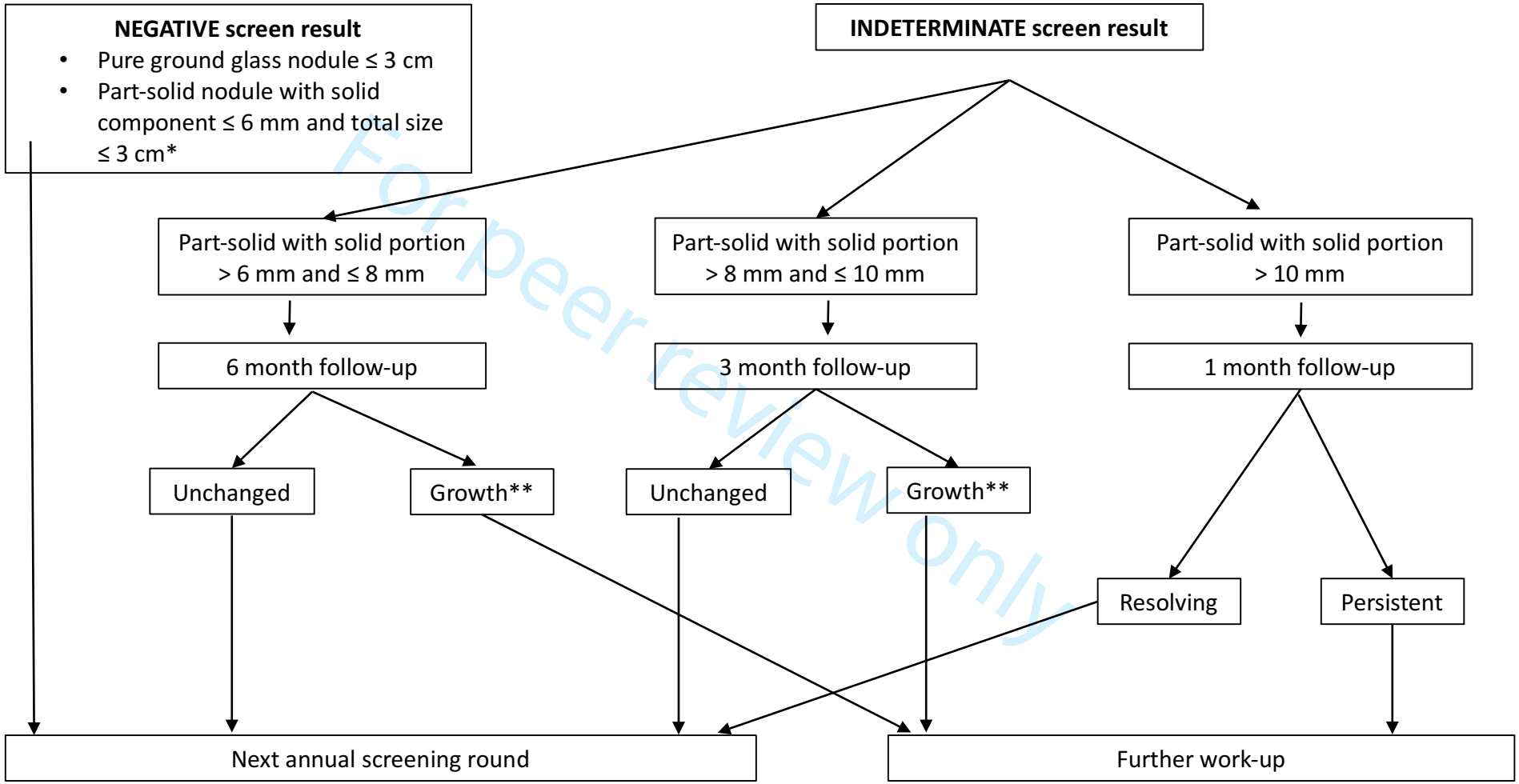
**list of collected outcome variables: *Duration of smoking cessation, COPD confirmed by spirometry, Coronary artery disease confirmed and treatment initiated (medical treatment or revascularization), Osteoporosis confirmed by additional densitometry, initiation of anti-osteoporosis treatment, Completion of the other recommended screenings*

BASELINE CT SOLID NODULES



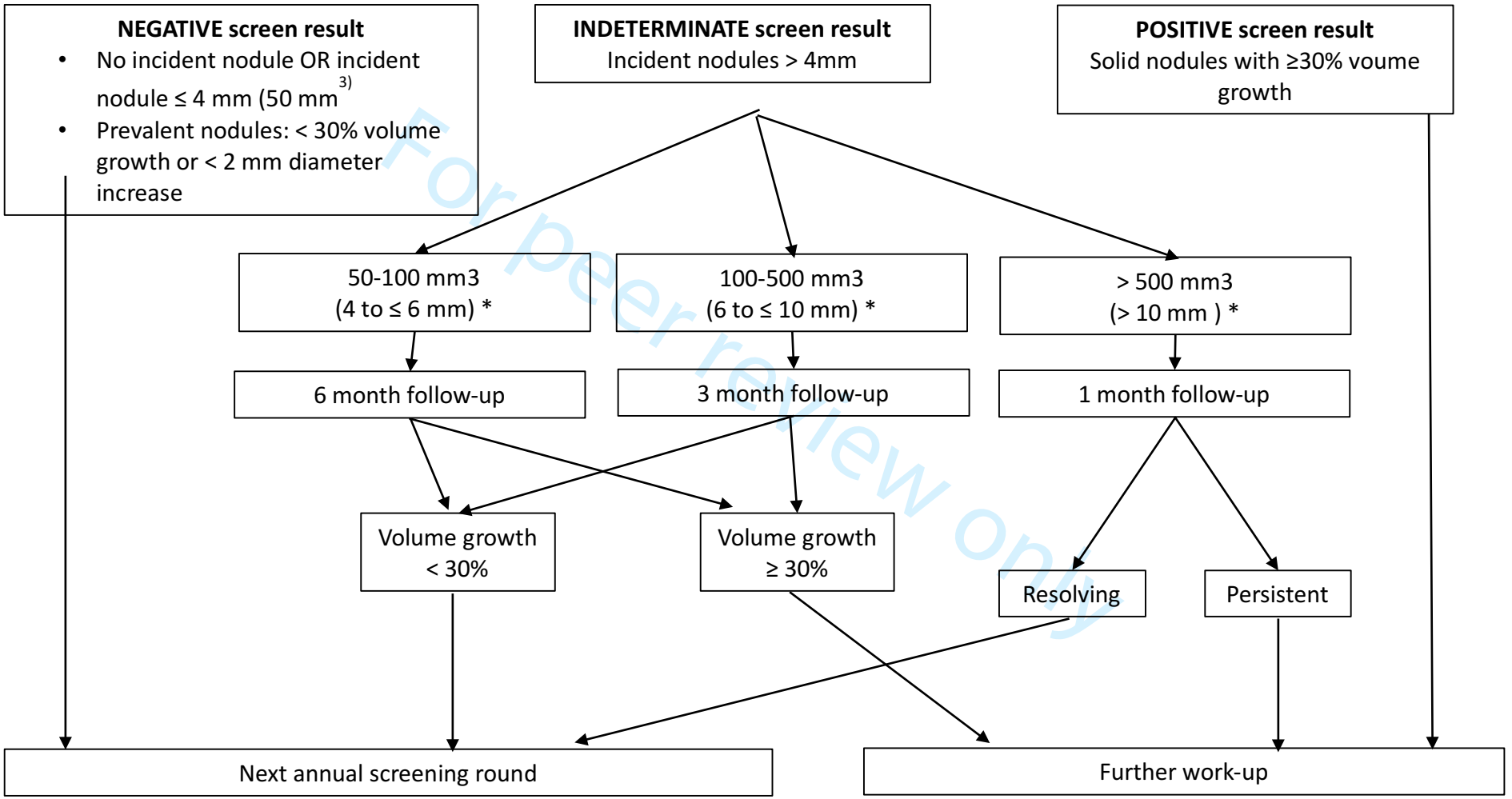
* In case segmentation has failed
** In case of a cystic airspace nodule, the solid portion should be taken into account
*** Pleural indentation, cystic component, air bronchogram or bubble like lucencies, spiculation

BASELINE CT SUBSOLID NODULES



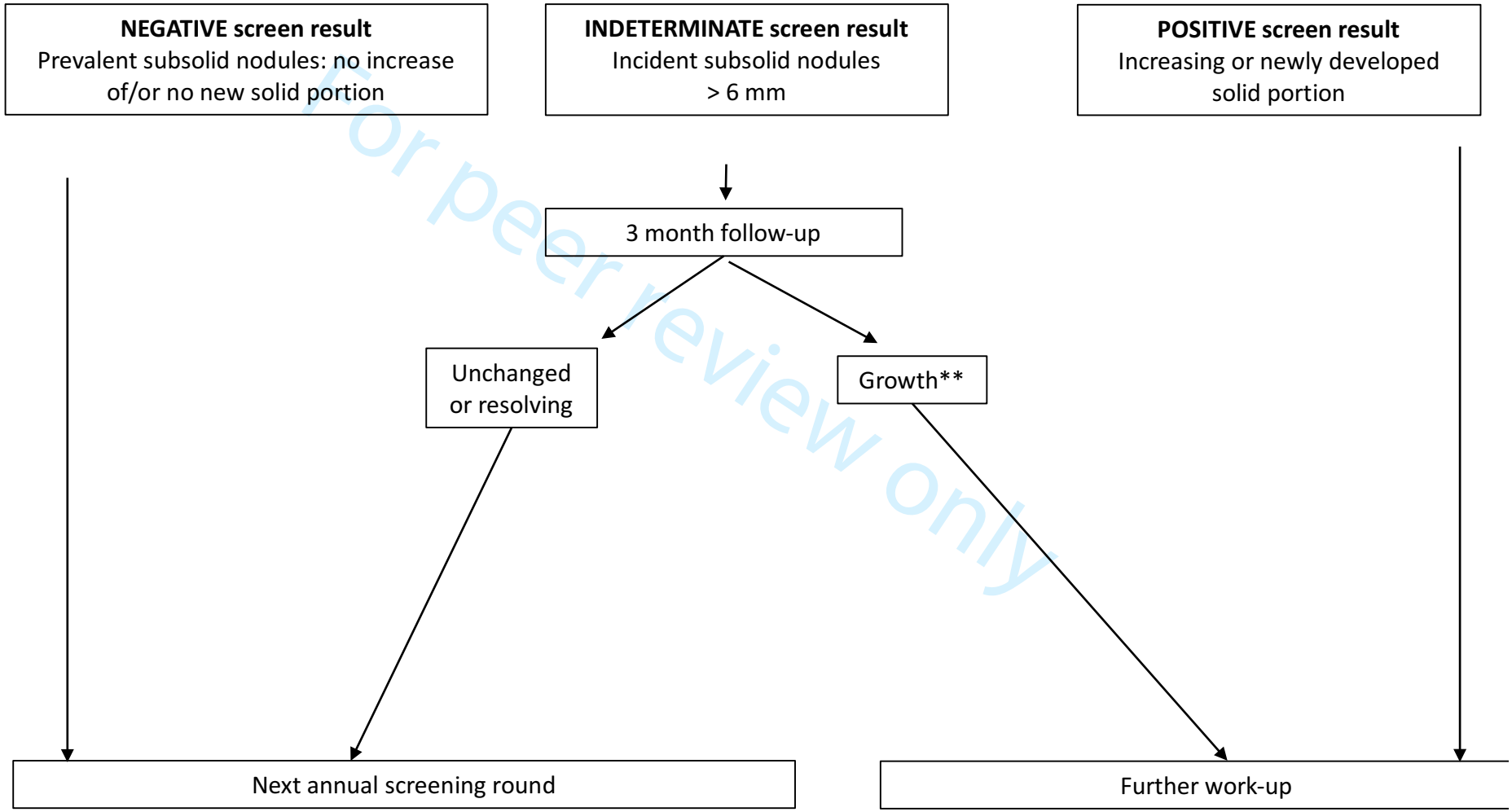
* For part solid and GGN without morphological criteria suggesting malignancy (bubble like lucencies, border of bulla, pleural indentation)
** Increase in solid portion of ≥ 2mm, measured on lung window setting

1-YEAR FOLLOW-UP CT SOLID NODULES



* In case segmentation has failed

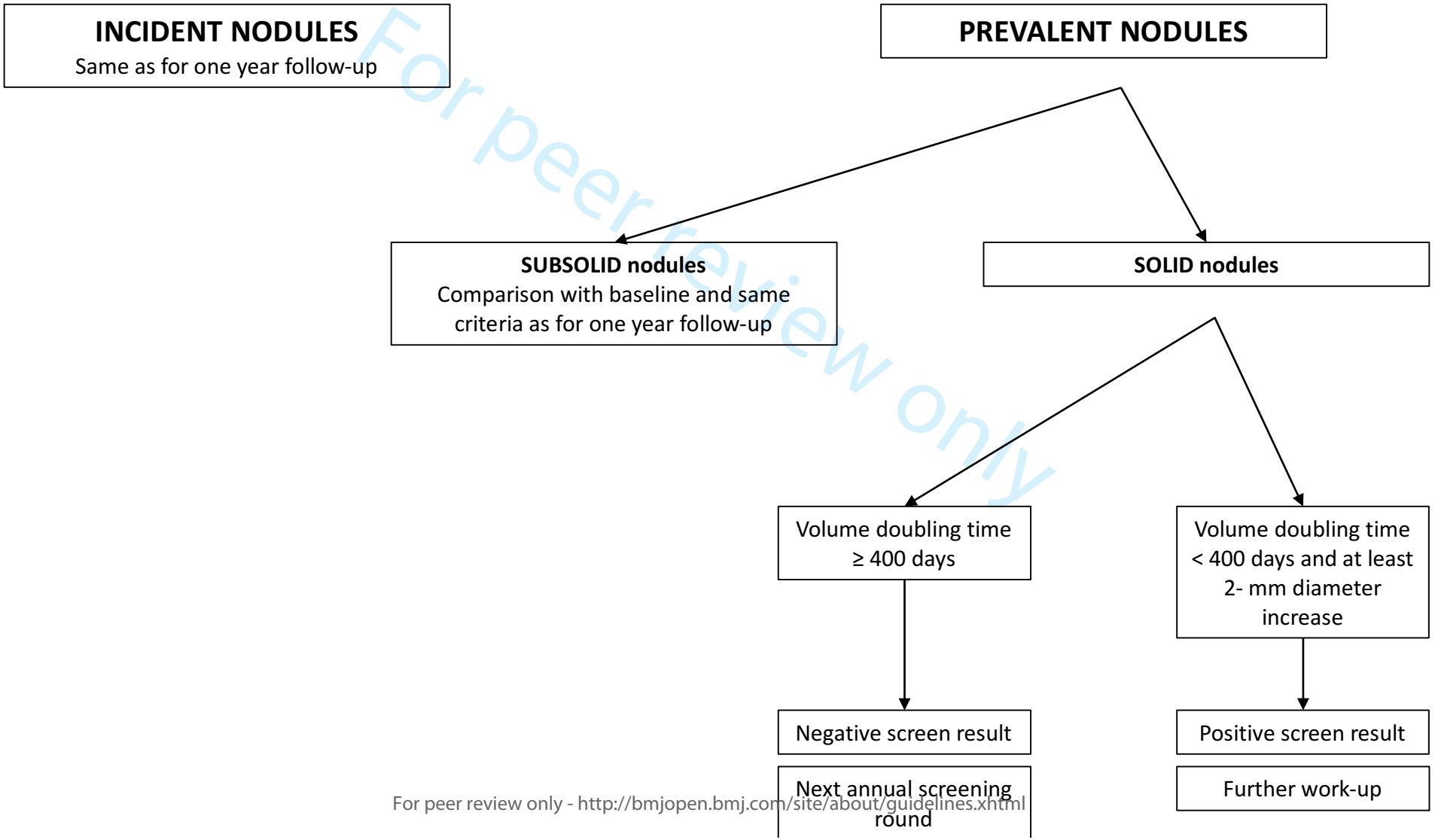
1-YEAR FOLLOW-UP CT SUBSOLID NODULES



* For part solid and GGN without morphological criteria suggesting malignancy (bubble like lucencies, border of bulla, pleural indentation)

** Increase in solid portion of ≥ 2mm, measured on lung window setting

2-YEAR FOLLOW-UP



		Reporting Item	Page Number
Administrative information			
Title	#1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	1
Trial registration	#2a	Trial identifier and registry name. If not yet registered, name of intended registry	1
Trial registration: data set	#2b	All items from the World Health Organization Trial Registration Data Set	1-3
Protocol version	#3	Date and version identifier	3
Funding	#4	Sources and types of financial, material, and other support	4
Roles and responsibilities: contributorship	#5a	Names, affiliations, and roles of protocol contributors	4
Roles and responsibilities: sponsor contact information	#5b	Name and contact information for the trial sponsor	4
Roles and responsibilities: sponsor and funder	#5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	5
Roles and responsibilities: committees	#5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	5
Main document			
Introduction			

Background and rationale	#6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	2
7Background and rationale: choice of comparators	#6b	Explanation for choice of comparators	NA
Objectives	#7	Specific objectives or hypotheses	4
Trial design	#8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, non-inferiority, exploratory)	4
Methods: Participants, interventions, and outcomes			
Study setting	#9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	5
Eligibility criteria	#10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	5
Interventions: description	#11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	5,6
Interventions: modifications	#11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving / worsening disease)	NA

Interventions: adherance	#11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return; laboratory tests)	8
Interventions: concomitant care	#11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	NA
Outcomes	#12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	7,8
Participant timeline	#13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	8
Sample size	#14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	8
Recruitment	#15	Strategies for achieving adequate participant enrolment to reach target sample size	9
Methods: Assignment of interventions (for controlled trials)			
Allocation: sequence generation	#16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	NA

Allocation concealment mechanism	#16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	NA
Allocation: implementation	#16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	NA
Blinding (masking)	#17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	NA
Blinding (masking): emergency unblinding	#17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	NA
Methods: Data collection, management, and analysis			
Data collection plan	#18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	9
Data collection plan: retention	#18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	9
Data management	#19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	9

Statistics: outcomes	#20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	9
Statistics: additional analyses	#20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	9
Statistics: analysis population and missing data	#20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	9,10
Methods: Monitoring			
Data monitoring: formal committee	#21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	11
Data monitoring: interim analysis	#21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	11
Harms	#22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	11
Auditing	#23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	11
Ethics and dissemination			

Research ethics approval	#24	Plans for seeking research ethics committee / institutional review board (REC / IRB) approval	15
Protocol amendments	#25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC / IRBs, trial participants, trial registries, journals, regulators)	15
Consent or assent	#26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	15
Consent or assent: ancillary studies	#26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	15
Confidentiality	#27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	15
Declaration of interests	#28	Financial and other competing interests for principal investigators for the overall trial and each study site	15
Data access	#29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	15
Ancillary and post trial care	#30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	NA
Dissemination policy: trial results	#31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	15
Dissemination policy: authorship	#31b	Authorship eligibility guidelines and any intended use of professional writers	16

Dissemination policy: reproducible research	#31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	12
Appendices			
Informed consent materials	#32	Model consent form and other related documentation given to participants and authorised surrogates	1,3
Biological specimens	#33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	NA

BMJ Open

Lung CAncer SCreening in French women using low-dose computed tomography and Artificial intelligence for DEtection: the CASCADE study protocol

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Lung CAncer SCreening in French women using low-dose computed tomography and Artificial intelligence for DEtection: the CASCADE study protocol

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Keywords: Lung cancer ; Early Detection of Cancer; Multidetector Computed Tomography; Artificial Intelligence

Abstract

Introduction

Lung cancer screening (LCS) using low-dose computed tomography (CT) has been demonstrated to reduce lung cancer-related mortality in large randomized controlled trials. Moving from trials to practice requires answering practical questions about the level of expertise of CT readers, the need for double reading as in trials, and the potential role of artificial intelligence (AI). Additionally, most LCS studies have predominantly included male participants with women being under-represented, even though the benefit of screening is greater for them. Thus, the aim of this study is to compare the performance of a single CT reading by general radiologists trained in LCS using artificial intelligence as a second reader to that of a double reading by expert thoracic radiologists, in a campaign for low-dose CT screening in high-risk women.

Methods and analysis This observational cohort study will recruit 2400 asymptomatic women aged between 50-74 years, current or former smokers with at least a 20 pack-year smoking history, in 4 different French district areas. Assistance with smoking cessation will be offered to current smokers. An initial low-dose CT scan will be performed, with subsequent follow-ups at 1 year and 2 years. The primary objective is to compare CT scan readings by a single LCS-trained, AI-assisted radiologist to that of an expert double reading. The secondary objectives are: to evaluate the performance of AI as a stand-alone reader; the

adherence to screening of female participants; the influence on smoking cessation; the psychological consequences of screening; the detection of COPD, coronary artery disease and osteoporosis on low-dose CT scans and the costs incurred by screening.

Ethics and dissemination Ethics approval was obtained from the Comité de Protection des Personnes (CPP) Sud-Est 1 (ethics approval number: 2021-A02265-36 with an amendment on 15 July 2022). Trial results will be disseminated at conferences, through relevant patient groups and published in peer-reviewed journals.

Strengths and limitations of this study

- The CASCADE study will answer important preliminary questions by exploring practical methods for CT readings before an organized large-scale lung cancer screening is implemented.
- The study will validate the single reading of low-dose CT scans by non-expert radiologists trained in lung cancer screening.
- The study will provide a prospective evaluation of artificial intelligence in lung cancer screening based on current low-dose CT technology.
- The results of this study regarding adherence to screening, its psychological consequences and its effect on smoking cessation will be based only on French participants, with the limitation that the results may not be generalizable to other countries.
- Due to the nature of the study design, missing data is expected in some patients.

Introduction

Background and rationale

Lung cancer is the leading cause of cancer death worldwide [1]. Less common than breast cancer, it has been the main cause of cancer death in women in the United States since 1987. This was not observed in France, because the incidence of smoking started later in the female population. However, the epidemiology of female lung cancer is extremely worrying in France as is also the case in Spain [2]. Lung cancer incidence and mortality in French women showed an average increase of 5% and 3% per year respectively during the period from 2010 to 2018 [3]. With an equivalent smoking history, the risk of developing lung cancer is 1.2 to 1.7 times higher in women than in men [4]. The results of the French KBP 2020 study conducted in 82 general hospitals which included 8,999 patients, were presented in early

2022. The proportion of women amongst lung cancer patients increased from 16% in 2000 to 34.6% in 2020, and in patients younger than 50 years, it increased to 41% [5]. When diagnosed on the basis of symptoms, 80% of patients have advanced lung cancer and are not eligible for surgical treatment, resulting in poor long-term survival [6]. Screening with low-dose computed tomography (CT) can detect lung cancer at earlier stages, thereby reducing lung cancer-related mortality in the screened population. In 2011, the National Lung Cancer Screening Trial (NLST) reported a 20% reduction in lung cancer- related mortality in the screened arm, at the cost of a high false positive rate [7]. In 2020, the NELSON study, reported a 26% and 33% reduction in lung cancer deaths at 10 years in male and female participants, respectively, as compared to controls [8]. The overall referral rate for suspicious nodules was only 2.1% in this study, which adopted an efficient nodule management strategy based on volumetry and volumetric growth estimation for indeterminate nodules. The Multicentric Italian Lung Detection (MILD) study also reported a reduction in lung cancer-related mortality of 39% in the screened arm [9]. The UKLS and LUSI trials also demonstrated a reduction in lung cancer mortality through screening, despite this being significant only in women in the LUSI trial [10,11].

While the medical benefit of screening is well established, the practicalities of its implementation still need to be evaluated, hence the need for implementation research programs [12,13].

Most lung cancer screening studies are based on double reading [8,11,13–18], with the exception of the NLST which involved only one expert for the reading. It is estimated that the number of individuals eligible for lung cancer screening in France varies between 2.5 and 3.7 million, depending on the inclusion criteria. Training radiographers is not an option as their performance is lower than that of experienced radiologists [19]. There are not enough expert thoracic radiologists for this task, especially if double reading is required, thus making it necessary to train general radiologists in lung cancer screening. Moreover, none of the lung cancer screening studies mentioned above, evaluated the role of artificial intelligence in screening. An ancillary study of 400 randomly selected CT exams in the NELSON trial reported a superior performance of computer-assisted lung nodule detection compared to double reading by radiologists, at the cost of 3.7 false positives per exam [20]. The development of modern algorithms based on deep learning could solve this problem [21–24]. Google engineers claimed to have developed a program capable of diagnosing lung cancer with a performance superior to that of human doctors [21]. However, their algorithm was

trained on NLST data, not on current CT technology, which uses iterative image reconstruction or deep learning. Finally, most lung cancer screening studies have primarily included male participants, with women being under-represented, leading the authors of the NELSON trial to conclude that further research is needed in this subgroup [8].

Objectives

Main objective: The main objective of the CASCADE study is to compare the performance of a single general radiologist trained in LCS using artificial intelligence as a second reader with that of the reference standard (a double reading by expert thoracic radiologists), in a campaign for low-dose CT screening in high-risk women.

Hypothesis: a single reading of the CT scans by a general radiologist, trained in screening, and assisted by an artificial intelligence algorithm which plays the role of a second reader, should have a performance comparable to that of a double reading by experts.

Secondary objectives: to evaluate:

- The performance of AI as a stand-alone reader
- The screening adherence according to the different modes of invitation
- The influence of screening on smoking cessation
- The detection of three comorbidities with smoking as the causative or additional risk factor: chronic obstructive pulmonary disease (COPD), coronary artery disease and osteoporosis
- The psychological consequences of screening
- The costs incurred by screening

Methods: Participants, interventions, and outcomes

Trial design: prospective cohort study.The study protocol is consistent with the recommendations of the European position statement on lung cancer screening, which states that individuals participating in screening programs should be informed about the benefits and harms of screening, smoking cessation should be offered to all current smokers, and the management of solid nodules should involve semi-automatically measured volume and volume doubling time [25].

We followed the recommendations of the STROBE checklist [26]

Study setting

The study will be conducted in four French cities, namely Paris, Rennes, Béthune and Grenoble, which represent different socio-economic profiles. It will then be disseminated in neighbouring areas. The recruitment centers will be a university hospital in Paris and community clinics for the other three cities.

Inclusion and exclusion criteria for participants.

Inclusion criteria

- Women aged 50 to 74 years
- Having at least 20 pack-year smoking history
- Current or former smokers who have no quit for more than 15 years

- Having given their consent and understood the need for a 2-year follow-up
- Affiliated to social security

Exclusion criteria

- Presence of clinical symptoms suggestive of malignancy (weight loss, hemoptysis) or ongoing infection (febrile cough, expectoration)
- Cancer within the previous 2 years
- History of lung cancer
- Follow-up at 2 years is impossible
- Chest CT scan in the previous 2 years

Eligibility criteria for individuals/study centers who will perform the interventions

- Pulmonologists: trained in the "5 As" strategy for smoking cessation
- Onsite general radiologists (first readers): trained in lung cancer screening according to the European Society of Thoracic Imaging (ESTI) lung cancer screening certification programme, available at https://www.myesti.org/lungcancerscreeningcertificationproject/
- Study centers: equipped with an artificial solution for lung nodule detection (Veye Lung Nodules, **version 3.9.2**, Aidence, Amsterdam, the Netherlands) and fulfilling the technical requirements by performing a test CT scan on a phantom

Interventions

- Low-dose CT scans performed at inclusion then at 1 year and 2 year follow-ups.

An additional CT scan will be needed if one of the three previously listed CT scan results is indeterminate. All CT examinations will be performed according to the technical

recommendations of the European Society of Thoracic Imaging (ESTI), available at https://www.myesti.org/content-esti/uploads/ESTI-LCS-technical-standards_2019-06-14.pdf

- CT scan reading modalities: general radiologist firstly without the use of AI, then with the use of AI as well as two independent expert thoracic radiologists.

- Consultation with a pulmonologist at the inclusion visit and then at the end of the study participation, as well as in the event of an indeterminate CT scan result, after the additional CT scan.

The inclusion visit will be carried out by a pulmonologist who will:

- Provide information on the methods, risks and benefits of screening presented in an information leaflet
- Check eligibility
- Offer help with smoking cessation via a tobacco dependence questionnaire (CDS, cigarette dependence scale) followed by a discussion on the benefits of cessation and its methods. A prescription for nicotine substitutes will be offered. The follow-up of this care will be conducted by telephone interviews with a nurse specialized in smoking cessation. Participants who request this will be referred to a specialized smoking cessation consultation.
- Look for signs suggestive of COPD according to the 6-question COPD test available on the French national social health insurance (CNAM) website (https://www.ameli.fr/assure/sante/themes/bpco/symptomes-diagnosticcomplications). In the event of a positive score, the result will be communicated to the participant and her attending physician, who will consider performing spirometry.
- Explain that a visual quantification of the coronary artery calcium score and a search for thoracic vertebral fractures related to osteoporosis will be performed during the CT reading. The results will be communicated to the participant and her attending physician for management.

- Questionnaires: The Hospital Anxiety and Depression Scale (HADS) questionnaire will be completed after each CT scan. The Cancer worry scale and Satisfaction with Decision scale questionnaires will be completed at the inclusion and end of study visits. The CDS questionnaire for current smokers will be completed at the inclusion visit.

Management of study participants

The management of study participants will be based on the consensus of the double expert reading. The criteria for positive, negative and indeterminate screen results can be found in the appendix. In summary, solid nodules with a volume of less than 100 mm^3 at baseline are considered a negative screen result, according to Horeweg et al [27]. For a positive screen result, the CASCADE scientific committee considered and adopted the initial threshold volume of 500 mm^3 which was used in the NELSON trial in order to avoid increasing the recall rate.

Outcomes

Main outcome: to demonstrate that the reading of CT scans by a general radiologist trained in screening, assisted by detection software, has a similar performance to that of expert double reading, using the NELSON study as a reference.

Main outcome measure: diagnostic performance (sensitivity, specificity, predictive values and likelihood ratios) of initial readings aided by detection software. The reference standard will be the pathological report for the positive screen results and for the negative screen results, a 2-year follow-up demonstrating stability or absence of nodules on CT.

Secondary outcomes:

1- Effectiveness of screening

2- Diagnostic performance of reading without AI as the second reader, in order to assess its additional value

3- Diagnostic performance of AI as a stand-alone reader

4- Agreement of the different readings

5- Adherence to screening

6- Impact of screening on smoking cessation

7- Psychological impact of screening

8- Number of comorbidities (COPD, coronary heart disease) diagnosed

9- Evaluation of the costs incurred by screening

10- Prevalence of osteoporosis in opportunistic screening

Secondary outcome measures:

1- Proportion of participants with a positive screen result and the proportion of cancers confirmed.

2- Sensitivity, specificity, predictive values and likelihood ratios of reading without AI.

3- Sensitivity, specificity, predictive values and likelihood ratios of AI as stand-alone reader.

4- Kappa coefficient between the different readings.

5- Number of participants compared to the number of eligible women, having all three CT scans, time needed to include the target number of participants.

6- Proportion who quit smoking at the end of the study.

7- Cancer worry scale, Satisfaction with Decision scale, HADS questionnaires translated into French.

8- Number of participants in relation to the number of women included, in whom treatment is started.

9- Total cost, average cost per woman, cost per case detected.

10- Presence of at least one thoracic vertebral fracture or an attenuation value for the T8 vertebral body measuring less than 100 Hounsfield Units.

Participant timeline

A timeline of the enrolment process, study visits, interventions, and assessments performed on participants is presented in Figure 1.

Sample size

The objective is to confirm a diagnostic performance comparable to that of the Nelson study after three CT scans [8]. The recruitment of 2400 women over two years will allow us to estimate a positive predictive value of 43.5% with a 95% confidence interval of [29.5% - 56.7%] as well as a rate of positive scans (true and false positives) of 2.1% (51/2400 women) with a 95% confidence interval of [1.6% - 2.7%]. The expected cancer rate at 2 years (0.9%, i.e. 22/2400 women) can be estimated with a 95% confidence interval of [0.5% - 1.3%].

Recruitment

The participants will be recruited through social networks (facebook, twitter ...), as well as through communications via town halls, regional print and television media, with the following announcement approved by the ethics committee:

"You are a female smoker or ex-smoker between 50 and 74 years old. You can participate in a lung cancer screening study in women by calling the following number: 06 15 06 58 35 Monday to Friday between 9 a.m. and 5 p.m. You can also contact us by email: cascade.cch@aphp.fr. Your eligibility criteria will be checked during the first telephone contact. If you are eligible, you will then be offered a consultation appointment with a pulmonologist to screen for the various tobacco-related pathologies".

The same leaflet will be included in the invitation letter to breast cancer screening in the four participating French regions, which will be sent by the Regional Cancer Screening Coordination Centers (Centres Régionaux de Coordination du Dépistage des Cancers, CRCDCs).

A web page is accessible for participants, containing a summary of the study, the information leaflet, as well as a short video presentation of the study(https://www.aphp.fr/actualite/depistage-du-cancer-du-poumon-par-scanner-faible-dose-lap-hp-lance-letude-pilote-cascade)

The total number of eligible women in the 4 participating French regions is 39,094. The inclusion target of 2,400 women corresponds to 6% of the eligible population.

Patient and Public Involvement

The project is motivated by previous experiences with patients and discussions with patient associations. Lung Cancer Europe (LuCE) a lung cancer patient advocacy group expressed its support for this study, estimating that the study will evaluate essential preliminary questions before large-scale lung screening is considered. The project places the patient at the center of the research process, by evaluating the patient's satisfaction with their decision and the psychological impact of the screening at different study time points.

Methods: Data collection, management, and analysis

Data collection methods

Clinical data will be collected in each center during the inclusion and end visits by the investigator or by a clinical research technician, supervised by the investigator. De-identified data will be collected on an electronic form, using the cleanweb software.

Reminders by telephone, post and email will be used to schedule appointments in order to collect the data from all participants. If the participant is lost to follow-up, the contact details of the participants' GP will be used in order to collect the information of a cancer diagnosis at 2 years.

Anonymized CT images and AI reports will be transferred via secure connections to a dedicated Picture Archiving and Communicating System (PACS SPHERE CASCADE), developed for the study. Expert readers will access CT images, but not AI reports via a secure encrypted connection, using a CE marked DICOM viewer allowing nodule segmentation and volume doubling time measurement (Veolity Lung Screening 1.7, MeVis Medical Solutions AG, Bremen, Germany).

Data management

The coordinating center (URC Cochin) will be responsible for the development of the electronic file, and they will ensure that the data is well collected.

Statistical analysis.

The statistical analysis will be carried out at Cochin Hospital Clinical Research Unit using R and/or SAS software version 9.3. A statistical analysis plan will be produced and validated by the study steering committee before freezing and analyzing the data. Data analysis and reporting will follow the STARD statement recommendations (http://www.equator-network.org).

The analysis will be carried out on all the participants included in the protocol.

Quantitative variables will be described as mean and standard deviation or median and interquartile ranges depending on the data distribution. Qualitative variables will be described as numbers and percentages.

Diagnostic performance (sensitivity, specificity, negative and positive predictive values, positive and negative likelihood ratios) will be calculated as usual. The proportion of women with a positive CT scan and the two-year cancer rate for the entire screened population will be estimated with their 95% confidence intervals using the exact binomial law.

The definition used for the presence or absence of cancer is as follows:

- lung cancer: positive histology result
- Absence of cancer: absence of nodule, or stability at 2 years, or negative histology result

In cases of persistent missing data regarding the main outcome (the information of cancer diagnosis at 2 years), multiple imputations with chained equations will be applied using the MICE package of the R statistical software.

Agreement between the different readings will be analyzed using the Kappa coefficient, provided with its 95% confidence interval.

The false positives and false negatives for each reading will be calculated using the above definition of lung cancer. The analysis of other endpoints will be mainly based on descriptive statistical methods.

Cost analysis

The cost analysis is based on a non-comparative study undertaken from a health system and payer perspective over a 2-year time timeframe. One expected outcome of the cost analysis is to advise at national level the need for the use of AI in lung cancer screening. The other reported cost data include the average screening costs with scenario analyses on screening uptake, the costs per cancer detected and the costs associated with the workup of thoracic

lesions detected by screening. These will be collected prospectively at the participant level only via the study case report form, administrative data will not be queried, partly due to regulatory difficulties but mainly because it cannot differentiate work-up/cancer costs from other costs. Screening program costs include:

- The fixed costs of screening invitation such as those involved if the program is implemented (printing invitation letters and additional postage costs), retrieved from the billing systems of the regional cancer screening organizations.
- The costs of the CT scan: we will use the social health insurance tariffs for the price of the most recent type of equipment, to which the radiologist fees will be added.
- The cost of the AI solution is the purchase price, annual volume estimates are subjected to scenario analyses.

In the event of a positive or indeterminate result, or an incidental finding, we will estimate the healthcare costs for the following 2 years. Consultations and examinations (additional CT scan, biopsies, coronary angiography, bone densitometry and generally any assessment directly attributable to the results of the initial scan) will be valued by taking into account the social health insurance tariffs, hospital admissions (inpatient and outpatient) from the most recent national cost study.

The total fixed and variable cost of the 2-year screening program will be estimated with and without AI, including all downstream healthcare costs. We will calculate the average cost per participating woman, the average cost per lung cancer detected and the average cost per any relevant finding.

Methods: Monitoring

Steering committee

The CASCADE study steering committee will have the overall responsibility for trial oversight, monitoring trial progress and protocol adherence.

Data monitoring

Data monitoring will be performed by research technicians who will alert the investigators by email in cases of missing data on the electronic report file.

A data monitoring committee comprising of a statistician and two methodologists will perform an interim analysis halfway through the inclusions. They will review the initial statistical assumptions, regarding the prevalence of lung cancer and the performance of initial readings, especially the rates of positive and indeterminate CT scans, in order to have low confidence intervals when calculating positive predictive values.

Harms

Screening can be anxiety-provoking, especially since the participants will not have immediate results, due to a double reading being necessary. Anxiety will be evaluated at each CT scan using the HADS questionnaire. Performing an additional CT scan in the event of an indeterminate result is also a potential source of stress, and the participants will be forewarned of this possibility, as this concerned 9% of the NELSON trial participants [8].

Auditing

An audit may be carried out at any time by persons appointed by the sponsor and it is independent of the investigators. Its objective is to ensure the quality of research, the validity of its results and compliance with the law and regulations in force.

Ethics and dissemination

Research ethics approval

The study protocol and the informed consent form template contained in the appendices have been approved by the Comité de Protection des Personnes (CPP) Sud-Est 1. Any modifications to the protocol which may impact on the conduct of the study will be submitted to this committee for its approval and subsequently communicated to the relevant parties.

Consent

Informed consent will be obtained from the trial participants during the inclusion visit with the pulmonologist. The sponsor will ensure that each person who takes part in the research has given their written consent for access to their individual data.

Confidentiality

During the research and at its end, the data collected on the participants will be de-identified/anonymized. Only the initials of the family name and first name will be recorded, accompanied by a coded number specific to the research indicating the order of subject inclusion.

Declaration of interests.

The investigators have no financial and other competing interests

Access to data

The data will be kept within the clinical research unit (URC) of Cochin Hospital.

Data access requests must be approved by the ethics committee, the CASCADE scientific committee and the sponsor APHP.

Dissemination

The study results will be disseminated at relevant conferences and societies, published in peer-reviewed journals without intervention of professional writers. It will also be disseminated through relevant patient groups. Authorship will be according to the International Committee of Medical Journal Editors (ICMJE) guidelines.

Trial status

Recruitment started on April 8, 2022 and is expected to end in April 2024

Acknowledgements

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Contributors MPR, HA, MW and IDZ constructed the protocol and design. MPR made the first draft of this manuscript. HA contributed with statistical advice and study design. MPR, HA, MW, GC, EC and IDZ contributed with a thorough evaluation of the design, method and manuscript. All authors accepted the final manuscript version.

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Competing interests: None declared

Patient and public involvement: Patients were involved in the design and dissemination plans of this research. Refer to the Methods section for further details.

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Figure legend

Figure 1: Participant timeline

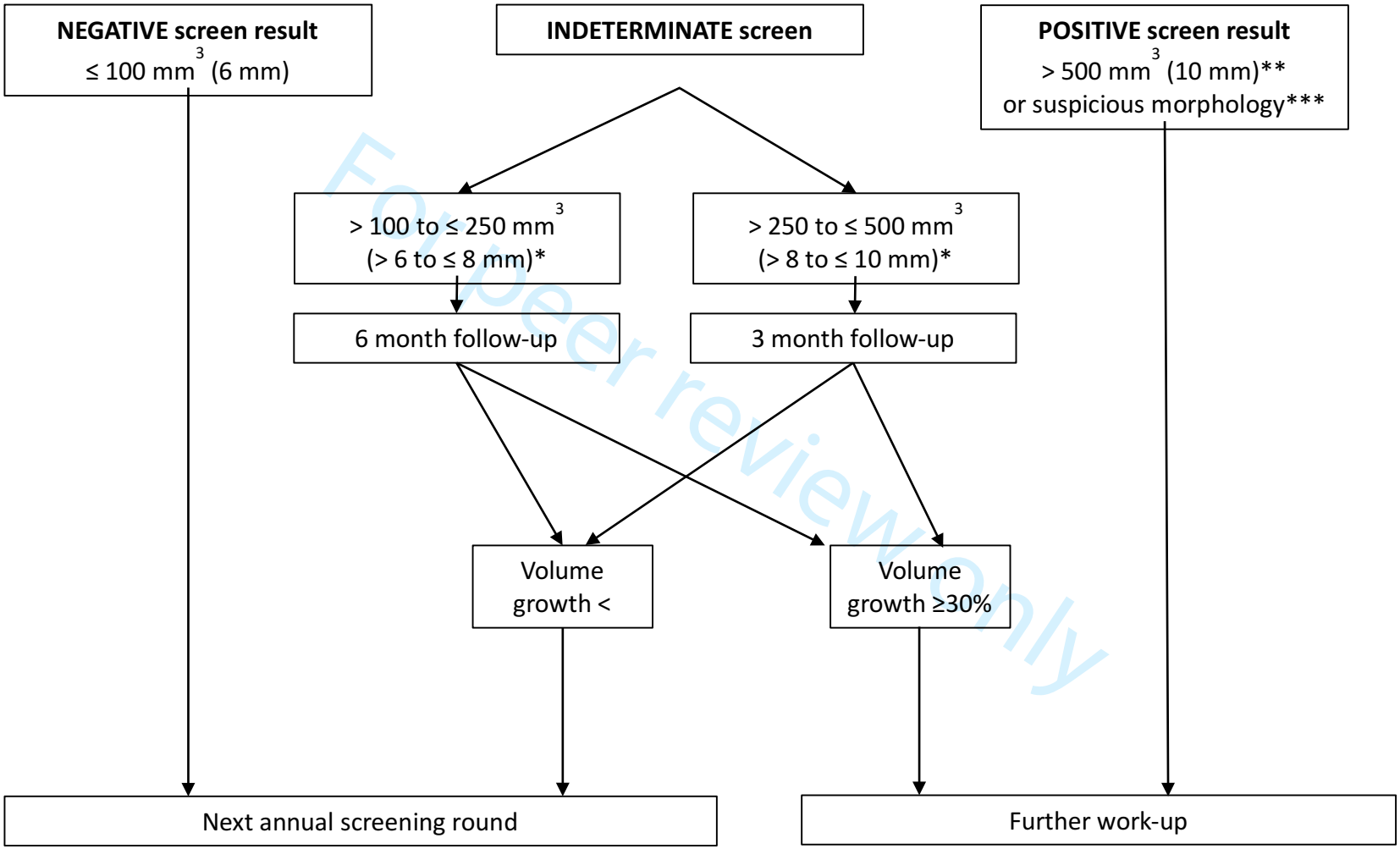
Word count: 3595

	Pre enrolment	Inclusion visit	Baseline visit (CT)	3 first weeks after baseline visit	1-year visit (CT)	2-year visit (CT)	End visit
Informed consent		X					
Eligibility screen	X	X					
ASSESSMENTS							
Baseline variables*		X					
Outcome variables**							X
INTERVENTIONS							
Five As' strategy prescription of nicotin substitutes for current smokers		X					
Telephone consultation for follow-up of smoking cessation				X			
Low-dose CT			X		X	X	
Questionnaires							
Cancer worry scale		X					X
Satisfaction with Decision scale		X					X
Hospital Anxiety and Depression scale			X		X	X	
Cigarette dependance scale		X					

* List of collected baseline variables: *Age of smoking onset, date of cessation, number of cigarettes per day, study level, family history of lung cancer, previously diagnosed coronary artery disease or osteoporosis, status in relation to other cancer screenings: breast, cervix, colon, How information about the study reached them*

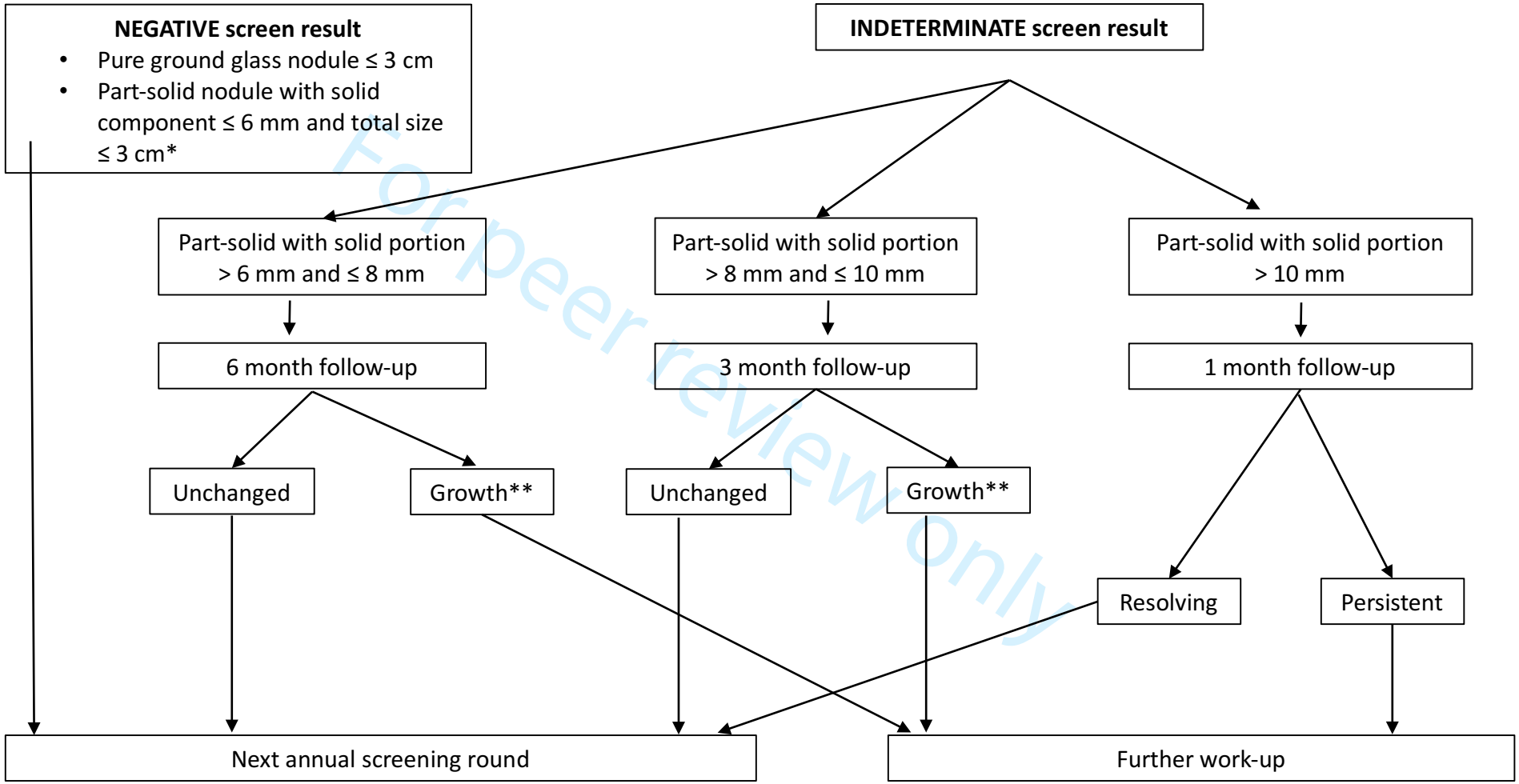
**list of collected outcome variables: *Duration of smoking cessation, COPD confirmed by spirometry, Coronary artery disease confirmed and treatment initiated (medical treatment or revascularization), Osteoporosis confirmed by additional densitometry, initiation of anti-osteoporosis treatment, Completion of the other recommended screenings*

BASELINE CT SOLID NODULES



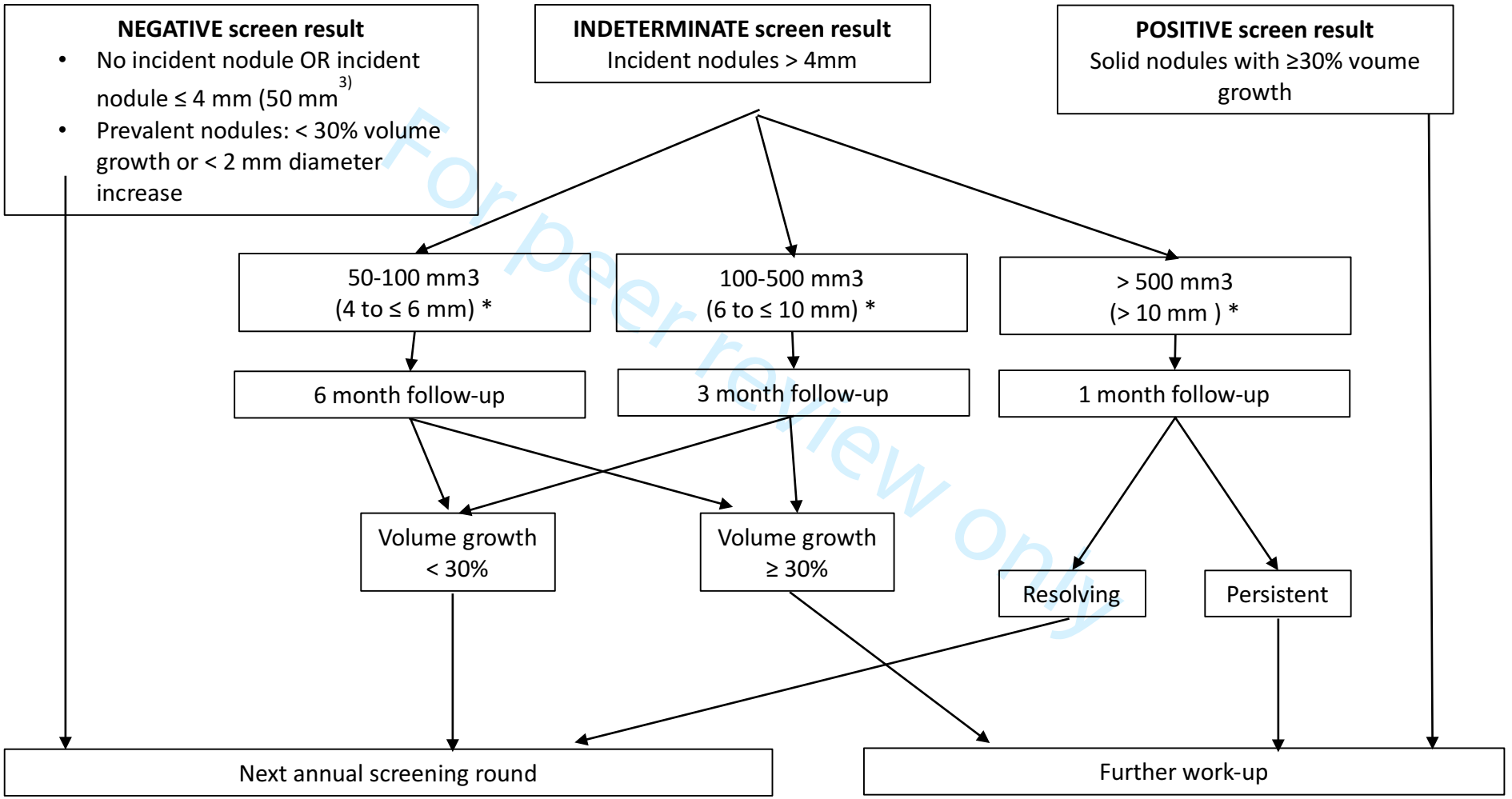
* In case segmentation has failed
** In case of a cystic airspace nodule, the solid portion should be taken into account
*** Pleural indentation, cystic component, air bronchogram or bubble like lucencies, spiculation

BASELINE CT SUBSOLID NODULES



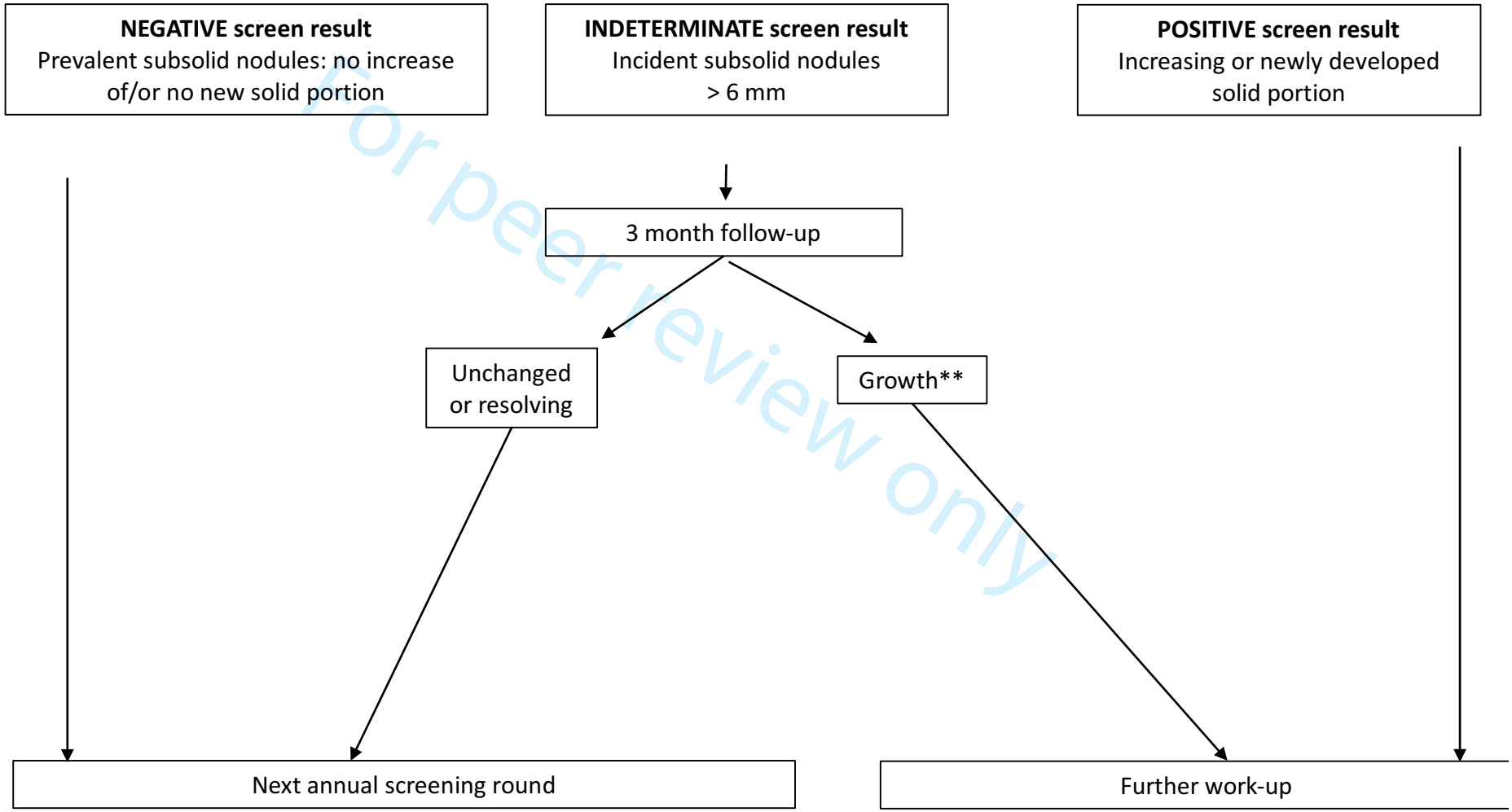
* For part solid and GGN without morphological criteria suggesting malignancy (bubble like lucencies, border of bulla, pleural indentation)
** Increase in solid portion of ≥ 2mm, measured on lung window setting

1-YEAR FOLLOW-UP CT SOLID NODULES



* In case segmentation has failed

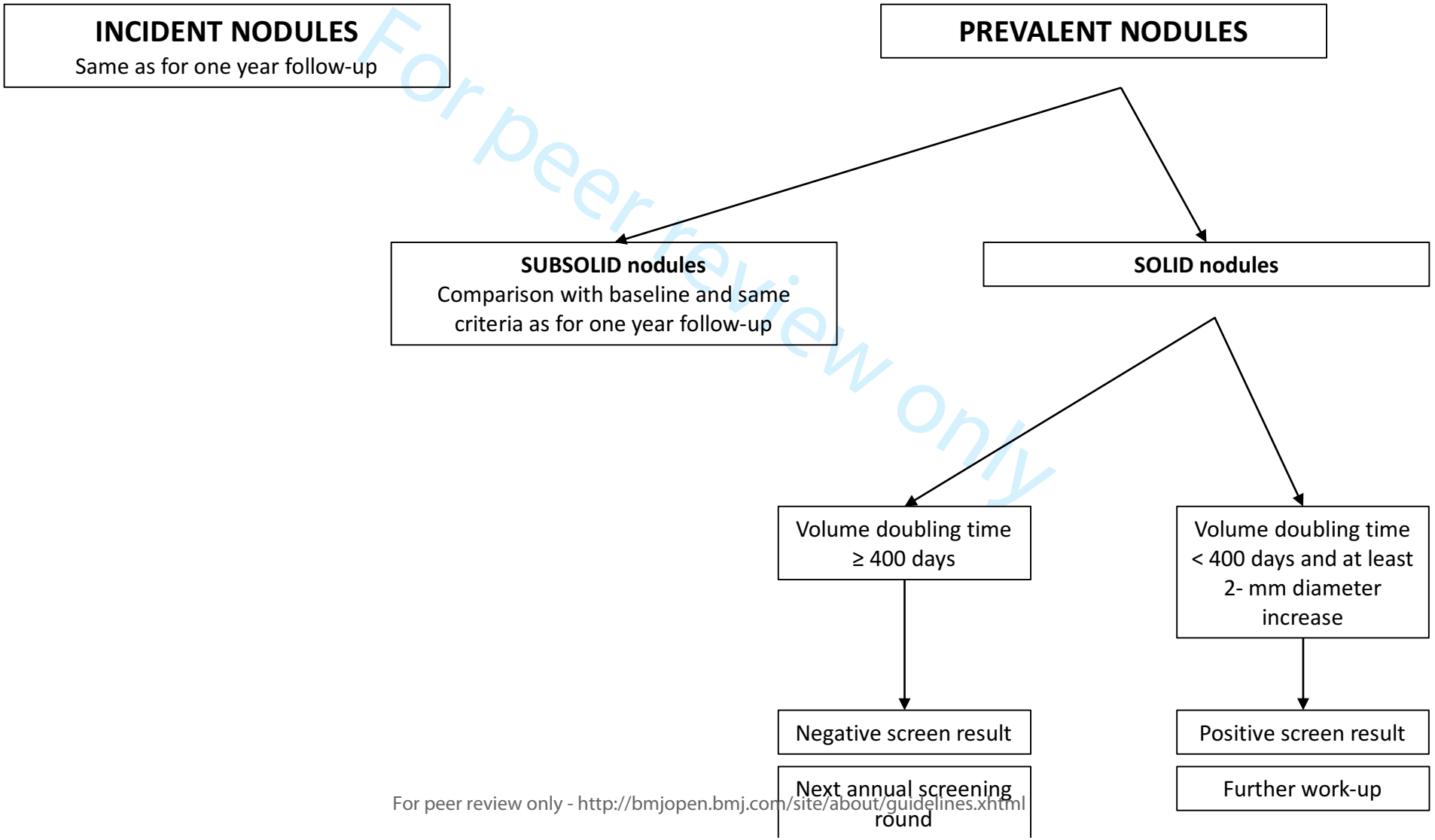
1-YEAR FOLLOW-UP CT SUBSOLID NODULES



* For part solid and GGN without morphological criteria suggesting malignancy (bubble like lucencies, border of bulla, pleural indentation)

** Increase in solid portion of ≥ 2mm, measured on lung window setting

2-YEAR FOLLOW-UP



STROBE Statement—Checklist of items that should be included in reports of ***cohort studies***

	Item No	Recommendation	
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	observational cohort study, abstract, page 1
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	NA, it is the study protocol
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	Page 2-4
Objectives	3	State specific objectives, including any prespecified hypotheses	Page 4
Methods			
Study design	4	Present key elements of study design early in the paper	Page 4
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	Page 5
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up	Page 5
		(*b*) For matched studies, give matching criteria and number of exposed and unexposed	NA
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	Outcomes page 7 Diagnostic criteria Appendix
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	Page 7-8
Bias	9	Describe any efforts to address potential sources of bias	
Study size	10	Explain how the study size was arrived at	Page 8
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	Page 10
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	Page 10
		(*b*) Describe any methods used to examine subgroups and interactions	NA
		(*c*) Explain how missing data were addressed	Page 10
		(*d*) If applicable, explain how loss to follow-up was addressed	Page 10
		(*e*) Describe any sensitivity analyses	Page 10

Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	NA study protocol
		(b) Give reasons for non-participation at each stage	NA study protocol
		(c) Consider use of a flow diagram	NA study protocol
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	NA study protocol
		(b) Indicate number of participants with missing data for each variable of interest	NA study protocol
		(c) Summarise follow-up time (eg, average and total amount)	NA study protocol
Outcome data	15*	Report numbers of outcome events or summary measures over time	NA study protocol
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	NA study protocol
		(*b*) Report category boundaries when continuous variables were categorized	NA study protocol
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	NA study protocol
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	NA study protocol
Discussion			
Key results	18	Summarise key results with reference to study objectives	NA study protocol
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	NA study protocol
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	NA study protocol
Generalisability	21	Discuss the generalisability (external validity) of the study results	NA study protocol
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present	In the document administrative information

	article is based

*Give information separately for exposed and unexposed groups.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at http://www.strobe-statement.org.