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ABSTRACT

Introduction: We review the current knowledge of CT screening for lung cancer and present an expert-based, joint protocol for the proper implementation of screening in the Nordic countries.

Materials and methods: Experts representing all the Nordic countries performed literature review and consensus for a joint protocol for lung cancer screening.

Results and discussion: Areas of concern and caution are presented and discussed. We suggest to perform CT screening pilot studies in the Nordic countries in order to gain experience and develop specific and safe protocols for the implementation of such a program.

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Background

Lung cancer is the leading cause of cancer death worldwide and also in the Nordic countries [1,2]. In spite of improvements in treatment of lung cancer over the last decades overall survival is still only in the 10–18% range, both in the US and Western Europe [1,2]. Early diagnosis by low dose CT (LDCT) screening has been shown to lead to a reduction in lung cancer mortality by 20% in the National Lung Screening Trial (NLST), a large randomized clinical trial, from the US [3,4]. Therefore, recommendations for the implementation of LDCT screening have been put forward by organizations involved in lung cancer management in the US; including The American Association for Thoracic Surgery (AATS) [5], Society of Thoracic Surgeons (STS) [6], American Lung Association (ALA) [7], National Comprehensive Cancer Network (NCCN) [8], American Cancer Society (ACS) [9] and the International Association for the Study of Lung Cancer (IASLC) [10]. After an extensive evaluation of benefits and harms, CT screening was recommended for implementation by the United States Preventive Services Task Force (USPSTF) [11] and approved by Medicare [12]. LDCT screening is being implemented in the US [13], and also in China guidelines for implementation of CT screening have been published [14].

In Europe, there are currently several randomized trials on-going or completed [15]. These include the NELSON trial in Belgium and the Netherlands [16–19], and studies from

Denmark [20–22], Germany [23,24] and the UK [25,26] but also four trials in Italy [27–30] (Table 1). In addition to this, observational studies in the International Early Lung Cancer Action Program (IELCAP) collaboration are currently running in Spain, Israel and Italy [31]. In most European countries, national health authorities have decided to await results from the NELSON screening trial before making decisions regarding implementation of LDCT screening for lung cancer [32]. It is expected that the mortality results in the NELSON trial will be published in 2017 [33]. Importantly, however, implementation of CT screening has been recommended by the European Respiratory Society (ERS) and European Society of Radiology (ESR) [34], the European Society of Medical Oncology (ESMO) [35] and also by Swiss University Hospitals [36].

In view of the substantial evidence now available regarding both the benefits and harms of LDCT screening for lung cancer, representatives of medical health care organizations in the Nordic countries have come to the conclusion that preparations for implementation of CT screening for lung cancer should be initiated in these countries. The similarity of the health care systems in the Nordic countries indicates that mutual benefits could be achieved by collaboration and harmonization between our countries with regard to CT screening. Therefore, representatives of the Nordic Thoracic Oncology Group with prior interest in or experience with CT

Table 1. European randomized lung cancer CT screening trials: selection criteria, enrollment and lung cancer detection rates.

Trial (Ref)	Selection criteria		Participants in CT arm of trial	Lung cancer detection rate Baseline (total in follow up)
	Age (years)	Tobacco exposure (pack years)		
NELSON [16,17]	50–75	<ul style="list-style-type: none"> • 15 cig/day 20 years • 10 cig/day 30 years 	7915	0.9% (2.6%)
DLCST [20,22]	50–70	<ul style="list-style-type: none"> • 20 	2052	0.8% (3.4%)
LUSI [23,24]	50–69	<ul style="list-style-type: none"> • 15 cig/day 25 years • 10 cig/day 30 years 	2029	1.1% (NA)
DANTE [28]	60–74	<ul style="list-style-type: none"> • 20 	1276	2.2% (4.7%)
ITALUNG [29]	55–69	<ul style="list-style-type: none"> • 20 	1406	1.5% (2.8%)
MILD [30]	<ul style="list-style-type: none"> • 49 	>20	1190 (Annual CT)	0.8% (2.4%)
UKLS [25,26]	50–75	LLP risk model: >5% LC risk next 5 years, and additional risk factors	1186 (Biennial CT) 2028	1.7% (NA)

screening have formed an expert study group to prepare this joint Nordic Protocol as a guidance to assure a shared and common platform for the proper implementation of future screening programs. The protocol describes general issues regarding lung cancer screening, but also provides specific recommendations for each Nordic country to consider.

Benefits and harms of CT screening

Possible benefits

The results from the NLST are the only proof so far of a mortality reduction following CT screening, but the size of the trial (53,452 participants) overrules smaller European trials that were so far underpowered regarding the issue of mortality reduction. The mortality results of the second largest trial, the NELSON trial (with 15,422 participants), is expected in 2017 [33]. Furthermore, pooling of the seven European trials is planned after publication of the NELSON results, and that pooled cohort will include over 36,000 participants [33].

The NELSON study is important to verify the findings in the NLST, or if no trends toward mortality benefit for CT screening will be identified, it will raise questions to the generalizability of the NLST. However, importantly the detection rates and LC stage distribution from the screening arm of the NELSON trial have so far been in line with the results from the NLST [37,38].

The NLST observed a reduction in lung cancer mortality of 20%, and all cause mortality of 6.7%, in the age group 55–74 years that had over 30 pack years of tobacco exposure [3,4]. Based on these results further modeling indicated that screening in the ages 55–80 years of age (who had smoked at least 30 packs years), would result in a life time reduction in lung cancer mortality by 14% [39]. Furthermore, as many smokers and ex-smokers worry about their health, having a negative (normal) CT – screening result might lead to a positive psychological effect with reduced stress and better quality of life [40]. Incidental findings of other malignancies, cardiovascular or pulmonary diseases may also be of benefit for the screened persons (see later section).

Possible harms

1. *Radiation exposure.* CT screening inevitably incurs radiation exposure, but with low dose technique in LDCT the effective radiation dose is about 1.5 milliSieverts (mSv) per examination. In the NLST participants received

an average of 8 mSv over 3 years and it was estimated that one radiation induced cancer per 2500 people screened could occur [41]. In the study by Brenner it was suggested that a >5% reduction in overall mortality from CT scan screening would outweigh the risks of radiation [42]. However, improvements in detector technology, automated exposure control techniques and interactive image reconstruction, have led to a further decrease in radiation exposure of 80% to a level around 0.2 mSv, without impairing image quality [34,43]. Still, radiation exposure will always have to be higher in obese individuals than in normal weight and should be recorded individually [34]. Radiation risk increases significantly if follow-up CT scans are performed using standard clinical protocols (old equipment with 4–18 mSv compared to 2–4 mSv for more modern equipment) instead of screening using LDCT settings (new equipment with 0.2 mSv). For this reason, the work-up of screen-detected nodules should remain within the screening program as long as possible [34].

2. *Psychological distress.* The distress caused by CT screening and a false-positive test results has been investigated in the NLST [44,45], the NELSON [46], DLCST [40,47] and UKLS trials [26,48]. The psychological profile of smokers and ex-smokers undertaking screening is presumably different from that of women being screened for breast cancer, as adverse psychological effects in both the DLCST, UKLS and NELSON were transient and seemed without serious consequences for the participants [40,46,48]. However, information to participants and care of patients with nodules in CT screening should take into consideration that studies of patients' reactions to detection of pulmonary nodules on CT scans shows that most participants immediately believe they have cancer. This may be prevented by providing careful information before screening [49].
3. *False positive diagnoses.* All of the RCTs on LC screening had clearly defined nodule management protocols but the criteria for a positive and negative test differed significantly. In the NLST the cut off in nodule size was set at 4 mm; which means that all nodules above this size were designated positive [3,4]. This explains why the false positive (FP) rate was as high as 24% [3,4]. Most other trials used a 5 mm (or 50 mm³) as a cutoff [16,20,23,25,27–30]. Further analysis has shown that even small changes in cutoff sizes from 4 to 6, 7 or 8 mm has

a major impact on the number of FP diagnoses, but results in missing only very few cancers [50,51]. Therefore, cutoff criteria for a positive test should be considered carefully. In the NELSON trial and DLCST nodule, size growth was measured by volumetrics and presumably this contributed to the observed low FP rates, with baseline FP rate up to 8% and incidence FP rate was 1–2% [16,20,22,52]. These FP rates have great consequences for the ensuing diagnostic work load [16,18,22]. Although 18,146 of LDCT participants in the NLST had a positive test, only 1.8% of them underwent a biopsy of the nodule, 3.8% underwent bronchoscopy and 4% underwent surgical resection of the tumor [3,4]. Adherence to guidelines and the use of multidisciplinary diagnostic and treatment conferences with participation of lung cancer experts are important tools for minimizing the harms of screening and inappropriate invasive diagnostic procedures [10,13,52].

4. **Overdiagnosis.** Overdiagnosis is the diagnosis by screening of a cancer that in the absence of screening would not have caused symptomatic disease or death in the life time of the person screened [53,54]. In lung cancer CT screening, the extent to which overdiagnosis occurs is difficult to determine because it in principle requires follow up until all participants in a given trial have died and their cause of death has been verified. A substudy in the NLST estimated an overdiagnosis rate of 18.5%, which amounted to 1.38 cases per 320 participants needed to screen to prevent one death [55]. The consequences of FP diagnoses, as described in the section above, may also contribute to overdiagnosis. Although overdiagnosis may reduce the benefits of screening, its true extent is yet to be determined [53–55]. Importantly the current estimates available from major LDCT screening trials suggest that in high-risk patients, the benefits of screening outweigh the risk of overdiagnosis [55,56].

Who should be screened?

Recommendations regarding individuals eligible for screening have mainly followed the NLST criteria regarding age and tobacco exposure, but some have also included individuals with lower or higher lung cancer risks (Table 2). The cost-effectiveness of CT screening may be increased by risk stratification and selecting high risk participants, but the

population that is screened will be reduced in number [57]. Such selection criteria could be higher tobacco exposure (more than 35 pack years) and age over 60 years of age [58]. These were the inclusion criteria in the UKLS trial in which participants with a 5% risk of getting LC within 5 years were included in the trial after evaluation according to the Liverpool Risk Model [25,59]. In the future genetic profiling may also contribute to inclusion criteria [60].

Due to the documented mortality benefit in this risk group in the NLST, we would recommend for the Nordic countries that the NLST criteria are used: 55–75 years of age, more than 30 pack years smoking history, current smoker or having quit smoking within last 15 years, and having no substantial comorbidity. However, we would also suggest that the use of risk stratification, as done in the UKLS, is tested beforehand in pilot projects in the Nordic countries, as this may increase cost-effectiveness.

Screening techniques and nodule management

LDCT should be performed according to ACR-RSNA [63,64] or ESR/ERS technical specifications [34] and should comprise the whole screening process as described in ‘the 10 pillars of screening’ published by RSNA [61]. The scanner should preferably be a multidetector LDCT with at least 16 detector rows providing isotropic high spatial resolution (slice thickness of about 1 mm with an increment of 0.7 mm) and an effective dose between 1 mSv for normal weight individuals and not more than 3 mSv for obese individuals [34]. Documentation of the actual screening CT radiation dose should be done in compliance with ACR-STR recommendations [61].

The optimal screening interval is yet to be determined. The effect seen in NLST was based on annual screening [3,4] but other studies have shown that biennial screening, after a baseline screening and a single annual incidence screening, does not lead to lower detection rates of LC [30,37,38]. However a 2.5 year interval has led to an increased frequency of interval cancers in the NELSON trial, and therefore is discouraged [38]. The suggested screening interval in the Nordic countries therefore should be one baseline screening followed by a single annual screening, and thereafter biennial screening in participants without pulmonary nodules. Participants with nodules should be followed annually or as specified in the management flowchart (Figure 1).

The use of volumetric measurements to assess growth in screen detected nodules has been used successfully in the

Table 2. Target populations at increased risk for lung cancer recommended for participation in CT screening programs.

Organisation	Age	Risk factors			Reference
		Tobacco exposure (exp.) (pack years)	Tobacco exp. Years since quit	Additional risk factors	
NLST	55–74	>30	<15	None	[3]
NCCN: Cat 1	55–74	>30	<15	None	[8]
NCCN: Cat 2A	50–74	>20	<15	Cancer history, Lung diseases, Family history LC, Radon exp., Occupational exp.	
USPSTF and ESR/ERS	55–80	>30	<15	None	[11,34]
ESMO	55–75	>30	<15	None	[35]

NLST: National Lung Screening Trial; NCCN: National Comprehensive Cancer Network; USPSTF: United States Preventive Services Task Force; ESR: European Society of Radiology; ERS: European Respiratory Society; ESMO: European Society of Medical Oncology.

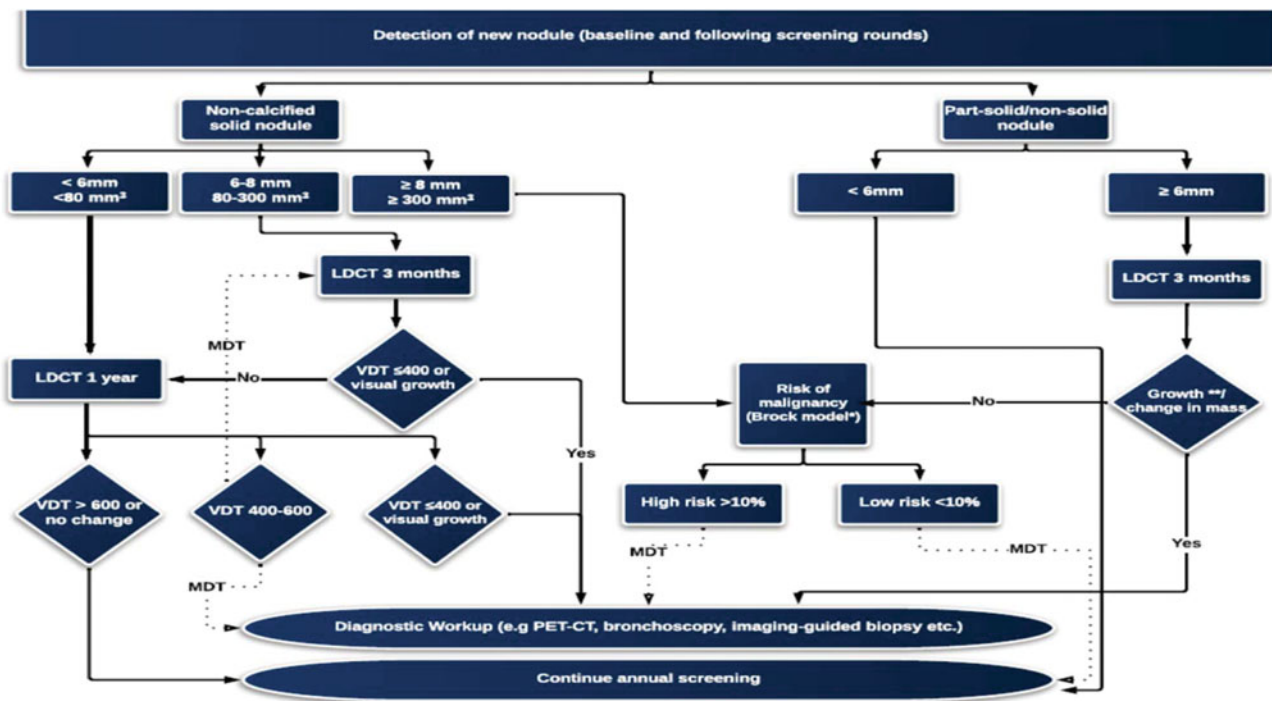


Figure 1. Management of screening detected nodules in the Nordic countries. In part based on BTS guidelines on management of pulmonary nodules 2015 [63]. *Risk prediction calculator available free of charge via website <https://brocku.ca/lung-cancer-risk-calculator> – choose full model with spiculation (McWilliams A, Tammemagi MC, Mayo JR, et al. Probability of cancer in pulmonary nodules detected on first screening CT. *N Engl J Med.* 2013;369:910–919). **Growth of solid areas in part solid/nonsolid nodules. Dotted arrow: Requires MDT consideration about further approach. LDCT: low dose CT; VDT: volume doubling time; PET-CT: positron emission tomography; MDT: multi-disciplinary team meeting.

NELSON trial and is recommended by ESR/ERS [34]. A positive screen is defined as a volume $>500 \text{ mm}^3$ (approximately 9.8 mm in greatest dimension) or a volume-doubling time <400 days [16]. This strategy has resulted in positive rates of 2.6% and 1.8%, respectively, compared with the 26.4% positive rate across all rounds of screening in the NLST [16,19]. The NELSON and UKLS trials have demonstrated the potential advantage of volumetric measurements in reducing the number of follow-up examinations needed for individuals with a positive test result [19,25]. Volumetric analysis has not been established as the radiological standard of care in the US or Europe but is now included in British Thoracic Society (BTS) guidelines [63]. Volumetrics will therefore presumably be more widely available, and should be integrated in future screening studies in the Nordic countries, as this improves the ability to distinguish benign from malignant disease [64,65].

Criteria for lung nodule identification, and for size, character and growth of nodules to define test as positive should be made [63]. A flowchart for management of nodules with a care pathway should be described as part of the protocol [63,66]. It is suggested that in the Nordic countries a lower size cut off of 6 mm for solid nodules be used as definition of a positive screen test in order to reduce the FP rate, in accordance with the NCCN guidelines from 2017 [8] (Figure 1).

Data on the number, size and character of all lung nodules should be collected. Especially nodules labeled as positive (suspicious) should be registered and reported in a structured reporting system, such as the Lung-RADS from the

US, or an equivalent. In addition the compliance with screening should be monitored.

Incidental findings

LDCT scanning provides not only information on the lungs, but also of other organs in the chest and upper abdomen. Therefore abnormalities of other organs than the lungs can show up and diseases other than lung cancer are discovered incidentally. These include abnormalities in the lungs (for example, emphysema, interstitial lung disease and bronchiectasis), breast, mediastinum, thyroid gland, thoracic and upper abdominal aorta, heart, pancreas, kidneys and liver [67]. Eight percent of LDCT scans in the NLST identified a clinically significant abnormality that was not suspicious of lung cancer [67]. However, in the NELSON and other trials incidental findings were generally not frequent (0.5–1.0%) [68–70].

Coronary artery calcifications was the most common incidental finding, as reported in other trials as well [71,72] and LDCT has been shown to allow for the estimation of calcium scores predictive of cardiovascular risk [71,72]. Furthermore, LDCT also allows the detection and quantification of emphysema, which may be used in the motivation to quit smoking [73].

The clinical consequence of these downstream incidental findings, however, is not yet defined nor is the benefit of intervention for these. Therefore, it is our recommendation in the Nordic Countries that the inclusion of these items in a screening protocol should only be done in a separate

formalized trial, and not as a part of the general public screening offered. Any incidental findings detected during screening should be reported and discussed with the participant, together with a referral to a relevant physician or multidisciplinary tumor (MDT) board. Furthermore, the potential for making these incidental findings should be discussed with the participating individuals when screening is prepared and offered.

Participant education and smoking cessation

Participants should be educated in benefits and harms of screening and information material should inform on both benefits and possible harms. Results of the screening should be communicated and explained to the participant in both writing and direct oral communication in case of a positive or indeterminate result. A negative (normal) result may be communicated in writing or direct oral communication. All test results have an impact on the persons receiving them, and this should be taken into consideration when organizing the screening protocol [49].

A smoking cessation program and spirometry should be an integrated part of the screening program, as smoking cessation still is the far most effective tool in the fight against lung cancer, but also cardiovascular diseases and Chronic Obstructive Pulmonary Disease (COPD) [10,11,13,20]. Analysis of smoking habits in the DLCST is consistent with the results from the NELSON study, and shows that participation in screening programs is a teachable moment in which participants can be informed of the harmful effect of smoking and receive smoking cessation counseling [74]. Therefore, comprehensive smoking cessation programs should be an integrated part of all future screening programs in the Nordic countries, but these should be adapted to the local conditions.

Despite enrollment in LC screening trials, some individuals continue to smoke. Younger age, lower socioeconomic status, being spouseless, low body mass index (BMI), smoking intensity and duration, and secondhand smoke exposure are associated with higher rate of continued smoking [75]. Evidence suggests that LDCT screening itself does not influence smoking behavior. This is supported by data from the ongoing NELSON trial where no difference in cessation rates between those undergoing LDCT screening and controls was seen [76]. However, those who had abnormal screening results suspicious for LC reported a 6% lower rate of smoking compared with those who had normal results [77–79].

Cost effectiveness and research

Healthcare costs and cost effectiveness of screening

The cost effectiveness of screening has so far only been evaluated in the US, Canada and the United Kingdom (UK), but to our best knowledge not in any of the Nordic countries. Black et al. examined the cost effectiveness of screening with LDCT in the NLST. The cost of CT screening per life-year and QALY gained (in US dollars) was \$52,000 and \$81,000, respectively [80]. Subgroup analyses demonstrated that it

was more cost efficacious to screen women than men (\$46,000 vs. \$147,000 per QALY gained), current smokers than former smokers (\$43,000 vs. \$615,000 per QALY gained), both for the oldest age groups and for the participants with the highest risk of cancer [80,81]. In Europe a cost of 8500 £per QALY gained was calculated, following a complete health technology assessment in the UKLS trial [26]. In the DLCST FP screening tests increased health care costs but a true-negative screening test also resulted in reduced costs [82]. Evaluation of the cost-effectiveness of LDCT screening should also take into account the fraction of patients who because of diagnosis in low stage by screening do not need expensive treatment with costly targeted drugs or immunotherapy for more advanced disease [83]. Based on the UKLS reports, it is expected that LC screening would also be cost effective in the Nordic countries, but more detailed calculations of the cost-effectiveness should be done in each country or as a joint Nordic task.

Research possibilities in lung cancer screening

Continuous research is essential to ensure persistent high quality in the screening programs. In the Nordic countries, the organized infrastructure provides opportunity for such research. Such important research areas at present include: (1) Biomarkers, including gene methylation, micro-ribonucleic acid and autoantibodies to be used for potential screening. (2) Demonstration projects with selection of high risk populations for CT screening (2–5% lung cancer risk). (3) Methods to recruit the ‘hard to reach population’ in order to increase the participation rate as much as possible [26]. (4) Optimal screening intervals in CT screening. Annual vs. biennial screening in addition to more individually tailored programs based on individual risk profiles. (5) Further development of minimal invasive treatment options in early lung cancer [84,85].

Requirements to a lung cancer screening center

All the current guidelines for CT screening state that screening should only be done in centers with multidisciplinary LC capabilities and organization [5,7,8,10,13,34]. The following MDT board certified capabilities should be available: pulmonology, pathology, radiology, thoracic surgery and oncology [5,7,8,10,34,61]. Furthermore, the center should be certified, authorized and accredited to do lung cancer screening [61] and the CT scanner capabilities (minimum 16 slice) with lung nodule volumetric software, and reporting system (i.e., Lung-RADS), radiation quality control should be available [34,61]. Radiologist or pulmonologists with CT guided biopsy expertise or other minimal invasive technology for biopsy of small lung nodules (<10 mm) [34,61] should also be on the multidisciplinary team and invasive pulmonology service available with advanced bronchoscopy, Endo Bronchial Ultra Sound (EBUS) and Esophageal Ultra Sound (EUS) [34].

There should also be PET or PET-CT scanner capabilities for diagnostic evaluation of suspicious nodules and preoperative staging [10,61].

A minimal invasive VATS surgery program is required to allow a full spectrum of surgical options (wedge resection, anatomical segmental resections, lobectomy, lymph node dissection, etc.) [5,7,10,36,61].

Finally data registration and research capabilities [34,61] have to be present and all cases should be reported to a national lung cancer CT screening register [34,61].

Requirements to a national lung cancer screening program in the Nordic countries

Central registration and authorization of screening centers has to be established in each country with a central national database and quality control available. Protocols for nodule and patient management have to be present in each country to ensure national quality standards, as for example the Lung RADS [61–63].

Harmonization of future national protocols with this joint common protocol in the Nordic countries is recommended. This would allow large joint research projects with pooling of data and make it possible to answer important research questions faster, but also create a forum for discussion, dissemination of knowledge and assistance on LC screening and treatment between the participating countries and centers.

Number of persons eligible for screening in the Nordic countries (Table 3)

Denmark: The total population is 5.5 mio. Based on data from the Copenhagen County Study the expected number of persons to be offered screening in Denmark based on the NLST criteria would be approximately: 106,041.

Norway: The total population is 5.0 mio. of whom 1,070,000 people are 55–75 years old. No direct data on numbers of smokers and ex-smokers are available but an estimate based on the Hordaland Study from 1996 indicates that approximately 96,300–128,400 individuals would fulfill the NLST criteria.

Sweden: The total population is 9.8 mio, of whom 2,315,320 are aged 55–75 years. The expected number of persons to be screened in Sweden based on NLST criteria, would therefore be approximately: 290,000.

Finland: The total population is 6.0 mio, of whom 1,408,876 people are aged 55–75 years. The expected number of persons to be screened in Finland based on the NLST criteria would be approximately: 125,130.

Table 3. Eligibility for lung cancer CT screening in the Nordic countries according to NLST criteria.

	Total population age 55–75 years	NLST criteria age 55–75 years	Age 60–75 years
Denmark	1.325511	106.041	81.331
Norway	1.070000	96.300–128.400	NA
Sweden	2.315320	265.049	173.512
Finland	1.408876	125.130	98.963
Iceland	333,000	9.711	NA

NLST criteria: age 55–75, >30 pack years smoking history and not quit more than 15 years ago.
NA: not available.

Iceland: The total population is 330,000. The expected number of persons to be screened in Iceland based on the NLST criteria would be approximately: 9700.

Implementation in the Nordic countries

Implementation of CT screening requires that several additional common key questions are addressed.

The expected participation rate should be estimated. In both the US [86] and in the UK [26,87], there is concern that the underserved hard-to-reach smoking population may not accept CT screening and thereby miss the benefits associated with screening. In a German study, the results of the NLST were extrapolated and the estimated participation rate expected to be 50% [88]. In the Nordic countries this might also be an issue, however, presumably to a lesser degree if screening is by population based recruitment. This will also be a challenge as recruitment of a high risk group based on smoking history will require the willingness of participants to share this information with the recruiting staff. In the UKLS, this was done by web based registration systems, but also personal contact [26]. It is not yet known if the hard to reach population will participate sufficiently in this process. In the UK, a specific project dealing with this aspect of screening recruitment is underway [89]. It is our opinion that especially in the Nordic Countries equal access to health care including screening for lung cancer is important and we therefore suggest that this should be the focus of a specific Nordic project.

It is recommended that a national authorization of LDCT screening centers is established and a plan for the number and geographical distribution of these is made.

It is recommended that an evaluation of what the expected demand for radiologists and other LC specialists will be and if there is a risk that there will be a shortage of qualified staff.

It is recommended that LDCT screening is introduced in a gradual phased manner in each country. This could be by the establishment of one or a few multidisciplinary screening centers to gain knowledge and experience in this new field, prior to subsequent expansion of the activity. Based on experience from the European screening trials it is recommended that the initial screened cohort in a center should not be less than 2000 individuals.

The national costs of LDCT screening and eventual derived cost of diagnostic investigations should be calculated for each country, and ways to secure funding should be explored.

Conclusions

It is the authors' opinion that implementation of LDCT screening for lung cancer in the Nordic countries should be considered now. We suggest to perform CT screening pilot studies in the Nordic countries in order to gain experience and develop specific and safe protocols for the implementation of such a program.

Disclosure statement

The authors report no conflict of interest.

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