

Design and Rationale of the HANSE Study: A Holistic German Lung Cancer Screening Trial Using Low-Dose Computed Tomography

Design und Rationale der HANSE-Studie: Eine ganzheitliche deutsche Lungenkrebs-Früherkennungs-Studie unter Verwendung von Niedrigdosis-Computertomografie



Authors

Jens Vogel-Claussen^{1,2} , Florian Lasch³, Benjamin-Alexander Bollmann^{4,2}, Katharina May⁵, Alexander Kuhlmann^{6,2}, Gerald Schmid-Bindert^{7,8}, Rudolf Kaaks^{9,10}, Jörg Barkhausen⁵, Sabine Bohnet^{11,12}, Martin Reck^{13,12}

Affiliations

- 1 Department of Diagnostic and Interventional Radiology, Hannover Medical School, Hannover, Germany
- 2 Biomedical Research in Endstage and Obstructive Lung Disease Hannover (BREATH), German Center for Lung Research, Giessen, Germany
- 3 Department of Biostatistics, Hannover Medical School, Hannover, Germany
- 4 Department of respiratory medicine, Hannover Medical School, Hannover, Germany
- 5 Department of Radiology and Nuclear Medicine, University Medical Center Schleswig-Holstein Campus Lübeck, Lübeck, Germany
- 6 Working Group Health Economics, Martin Luther University Halle Wittenberg, Halle, Germany
- 7 Oncology Medical Department, AstraZeneca GmbH, Hamburg, Germany
- 8 Medical Faculty Mannheim, Heidelberg University, Heidelberg, Germany
- 9 Translational Lung Research Center Heidelberg (TLRC-H), German Center for Lung Research, Giessen, Germany
- 10 Division of Cancer Epidemiology, German Cancer Research Center, Heidelberg, Germany
- 11 Department of Pulmonology, University Medical Center Schleswig Holstein Campus Lübeck, Lübeck, Germany
- 12 Airway Research Center North (ARCN), German Center for Lung Research, Giessen, Germany
- 13 Department of Thoracic Oncology, LungenClinic Grosshansdorf GmbH, Grosshansdorf, Germany

Key words

screening, lung cancer, low-dose CT

received 04.02.2022

accepted 29.04.2022

published online 02.08.2022

Bibliography

Fortschr Röntgenstr 2022; 194: 1333–1345

DOI 10.1055/a-1853-8291

ISSN 1438-9029

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Georg Thieme Verlag KG, Rüdigerstraße 14,
70469 Stuttgart, Germany


Correspondence

Prof. Jens Vogel-Claussen

Institut für Diagnostische und Interventionelle Radiologie,
Medizinische Hochschule Hannover, Carl-Neuberg Str. 1,
30625 Hannover, Germany

Tel.: +49/511/532 34 21

vogel-claussen.jens@mh-hannover.de

 Supplementary material is available under:
<https://doi.org/10.1055/a-1853-8291>

ABSTRACT

Background Despite the high prevalence and mortality of lung cancer and proven effectiveness of low-dose computed tomography (LDCT) to reduce mortality, Germany still lacks a national screening program. The German Institute for Quality and Efficiency in Health Care (IQWiG) and the Federal Office for Radiation Protection (BfS) both published positive scientific evaluations recommending a quality-controlled national screening program. IQWiG underlined the importance of a clear risk definition, integrated smoking cessation programs, and quality assurance, highlighting the necessity of procedural optimization.

Methods and Objectives In the HANSE study, former and current smokers aged 55–79 years are assessed for their lung cancer risk by the NELSON and PLCO_{M2012} risk scores. 5000 high-risk participants, defined as PLCO_{M2012} 6-year risk

≥ 1.58 % or fulfilling NELSON risk inclusion criteria, will be screened by LDCT at baseline and after 12 months. Lung nodules are analyzed by a modified Lung-RADS 1.1 score of the HANSE study, and values of emphysema and coronary calcium are determined and randomly reported to the participants. 7100 low-risk participants serve as a control. All patients are followed-up for up to 10 years. The sensitivity and specificity of the two risk assessments and LDCT screening, effects of the randomized LDCT reporting, efficiency of lung nodule management, and several other factors are assessed to analyze the success and quality of the holistic screening program.

Conclusion The HANSE study is designed as a holistic lung cancer screening study in northern Germany to answer pressing questions for a successful implementation of an effective German lung cancer screening program.

Key Points:

- HANSE is designed to address pressing questions for the implementation of lung cancer screening in Germany.
- HANSE compares NELSON and PLCO_{M2012} risk assessments for optimal definition of the high-risk group.
- HANSE integrates cardiac calcium and pulmonary emphysema scoring in a holistic screening approach.

Citation Format

- Vogel-Claussen J, Lasch F, Bollmann B et al. Design and Rationale of the HANSE Study: A Holistic German Lung Cancer Screening Trial Using Low-Dose Computed Tomography. *Fortschr Röntgenstr* 2022; 194: 1333–1345

ZUSAMMENFASSUNG

Hintergrund Trotz der hohen Prävalenz und Mortalität von Lungenkrebs und der nachgewiesenen Wirksamkeit von Niedrigdosis-Computertomografie (LDCT) zur Senkung der Mortalitätsrate existiert in Deutschland noch kein nationales Früherkennungsprogramm. Das Deutsche Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (IQWiG) wie auch das Bundesamt für Strahlenschutz (Bfs) haben positive wissenschaftliche Bewertungen mit Empfehlungen für ein qualitätskontrolliertes nationales Früherkennungsprogramm

veröffentlicht. Das IQWiG betonte die Notwendigkeit klar definierter Risikokriterien, der Integration eines Rauchstopp-programms sowie der Sicherstellung hoher Qualitätsstandards, was die Bedeutung von Prozessoptimierungen unterstreicht.

Methoden & Ziele In der HANSE-Studie werden ehemalige und aktive Raucher im Alter von 55–79 Jahren bezüglich ihres Lungenkrebsrisikos anhand der NELSON und PLCO_{M2012}-Kriterien untersucht. 5000 Probanden mit hohem Risiko, definiert als PLCO_{M2012} 6-Jahres-Risiko ≥ 1,58 % oder Erfüllen der NELSON-Kriterien, werden mittels LDCT zur Baseline sowie nach 12 Monaten untersucht. Lungenknötchen werden anhand eines modifizierten Lung-RADS 1.1 Scores der HANSE-Studie analysiert und zusätzlich Werte eines möglichen Lungenemphysems und koronaren Kalziums bestimmt und dem Befundbericht an die Probanden randomisiert beigefügt. 7100 Probanden mit niedrigem Risiko dienen als Kontrollgruppe. Alle Probanden werden für bis zu 10 Jahre nachverfolgt. Die Sensitivität und Spezifität der Risiko-Kriterien und der LDCT-Untersuchung, die Effekte der randomisierten LDCT-Befundbriefinhalte, die Effizienz des Knoten-Managements sowie weitere Parameter werden untersucht, um den Erfolg und die Qualität dieses holistischen Früherkennungsprogramms zu überprüfen.

Schlussfolgerung Die HANSE-Studie ist als holistische Lungenkrebs-Screening-Studie in Norddeutschland konzipiert und dient der Beantwortung drängender Fragen für eine erfolgreiche Implementierung eines Lungenkrebsfrüherkennungsprogramms in Deutschland.

Kernaussagen

- Die HANSE-Studie ist als Vorreiter eines Früherkennungsprogramms für Lungenkrebs in Deutschland konzipiert.
- HANSE vergleicht die NELSON-Risikobewertung und den PLCO_{M2012}-Score zur besseren Definition der Hochrisikogruppe.
- HANSE integriert koronares Kalzium-Scoring und den Lungenemphysem-Score in ein ganzheitliches Screening-Programm.

Background and Rationale

In Germany, lung cancer is the leading cause of cancer death among men and the second leading cause among women just after breast cancer [1]. Smoking is the main risk factor for lung cancer development, accounting for approx. 9/10 cases in men and 6/10 cases in women [2].

If lung cancer is detected at early stages, it is amenable for curative treatment. The 5-year survival rates in stage I patients in Germany are 78 % for women and 58 % for men with a rapid decline at higher stages [2]. Since approximately 70 % of patients are diagnosed at late stages, with 5-year survival rates of 5 % for women and 3 % for men at stage IV, early detection remains a

major objective and great efforts are made to identify patients at high-risk of developing this disease in screening programs.

The US National Lung Screening Trial (NLST) demonstrated a benefit for the high-risk population by screening with low-dose computed tomography (LDCT) when compared to radiography. The criteria for assignment as high-risk were age 55–74 years, ≥ 30 pack-years of tobacco consumption, and < 15 years of quit time for former smokers. Subjects at high risk were randomly assigned to undergo 3 rounds of annual screenings with LDCT or chest radiography. In the LDCT group, more cancers were detected, including early-stage cancers, and a 20 % reduction in mortality from lung cancer as well as a 6.7 % reduction in all-cause mortality at the 6.5-year median follow-up were observed. [4].

In European countries, the NELSON trial also demonstrated a significant reduction in lung cancer mortality, and a meta-analysis of 5 randomized controlled trials confirmed a 15% reduction of lung cancer mortality [5] (e. g., LUSI trial in Germany [6] and the NELSON trial in Netherlands/Belgium [7]).

Lung Cancer Screening in Germany

Despite the high prevalence and mortality of lung cancer as well as the potential benefit of LDCT, a national screening program has not been implemented in Germany to date.

In 2020, the German Institute for Quality and Efficiency in Health Care (IQWiG) published an assessment of LDCT screening for lung cancer [8]. This report concludes that, in the high-risk population, the expected benefits outweigh the risks of a lung cancer screening (LCS) program but also specifies important criteria for implementation:

1. Need for determination of criteria that define a high-risk population.
2. Integration of access to a smoking cessation program.
3. Implementation of obligatory quality assurance measurements.

In December 2021, the Federal Office for Radiation Protection (BfS) also published a positive scientific evaluation in accordance with § 84 (3) of the radiation protection law with recommendations for the structure and implementation of a national LCS program [9]. Based on this evaluation and according to § 84 (2) of the radiation protection law, the Federal Ministry for the Environment, Nature Conservation, Nuclear Safety and Consumer Protection (BMUV) is now empowered to stipulate by ordinance definitions of the recommended screening test and screening conditions for the early detection of lung cancer. This ordinance is expected in 2022. A final implementation decision by the Federal Joint Committee of health insurances and providers (G-BA) is mandatory within 18 months of this ordinance.

Selection of the high-risk population

LCS should be targeted at individuals with a high risk of developing lung cancer, such that the expected benefits (mortality reduction) outweigh the risks of adverse effects, notably false-positive diagnoses and overdiagnosis, in comparison to financial costs [10, 11]. Traditionally, the target population has been defined by concise criteria including age and lifetime cumulative smoking history [4, 6]. However, several studies have shown that a more refined risk model of lung cancer including additional risk information (e. g., preexisting medical diagnosis of COPD, family history of cancer) can improve the targeting of CT screening [12, 13]. One such model that has shown good discrimination and calibration in multiple studies and populations worldwide was developed in the Prostate, Lung, Colorectal, and Ovarian (PLCO) Cancer Screening Trial (PLCO_{M2012} model) [14] and has been shown to generally improve sensitivity with equal specificity [12, 14].

LDCT lung nodule management in LCS

Another factor to optimize the sensitivity and specificity of lung cancer detection is lung nodule management. LDCT screening is highly sensitive for lung nodule detection. However, the vast

majority of nodules is benign. In recent years, several standardized scoring and reporting systems have been proposed, which are essential to guide nodule management in screening programs [6, 14]. Recently, Lung-RADS (**R**eporting **a**nd **D**ata **S**ystem) version 1.1. was optimized in this regard, integrating volume-based measurements and nodule-based risk modelling to guide management [15].

Benefits of an LDCT screening program for secondary diagnoses

Besides early lung cancer detection, there is evidence for the LDCT-based identification of individuals being at increased risk for developing respiratory and cardiovascular diseases [16, 17]. Although LDCT uses a non-triggered acquisition protocol, it allows simultaneous, quantitative assessment of coronary calcification (Agatston score [18]), which has been shown to correlate with the rate of future myocardial infarction, stroke, and death due to cardiovascular disease [19, 20]. This has the potential to combine an LCS program with cardiovascular event prevention.

Closely following German and European recommendations [9, 21, 22], the HANSE Study is designed to investigate important unresolved issues, such as comparative evaluation of risk criteria for targeting LDCT screening, LDCT effectiveness in cancer detection, efficiency of lung nodule management protocols, and effects of LDCT secondary diagnoses, like coronary heart disease and emphysema, in a holistic quality-controlled LCS program. Since the first patient was included in the HANSE study on July 23, 2021, the results of the HANSE study will be available when a national program is implemented.

Methods

Objectives and study endpoints

The HANSE study (clinicaltrials.gov identifier: NCT04913155) is a northern German multicenter prospective randomized population-based cohort study with 3 German cancer society- (DKG-) certified lung cancer centers as recruitment sites within the German Center for lung research (DZL): Hannover, Lübeck, and Großhansdorf. The HANSE study aims to provide evidence supporting the implementation of a holistic and effective LCS program in Germany. While there is general consensus that LCS programs must be recommended only for a high-risk population, it remains unclear what the best approach is to define this high-risk population. There is now growing evidence that selecting participants based on individual cancer risk, rather than age and smoking history alone, can increase benefit while at the same time reducing associated risks [23]. To address this important open scientific question, the primary endpoint of this trial was chosen to directly compare the positive predictive value (PPV) of NELSON and PLCO_{M2012} in a German population.

All study endpoints are summarized in ► **Table 1**.

Recruitment

Within 12 months, 5000 high-risk subjects, based on PLCO_{M2012} risk scores or NELSON risk inclusion criteria, as well as about

► **Table 1** Overview of study endpoints.

► **Tab. 1** Übersicht der Studien-Endpunkte.

HANSE study endpoints – overview table

End point category	Description	Time point of analysis
Primary endpoint	Comparison of the positive predictive values for lung cancers detected in PLCO _{M2012} -selected vs. NELSON-selected high-risk groups	After 2 annual LDCT screening rounds
Key secondary endpoints	Comparison of both risk scores as selection criteria (PLCO _{M2012} vs. NELSON) with regards to (in hierarchical order):	
#1	Proportion of individuals participating in the screening program within the high-risk study population	After 1 st LDCT screening round
#2	Proportion of lung cancers detected (screen and clinical) within the overall study population* (sensitivity)	After 5 years
#3	Proportion of lung cancers detected in the identified high-risk population (PLCO _{M2012} or NELSON-positive)	After 1 st and 2 nd LDCT screening round
#4	Specificity within the overall population*	After 5 years
Further secondary endpoints		
#5	Efficacy of randomized LDCT coronary calcium reporting by comparing initiation rates of cardiovascular prevention measures after 1 year as well as rates of all-cause mortality and of MACE after 5 and 10 years of study in the whole study population and between randomized groups	After 1, 5 and 10 years
#6	Efficiency of nodule management algorithms (LungRads1.1 alone or LungRads1.1 + PanCan Model (2b) or PanCan Model (2b) alone) with regards to number of cancer cases in the three sorted participant groups: (a) next surveillance scan, (b) early recall scan, or (c) diagnostic evaluation recommended	After 1 st LDCT screening round
#7	Success of the screening program:	
	a) with regards to participant response rate and study recruitment	After 1 st LDCT screening round
	b) Reliability of the participants' transferred personal data including PLCO _{M2012} risk scoring (self-reported vs. on-site assessment)	After 1 st LDCT screening round
	c) Percentage of participants receiving LDCT scan and report, according to DRG guidelines [26] (number of diagnostic CTs/number of all CTs)	After 1 st LDCT screening round
	d) Percentage of participants receiving adequate follow-up procedures	After 1 st LDCT screening round
#8	Quality of screening program, calculated with regards to:	
	a) LDCT reading performance CAD vs. different physician-based reads in LungRADS ≥ 3 detection as well as time between LDCT and mailing of final report	After 1 st and 2 nd LDCT screening round
	b) Quality of lung nodule management (rate of interventions, cancers, true and false-diagnostic fractions and treatments, positive predictive value)	After 1 st and 2 nd LDCT screening round
	c) Frequency of detection and management of clinically relevant incidental findings from LDCT	After 1 st and 2 nd LDCT screening round
	d) LDCT dose management	After 1 st and 2 nd LDCT screening round
#9	Success of smoking cessation in the whole study population and depending on LDCT reporting (e. g., emphysema score) in the high-risk group , evaluated by questionnaires and by urine cotinine testing	After 2 LDCT screening rounds and after 5 and 10 years
#10	Evaluation of various blood-based biomarkers in positive LDCT cases with subsequent biopsy to improve the positive predictive value of the LDCT test	After 2 LDCT screening rounds
#11	a) Cost-effectiveness modeling to investigate LDCT screening impacts on morbidity, mortality, and socio-economic long-term costs	After 2 LDCT screening rounds
	b) Cost-effectiveness comparison of different participant recruitment strategies in terms of recruitment of qualified screening subjects	After 1 st LDCT screening round

► **Table 1** (Continuation)

HANSE study endpoints – overview table		
End point category	Description	Time point of analysis
#12	Emotional and psychological consequences of the LDCT screening will be evaluated by a voluntary survey, collecting data on the psychological and socioeconomic background as well as on smoking cessation, lung, and cardiovascular health	After 2 LDCT screening rounds

CAD: Computer aided detection; COPD: chronic obstructive pulmonary disease; CT: computed tomography; LDCT: low-dose computed tomography; MACE: major adverse cardiovascular events; PLCO_{M2012}, modified criteria of the Prostate, Lung, Colorectal, and Ovarian (PLCO) Cancer Screening Trial; DRG: Deutsche Röntgengesellschaft, * overall study group = high risk group + low risk group participating in the HANSE study.
 CAD: Computergestützte Detektion; COPD: chronisch-obstruktive Lungenerkrankung; CT: Computertomografie; LDCT: Niedrigdosis-Computertomografie; MACE: schwere kardiale Komplikationen; PLCO_{M2012}: modifizierte Kriterien der Prostata, Lungen, Kolorektal und Ovarial Krebs-Screening-Studie; DRG: Deutsche Röntgengesellschaft, * Gesamtstudiengruppe = Hochrisikogruppe + Niedrigrisikogruppe, die an der HANSE-Studie teilnehmen.

► **Table 2** NELSON inclusion criteria and PLCO_{M2012} risk score.

► **Tab. 2** NELSON-Einschlusskriterien und PLCO_{M2012} Risikoscore.

NELSON risk inclusion criteria [10]	PLCO _{M2012} risk score ≥ 1.58 % (6 years) [19]
Current smoker or former smoker (smoking quit time ≤ 10 years) > 15 cigarettes/day for > 25 years > 10 cigarettes/day for > 30 years	Age Ethnic group Education BMI COPD Personal history of cancer Family history of lung cancer Smoking status (current/former) Smoking intensity Duration of smoking Smoking quit time

BMI: body-mass index; COPD: chronic obstructive pulmonary disease; PLCO_{M2012}: modified criteria of the Prostate, Lung, Colorectal, and Ovarian (PLCO) Cancer Screening Trial.
 BMI: Body-Mass-Index; COPD: chronisch obstruktive Lungenerkrankung; PLCO_{M2012}: modifizierte Kriterien der Prostata, Lungen, Kolorektal und Ovarial Krebs-Screening-Studie.

7100 low-risk volunteers are currently included in the HANSE study. Both groups consist of current and former smokers in the age range of 55–79 years. The inclusion and exclusion criteria are summarized in ► **Table 3**.

It is known from other studies, esp. from the LCS program in the US, that effective recruitment to LCS is hindered by several obstacles ranging from the exact definition of the high-risk population to contacting and motivating former and current smokers to participate in an LCS program [24]. Since persons in this high-risk group are of a higher age and tend to exhibit specific emotional and psychological barriers to LCS participation, potential subjects are informed and recruited via different communication channels and strategies: Subjects in the suitable age range are identified via local registries and contacted by mail. Additional

► **Table 3** Inclusion and exclusion criteria.

► **Tab. 3** Ein- und Ausschlusskriterien.

Inclusion criteria	Exclusion criteria
Male and female subjects aged 55–79 years	Comorbidity which would unequivocally contraindicate either screening or treatment if lung cancer is detected
Current or former smokers	History of chest CT within the past year preceding the invitation
Subjects with calculated risk score PLCO _{M2012} ≥ 1.58 % (6 years) or NELSON inclusion criteria*	Inability to undergo LDCT (e. g. ≥ 200 kg body weight, inability to lie flat)
Able and willing to give written informed consent	Pregnancy
	Risk of non-compliance with study procedures: <ul style="list-style-type: none"> ▪ Unable to give written consent ▪ Patient's inability to fill in the questionnaire ▪ Very limited knowledge of the German language ▪ Inability to travel, residents of care facilities, etc.

CT: computed tomography; LDCT: low-dose computed tomography; PLCO_{M2012}: modified criteria of the Prostate, Lung, Colorectal, and Ovarian (PLCO) Cancer Screening Trial.

CT: Computertomografie; LDCT: Niedrigdosis-Computertomografie; PLCO_{M2012}: modifizierte Kriterien der Prostata, Lungen, Kolorektal und Ovarial Krebs-Screening-Studie.

* Participants not fulfilling this criterion will be asked to volunteer by contributing long-term outcome data informing of the development of lung cancer or death from lung cancer (about n = 7100 randomly selected from all 3 centers, low-risk group).

Probanden, die dieses Kriterium nicht erfüllen, werden gebeten, freiwillig ihre Langzeitdaten im Falle des Auftretens von Lungenkrebs oder des Versterbens zur Verfügung zu stellen (etwa n = 7.100, randomisiert ausgewählt von allen 3 Studienzentren, Niedrigrisiko-Kohorte).

recruitment efforts via local physicians (general practitioners (GPs), specialists) and campaigns targeting the general public via radio, television, and social networks are performed in order to avoid selection bias and to reach recruitment goals.

Interested individuals are informed via a study website (www.hanse-lungencheck.de) and can register directly via the website, via mail, or by contacting a telephone hotline. Self-reported health data are used to pre-qualify subjects based on PLCO_{M2012} risk score and/or NELSON inclusion criteria.

Definition of high-risk and low-risk groups

Subjects with a preliminary PLCO_{M2012} risk score $\geq 1.58\%$ (6 years) [14] or fulfilling NELSON risk inclusion criteria [7] (see ► **Table 2**) are considered high-risk subjects and are invited to LDCT screening at one of the study centers. This PLCO_{M2012} risk score cut-point of 1.58% (6-year risk) was estimated to result in an equal proportion of German men and women aged 55–79 in the general population to be eligible for lung cancer screening as with the NELSON inclusion criteria. While NELSON criteria select individuals only based on smoking history and age, the PLCO_{M2012} model also weighs in body mass index, education status, ethnicity, family history of cancer and preexisting COPD/Emphysema, to calculate an individual cancer risk based on an algorithm previously validated in large screening cohorts [14]. Subjects were selected for participation if they had a risk of $> 1.58\%$ to develop lung cancer within the next 6 years according to the PLCO_{M2012} model. On site, risk scores are validated and additional assessment of the medical condition, medical history, and current medication are performed by a qualified physician. High-risk participants fulfilling all eligibility criteria are offered two LDCT screening rounds (baseline and after 1 year).

Subjects not meeting the NELSON or PLCO_{M2012} criteria (low-risk group) do not undergo LDCT screening but are asked to volunteer by contributing long-term outcome data. Information on smoking cessation, cardiovascular events, and development of lung cancer will be collected by questionnaires during the first screening round and after the 5- and 10-year follow-up. In addition, regional and national cancer registries will be used to gain information on all-cause mortality and death from lung cancer.

Randomization

High-risk participants are randomized with regards to the content of the LDCT reports which are sent to the participants and their treating GP before they receive the first LDCT. Randomization does not affect the LDCT procedure but only determines additional reporting of the coronary calcium score and the emphysema score, leading to four different reporting groups:

- Reporting group 1: Modified Lung-RADS 1.1 score only (= basic report)
- Reporting group 2: basic report + coronary calcium score
- Reporting group 3: basic report + emphysema score
- Reporting group 4: basic report + coronary calcium score + emphysema score

A randomization ratio of 1:1 and a 2-factorial design ($\frac{1}{4}$ coronary calcium score only; $\frac{1}{4}$ emphysema score only, $\frac{1}{4}$ both; $\frac{1}{4}$ none)

provide equally sized groups of subjects including age and sex stratification. The non-reported coronary calcium and emphysema scores are kept confidential during the entire study duration except for clinically relevant incidental findings, which will be included in the CT report to ensure follow-up care as part of the clinical routine.

Longitudinal follow-up

All participants will be followed for up to 10 years. After a minimum of 5 years, participants will be contacted by mail to inquire if they have been diagnosed with lung cancer since recruitment. Non-responders will be contacted by phone. All participants will be followed by local registries. New lung cancer cases will be verified using official hospital or cancer registry documents. The minimum follow-up period of 5 years was chosen to account for the sojourn-time bias [25] between tumor and symptom occurrence and cancer diagnosis in the low-risk group.

In addition, all-cause mortality rates and major adverse cardiovascular event rates (MACE: nonfatal stroke, nonfatal myocardial infarction, and cardiovascular death) as well as long-term smoking cessation rates will be collected after 5 and 10 years.

Study scheme

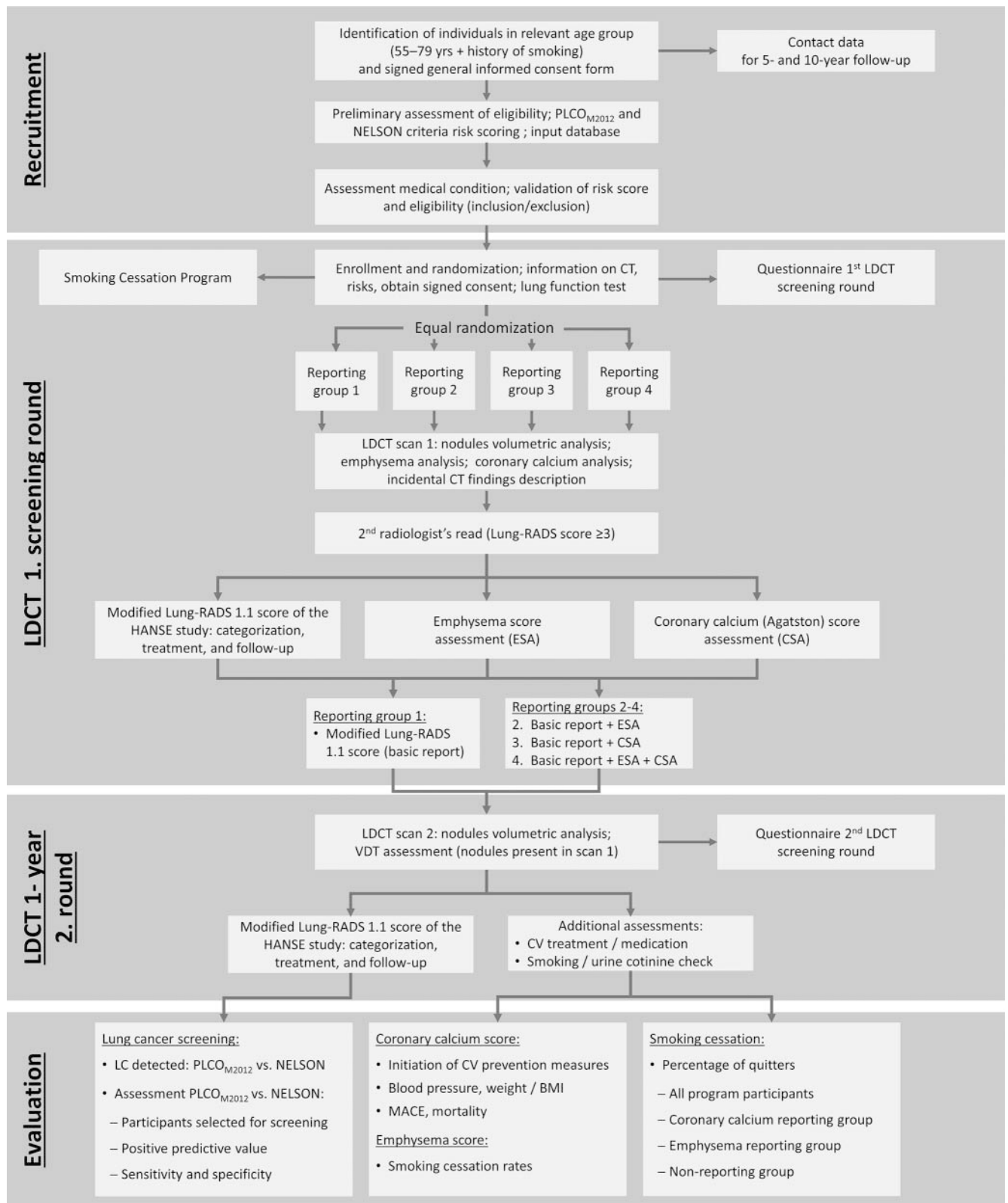
The study scheme of both LDCT screening rounds is summarized in ► **Fig. 1**.

LDCT protocol

To ensure high-quality chest CT with sufficient capacity, a truck-based CT scanner is used for all 3 study sites. Low-dose chest CT scans (100 kV, 300mA, pitch 0.8, 0.33 s gantry rotation time) are acquired using a 128-slice Siemens SOMATOM go.Top CT (Siemens Healthineers, Forchheim, Germany) in a single short (3 sec) inspiratory breath hold with the patient's arms overhead. The use of an additional Sn (Tin) pre-filtration, hardening the X-ray spectrum and eliminating lower energy photons, together with the use of a sinogram-affirmed iterative image reconstruction (SAFIRE) will enable high image quality acquisitions of < 1 mSv effective dose, depending on patient size. 1 mm axial slices are reconstructed with a lung kernel (Br64) and a soft tissue kernel (Br35). The radiation dose will be recorded for each CT exam.

Chest LDCT reading

The LDCT reads are independently read by a trained and experienced chest radiologist (> 10 years of experience) and an experienced radiology resident (> 3 years of experience) with special training in LCS for quality assurance. The radiologists are supported by state-of-the-art artificial intelligence (AI)-based lung nodule detection software (Coreline Soft, Seoul, South Korea) with automated volume analysis, integrated Lung-RADS 1.1 classification [15], volume doubling time (VDT) calculation, and nodule risk calculation using the PanCan (Brock University) nodule malignancy probability calculator (2b) for lung nodules [26], a model that is based on nodule characteristics and location combined with patient characteristics such as age, female sex, or emphysema. In the case of multiple nodules, the highest Lung-RADS 1.1 score determines the categorization. The Lung-



► **Fig. 1** Flowchart study scheme. BMI: body mass index; COPD: chronic obstructive pulmonary disease; CT: computed tomography; CV: cardiovascular; LDCT: low-dose computed tomography; MACE: major adverse cardiovascular event; PLCO_{M2012}: modified criteria of the Prostate, Lung, Colorectal, and Ovarian (PLCO) Cancer Screening Trial; VDT: volume doubling time.

► **Abb. 1** Übersichtsdiagramm des Studienverlaufs. BMI, Body-Mass-Index; COPD, chronisch-obstruktive Lungenerkrankung; CT, Computertomografie; CV, kardiovaskulär; LDCT, Niedrigdosis-Computertomografie; MACE, schwere kardiale Komplikationen; PLCO_{M2012}, modifizierte Kriterien der Prostata, Lungen, Kolorektal und Ovarial Krebs-Screening-Studie; VDT, Volumenverdopplungszeit.

RADS 1.1 score of the HANSE study was adjusted for the growth definition according to the European position statement on LCS [27] (for details, see ► **Table 4**). In the Lung-RADS 1.1 4a category, solid nodules with a PanCan risk score < 10 are recommended for 3-month follow-up, while solid nodules with a PanCan risk score > 10 are recommended to undergo PET-CT after multidisciplinary team (MDT) conference discussion. Cases with a Lung-RADS score ≥ 3 are read by a second radiologist. In cases of disagreement between the first and second reader, a final consensus read in the radiological conference is performed. Also, the coronary artery calcium (Agatston Score) and the percent emphysema are automatically calculated using AI-based software (Coreline Soft, Seoul, South Korea).

Chest LDCT report

The LDCT report contains a brief description of the modified Lung-RADS 1.1 score of the HANSE study (for details, see ► **Table 4**) result including follow-up recommendations. In the case of an MDT recommendation, the highest scoring lung nodule is depicted together with a size measurement. All participants with Lung-RADS scores ≥ 3 are informed about their findings via phone call by the reporting radiologist before mailing of the report. In addition, depending on the randomization group, the percent emphysema and coronary calcium scores will be reported. All reports are sent via mail to the participant and to their GP if permitted by the patient. Each report is generated automatically after final nodule classification within the lung nodule detection software (Coreline Soft, Seoul, South Korea) (for details, see **Supplementary Table 3**).

Study procedures

First LDCT screening round

All participants are asked whether they receive treatment for any clinical conditions. A comprehensive medical history is obtained as well as blood pressure, heart rate, and BMI data (height and weight). Prior to LDCT scan, all included participants in the high-risk group receive a lung function test and a voluntary blood draw for biomarker analysis in future studies.

Additionally, before undergoing LDCT assessment, all participants are counselled for smoking cessation. Specifically, voluntary participation in local certified smoking cessation programs such as “Das Rauchfrei Programm” (<https://www.mhh.de/pneumologie/rauchfrei>) is encouraged. In addition, an information brochure about smoking cessation and available local certified smoking cessation programs and further online information material are offered to each participant.

Following the first LDCT assessment, intervals of follow-up scans are scheduled according to the modified Lung-RADS 1.1 score of the HANSE study (► **Table 4**) [15].

All subjects of the high-risk group are asked to participate in a survey to evaluate their emotional and psychological condition during the screening process. Additionally, questionnaires evaluating the socioeconomic background, smoking cessation, lung and cardiovascular health as well as the subject's reported quality

of life (based on the EQ-5D-5 L questionnaire) are provided to the patients.

Second LDCT screening round after 1 year

Study procedures and questionnaires correspond to the first LDCT screening round. Evaluation of newly identified lung nodules will be performed according to the modified Lung-RADS 1.1 score of the HANSE study (► **Table 4**). Follow-up LDCT assessment of solid nodules will be based on the volume doubling time (VDT) as a key driver for recommendations on the further course of action.

In addition, all participants will be asked whether they initiated prevention measures or treatments for any cardiovascular conditions during the study. The success of the smoking cessation program will be evaluated using a questionnaire, combined with a urine cotinine check in quitters.

Long-term performance and cost-effectiveness

A comprehensive microsimulation platform for the assessment of the long-term performance and cost-effectiveness of nationwide LCS with LDCT will be developed based on the HANSE study data. The main objectives of the modelling study are to investigate the impact of different components of LDCT LCS on long-term all-cause mortality and cost-effectiveness. Key components include risk score-based selection criteria, nodule management protocols, threshold values of imaging biomarkers for cardiovascular diseases and chronic obstructive pulmonary disease (COPD), and inclusion of smoking cessation programs.

The stochastic microsimulation model simulates individual life histories of the HANSE study: no LC screening, LC screening focusing on lung cancer only, LC screening including cardiovascular and lung comorbidity assessment, comprehensive LC screening plus a smoking cessation program. A team of clinical and health economic experts will define the detailed structure of the model.

For each screening scenario, a Monte Carlo simulation (MCS) with 1,000 iterations will be performed to estimate expected outcomes and MCS-based confidence intervals. Primary outcomes of the analysis are long-term all-cause mortality, additional costs per quality-adjusted life year (QALY) gained, per life year (LY) gained, or per death averted. Efficiency frontiers will be constructed for each primary outcome to identify efficient screening scenarios and calculate the incremental cost-effectiveness of these scenarios.

Biomarker program

For further scientific investigations, a biomarker program is part of the study. All patients undergoing tissue sampling due to suspicious findings according to the modified Lung-RADS v1.1 score of the HANSE study criteria (score 4B or 4X) will be invited to participate in the translational biomarker program using a separate informed consent form. For the program, a blood sample for epigenetic profiling is taken during the clinical-routine examination in preparation for tissue sampling. The findings of the biomarker analysis will be correlated to the pathological results of the radiological and histopathological finding. Various blood-based biomarkers in positive LDCT cases with subsequent biopsy will be evaluated on the PPV of the LDCT test.

► **Table 4** Modified Lung-RADS 1.1 score of the HANSE study.

► **Tab. 4** Modifizierter Lung-RADS 1.1 Score der HANSE-Studie.

HANSE LDCT Evaluation

Modifizierte Lung-RADS Version 1.1 mit integrierter Volumenverdopplungszeit (VDT)[#]

Kategorie	Lung-RADS Score	Befunde	Vorgehen/Management	Malignitätsrisiko	Geschätzte Populationsprävalenz
Unvollständig	0	Frühere CT-Untersuchung(en) des Brustkorbs wurden zum Vergleich lokalisiert Ein Teil oder die gesamte Lunge kann nicht ausgewertet werden	Zusätzliche Lungenkrebs-Screening-CT-Bilder und / oder ein Vergleich mit früheren Thorax CT-Untersuchungen sind erforderlich	n/a	1 %
Negativ Keine Knoten und definitiv benigne Knoten	1	Keine Lungenknoten Knoten mit spezifischen Verkalkungen: vollständige, zentrale, popcornähnliche, konzentrische Ringe und fetthaltige Knoten	Fortsetzung des jährlichen Screenings mit LDCT in 12 Monaten	< 1 %	90 %
Gutartiges Erscheinungsbild oder Verhalten Knoten mit einer sehr geringen Wahrscheinlichkeit, aufgrund ihrer Größe oder mangelnden Wachstums zu einem klinisch aktiven Krebs zu werden	2	Perifissurale(r) Knoten (siehe Punkt 11) 524 mm ³ (< 10 mm) Solide(r) Knoten < 113 mm ³ (< 6 mm) neu < 34 mm ³ (< 4 mm) Subsolide(r) Knoten < 113 mm ³ (< 6 mm Gesamtdurchmesser) bei Baseline-Screening Milchglas-Knoten (GGN) < 14 137 mm ³ (< 30 mm) oder ≥ 14 137 mm ³ ≥ 30 mm und unverändert oder langsam wachsend Kategorie 3 oder 4 Knoten unverändert für ≥ 3 Monate oder VDT > 600 Tage			
Wahrscheinlich gutartig wahrscheinlich gutartige Befunde – kurzfristiges Follow-Up vorgeschlagen; umfasst Knoten mit einer geringen Wahrscheinlichkeit, ein klinisch aktiver Krebs zu werden	3	Solide(r) Knoten ≥ 113 bis < 268 mm ³ (≥ 6 bis < 8 mm) bei Baseline Screening oder neu 34 bis < 113 mm ³ (≥ 4 mm bis < 6 mm) Subsolide(r) Knoten ≥ 113 mm ³ (≥ 6 mm Gesamtdurchmesser) mit solider Komponente < 113 mm ³ (< 6 mm) oder neu < 113 mm ³ (< 6 mm Gesamtdurchmesser) Milchglas-Knoten (GGN) ≥ 14 137 mm ³ (≥ 30 mm) bei Baseline-CT oder neu	6-monatiges LDCT	1–2%	5 %

► **Table 4** (Continuation)

HANSE LDCT Evaluation					
Modifizierte Lung-RADS Version 1.1 mit integrierter Volumenverdopplungszeit (VDT) [#]					
Kategorie	Lung-RADS Score	Befunde	Vorgehen/Management	Malignitätsrisiko	Geschätzte Populationsprävalenz
Wahrscheinlich verdächtig Befunde, für die zusätzliche diagnostische Tests empfohlen werden	4A	Solide(r) Knoten ≥ 268 bis < 1767 mm ³ (≥ 8 mm bis < 15 mm) bei Baseline Screening oder VDT 400–600 Tage (zur initialen Baseline LDCT) [#] oder neu 113 bis < 268 mm ³ (6 mm bis < 8 mm)	3-monatiges LDCT; PET/CT kann verwendet werden, wenn eine feste Komponente von ≥ 8 mm vorhanden ist, insbesondere, wenn die *Wahrscheinlichkeit von Malignität > 10 % beim initialen Baseline LDCT ist.	5–15 %	2 %
		Subsolide(r) Knoten ≥ 113 mm ³ (≥ 6 mm) mit soliden Komponenten ≥ 113 bis < 268 mm ³ (≥ 6 mm bis < 8 mm) oder mit einer neuen oder wachsenden† < 34 mm ³ (< 4 mm) soliden Komponente			
		Endobronchiale(r) Knoten			
Verdächtig Ergebnisse, für die zusätzliche diagnostische Tests und/oder Gewebeproben empfohlen werden	4B	Solide(r) Knoten ≥ 1767 mm ³ (≥ 15 mm) oder VDT < 400 Tage (zur initialen Baseline CT) [#] oder neu ≥ 268 mm ³ (≥ 8 mm) oder VDT < 600 Tage bei neuen Knötchen im Screening [#]	Thorax-CT mit oder ohne Kontrastmittel, PET-CT und/oder Gewebeentnahme in Abhängigkeit von der *Wahrscheinlichkeit von Malignität und Komorbiditäten. PET/CT kann verwendet werden, wenn eine feste Komponente von ≥ 8 mm vorhanden ist. Für neue große Knoten, die sich bei einem jährlichen LDCT-Screening entwickeln, kann eine 1-monatige LDCT empfohlen werden, um potenziell infektiöse oder entzündliche Erkrankungen zu behandeln.	> 15 %	2 %
		Subsolide(r) Knoten eine solide Komponente ≥ 268 mm ³ (≥ 8 mm) oder eine neue oder wachsende ≥ 34 mm ³ (≥ 4 mm) solide Komponente			
4X	Kategorie 3 oder 4 Knoten mit zusätzlichen Merkmalen oder bildgebenden Befunden, die den Verdacht auf Malignität erhöhen				
Andere klinisch signifikante oder potenziell klinisch signifikante Befunde (nicht Lungenkrebs)	S	Modifikator – kann zur Codierung der Kategorie 0–4 hinzugefügt werden	Je nach spezifischem Befund	n/a	10 %
Volumetrische Messungen	1,5 mm = 1,8 mm ³ 4 mm = 33,5 mm ³ 6 mm = 113,1 mm ³ 8 mm = 268,1 mm ³		10 mm = 523,6 mm ³ 15 mm = 1767,1 mm ³ 20 mm = 4188,8 mm ³ 30 mm = 14 137,2 mm ³		

Wichtige Hinweise zur Verwendung:

1. negatives Screening: bedeutet nicht, dass ein Individuum keinen Lungenkrebs hat
2. Größe: Um den mittleren Knotendurchmesser zu berechnen, messen Sie sowohl die lange als auch die kurze Achse auf einen Dezimalpunkt und geben Sie den mittleren Knotendurchmesser auf einen Dezimalpunkt an
3. Größenschwelle: Wird bei der ersten Erkennung von Knoten angewendet, die wachsen und eine höhere Größenkategorie erreichen

4. Wachstum:

Bei soliden Knoten im Baseline-LDCT:

VDT >600 Tage: normales Screening-Intervall (12 Monate)

VDT 400–600 Tage (initial vom Baseline-LDCT): Management nach Lung-RADS 4A in der MDT-Konferenz

VDT <400 Tage: Management nach Lung-RADS 4B in der MDT-Konferenz

Bei neuen soliden Knoten im Vergleich zur Voraufnahme:

VDT >600 Tage: normales Screening-Intervall (12 Monate)

VDT <600 Tage: Management nach Lung-RADS 4B in der MDT-Konferenz

† Subsolide Knoten:

Wachstum der soliden Komponente: > 1.5 mm (> 2 mm³)

5. Prüfungskategorie: Jede Untersuchung sollte, basierend auf dem Knoten mit dem höchsten Verdachtsgrad, von 0 bis 4 codiert werden

6. Prüfungsmodifikatoren: S-Modifikatoren können der Kategorie 0–4 hinzugefügt werden

7. Lungenkrebsdiagnose: Sobald bei einem Patienten Lungenkrebs diagnostiziert wurde, kann eine weitere Behandlung (einschließlich zusätzlicher Bildgebung wie PET/CT) zum Zwecke der Lungenkrebs-Inszenierung durchgeführt werden. Dies ist kein Screening mehr.

8. Definitionen von Practice audits: Ein negativer Screen wird als Kategorie 1 und 2 definiert. Ein unklares Ergebnis wird als Kategorie 3 definiert. Ein positiver Screen wird als Kategorie 4 definiert.

9. Kategorie 4 Management: Dies basiert auf der Wahrscheinlichkeit einer Malignität auf der Grundlage der Patientenbewertung, der Patientenpräferenz und des Malignitätsrisikos. Radiologen wird empfohlen, bei der Abgabe von Empfehlungen das Bewertungsinstrument von McWilliams et al. zu verwenden <https://www.nejm.org/doi/pdf/10.1056/NEJMoa1214726?articleTools=true>.

10. Kategorie 4X: Knötchen mit zusätzlichen bildgebenden Befunden, die den Verdacht auf Lungenkrebs erhöhen, wie Spikulation, GGN, dessen Größe sich in 1 Jahr verdoppelt, vergrößerte Lymphknoten usw.

11. Solide Knoten mit glatten Rändern, einer ovalen, linsenförmigen oder dreieckigen Form und einem maximalen Durchmesser von weniger als 10 mm (perifissurale Knötchen) sollten als Kategorie 2 eingestuft werden

12. Knoten der Kategorien 3 und 4A, die im Intervall-CT unverändert bleiben, sollten als Kategorie 2 codiert werden, und die Personen sollten innerhalb von 12 Monaten erneut zum Screening kommen

13. LDCT: Low-dose-Thorax-CT; MDT-Konferenz: multidisziplinäre Team (MDT)-Konferenz

14. MDT-Konferenz für alle Lung-RADS 4 Fälle.

*weitere Quellen: <https://www.acr.org/Clinical-Resources/Reporting-and-Data-Systems/Lung-Rads>

*Link zum Lung-RADS calculator: <https://brocku.ca/lung-cancer-screening-and-risk-prediction/risk-calculators/>

#European position statement on lung cancer screening Lancet Oncol 2017, 18:e754–766.

In addition, blood samples will also be collected voluntarily from the high-risk group at the first and second screening visit for future research. Assessment of additional translational biomarkers and correlation to pathological findings might open a new window of opportunity for increasing the sensitivity of LCS.

Measures of quality and success

Controlled interdisciplinary diagnostic and treatment algorithms within the context of certified lung cancer centers offer the highest available standard of care for patients with suspicious findings in the HANSE study. Quality and success parameters as listed in ► **Table 1** (#7, #8, and #9) will be analyzed to guide future implementation in Germany.

Primary analysis

The primary analysis will be conducted in all participants within the high-risk population.

The primary and key secondary endpoints will be tested in a hierarchical order, thereby controlling the overall type-I error rate at 5%. Therefore, no correction of p-values for multiple testing needs to be performed. All secondary parameters will be considered explorative. For testing the null hypothesis of equal PPVs for lung cancer detected in PLCO_{M2012}-selected versus NELSON-selected individuals, the weighted generalized score statistic developed by Kosinski will be used [29]. Details of the sample size calculation, statistical analyses, data flow, and limitations of the study are described in the supplements.

Discussion

As with any registry-based study with voluntary participation, the HANSE study is prone to bias. Not all potential high-risk cases may be willing to take part in the study, and even with a broad information campaign by different communication channels, acceptance of an LCS program might be stronger in younger and less comorbid subjects with a lower risk to develop lung cancer [24]. On the other hand, participants referred by local physicians may be older with more comorbidities. To cope with this potential bias, individually tailored invitation mailings based on local registries were implemented. We expect recruitment via individually tailored invitation mailings based on local registries to be most effective with a low selection bias. The expected high proportion of participants recruited by mailings based on local registries is likely to ensure representativeness of the German population in this “real-world setting” approach.

In addition, there is the risk of lung cancer overdiagnosis with increasing age and comorbidities [10]. The PLCO_{M2012} risk score is known to select participants that are slightly older with more comorbidities compared to the inclusion criteria based on age and smoking history [23]. On the other hand, life expectancy in Germany has been steadily increasing during the last decades, warranting further exploration of the hot topics overdiagnosis and comorbidities. The HANSE study explores these questions in a prospective northern German cohort including participants between 76 and 79 years old, which are currently not included in the lung cancer screening recommendations for Germany by the BfS from 2021 [9].

Clinically not apparent lung cancer cases in the low-risk population will be missed, since this group will not receive any intervention and is not undergoing LDCT. However, volunteers in the low-risk group will be followed up for up to 10 years to calculate the proportion of clinically detected lung cancers.

In summary, HANSE is designed to address critical open issues concerning the implementation of a national lung cancer screening program. Prospective comparison of the two selection criteria, NELSON smoking status and $PLCO_{M2012} \geq 1.58\%$ (6 years), will provide information about which risk scoring method to be used for optimal definition of the high-risk population in the future. Future results of the HANSE study will be available when a national lung cancer screening program is implemented.

Summary/key points/clinical relevance

- The HANSE study is designed to address critical open issues concerning the implementation of a national lung cancer screening program.
- Prospective comparison of the NELSON and $PLCO_{M2012}$ selection criteria will provide information about the efficacy of both scoring models regarding the definition of the high-risk group for future lung cancer screening programs.
- The HANSE study will assess whether reporting of the coronary calcium score and emphysema scores has an influence on initiation of preventive cardio-vascular therapy and smoking cessation.
- Lung nodule management algorithms as well as technical, psychological, quality and socioeconomical aspects of implementing a holistic screening program will be analyzed.
- Assessment of additional translational biomarkers and correlation to pathological findings might open a new window of opportunity for increasing the sensitivity of lung cancer screening

Funding

The HANSE study is funded by AstraZeneca GmbH (Wedel, Germany) and the German Center for Lung Research (DZL).

Conflict of Interest

The authors declare that they have the following conflicts of interest:
 J. Vogel-Claussen: Research project support by BMBF, Siemens Healthineers, Boehringer Ingelheim, Novartis, GlaxoSmithKline.
 Speaking fees by Boehringer Ingelheim, Astra Zeneca, Novartis, Siemens Healthineers, Coreline Soft.
 M. Reck: Speaking and consulting fees by Amgen, AstraZeneca, BMS, Beigene, Boehringer-Ingelheim, Lilly, Merck, MSD, Mirati, Novartis, Pfizer, Roche, Sanofi.
 B.A. Bollmann: Speaking fees by AstraZeneca, Boehringer Ingelheim, MSD, Bristol-Myers-Sqibb und Roche.
 G. Schmid-Bindert is an employee of AstraZeneca.
 The other authors declare that they have no conflict of interest.

Acknowledgement

We thank Dr. Annegret Zurawski and Katharina Bünemann for their support in setting up the HANSE study. We thank Dr. Claudia Lorenz-Schlüter and Dr. Johannes Gerlach (Alcedis GmbH, Gießen, Germany) for medical writing assistance.

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