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Screening for Early Lung Cancer, Chronic Obstructive Pulmonary Disease, and Cardiovascular Disease (the Big-3) Using Low-dose Chest Computed Tomography

Current Evidence and Technical Considerations

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Abstract: Lung cancer, chronic obstructive pulmonary disease, and cardiovascular disease are highly prevalent in the general population and expected to cause most deaths by 2050. For these “Big-3,” treatment might cure, delay, or stop the progression of disease at a very early stage. Lung nodule growth rate (a biomarker for lung cancer), emphysema/air trapping (a biomarker for chronic obstructive pulmonary disease), and coronary artery calcification (a biomarker for cardiovascular disease) are imaging biomarkers of early stages of the Big-3 that can be acquired with low-dose computed tomography (CT). We hypothesize that a (combined) low-dose CT examination for detection of all 3 diseases may significantly improve the cost-effectiveness of screening in the future. We review the current evidence of the imaging biomarkers for the detection of the Big-3 diseases and present the potential health economic potential of Big-3 screening. Furthermore, we review the low-dose CT protocols to acquire these biomarkers and describe the technical considerations when combining the CT protocols for the different biomarkers.

Key Words: biomarkers, tomography, x-ray computed, lung neoplasms, emphysema, pulmonary disease, chronic obstructive, cardiovascular diseases, arteriosclerosis

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Lung cancer, chronic obstructive pulmonary disease (COPD), and cardiovascular disease (CVD) are highly prevalent in the general population and are expected to be

the leading causes of deaths by 2050. For these “Big-3,” early detection and treatment might cure, delay, or stop disease progression and reduce morbidity and mortality. Early detection of the Big-3 can be achieved by quantitative imaging of lung nodule growth rate (a biomarker for lung cancer), emphysema (a biomarker for COPD), and coronary artery calcium (CAC) (a biomarker for CVD) with low-dose chest computed tomography (CT).

After the National Lung Screening Trial’s (NLST) publication of a 20% reduction in lung cancer–specific mortality in high-risk screenees receiving an annual chest CT versus annual chest radiography,¹ lung cancer screening by annual low-dose, nongated, non–contrast-enhanced CT has been implemented in the United States. According to the US Preventive Services Task Force, all persons aged 55 to 80 years who smoked 30 pack-years and currently smoke or quit within the past 15 years are eligible for lung cancer screening.² In Europe, the results of the Dutch-Belgian randomized lung cancer screening trial (NELSON trial) are awaited before a decision on the implementation of lung cancer screening in Europe is made. However, various medical societies agree that preparations for lung cancer screening should be made already.^{3,4} Furthermore, cardiovascular disease and COPD, besides lung cancer, are responsible for a relatively high disease burden, with disability-adjusted life years of 5.0, 3.4, and 2.9, respectively.⁵ This results from the relatively high number of years lived with the disability (respectively 4.8, 3.1, and 0.2) and/or years of life lost (respectively 5.5, 4.2, and 9.5 y),⁵ altogether leading to a high burden on the health system and increasing health care costs. However, the benefit of CVD screening and COPD screening in terms of mortality reduction has not been proven yet. Nevertheless, the Big-3 share the main risk factors, aging, early stages of all these diseases usually do not manifest far before midlife, and smoking. Therefore, especially in the high-risk group eligible for lung cancer screening, the higher incidence of emphysema and CAC can be expected compared with a nonsmoking population. Moreover, the lungs and heart are in the same field of view, and therefore combined screening could be feasible. By extending the screening program to all 3 diseases using a (combined) low-dose CT in screenees not previously diagnosed with COPD and CVD, cost-effectiveness and the health benefits of screening may be improved significantly.⁶

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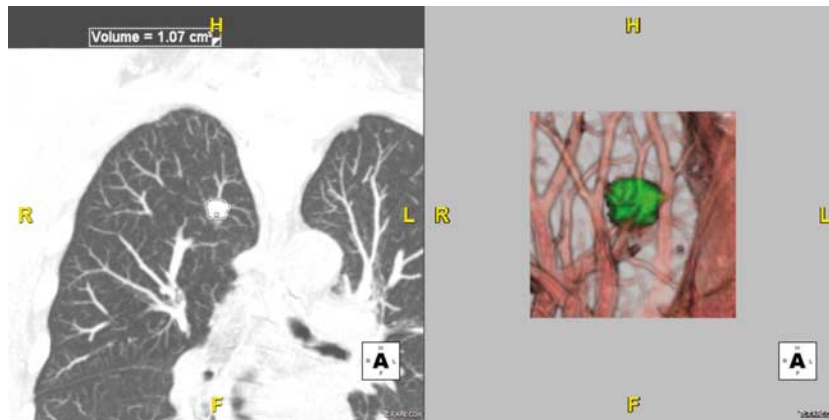


FIGURE 1. Example of semiautomated volume measurement of a baseline-detected pulmonary nodule. In the right upper lobe, a noncalcified solid nodule with a volume of 1050 mm³ was detected. The nodule was classified as a squamous cell carcinoma. F indicates feet; H, head; L, left; R, right.

This review provides an overview of current evidence and technical considerations of (combined) CT protocols for early detection of the Big-3 diseases with low-dose chest CT.

LUNG NODULE GROWTH RATE AS CT IMAGING BIOMARKER FOR LUNG CANCER

Current Evidence of CT Lung Cancer Screening

Both the Early Lung Cancer Action Program (ELCAP) and NLST, as well as the European lung cancer screening studies, showed that most lung cancers detected in CT lung cancer screening participants are stage I cancers.^{1,7–15} This indicates that screening by low-dose chest CT can detect lung cancer at an early stage, and thus potentially improve survival. Up until now, none of the European randomized-controlled lung cancer screening trials could reproduce the mortality benefit for the CT screen group, as found in the NLST.^{12–15} However, the European studies that published their final results so far were not powered to show a mortality difference between the study arms. The results on mortality outcome of the largest European lung cancer screening study, the NELSON study, are eagerly awaited.¹⁶

Following the screening studies, pooling of the European studies may be valuable to answer some important subquestions with regard to implementation of CT lung cancer screening, for instance determination of the optimal screen population, and determination of optimal screen intervals.¹⁷

Nodule Measurement Techniques

Early-stage lung cancer presents as a small, sub-centimeter, lung nodule. In about 50% of screenees, at least one pulmonary nodule is found.^{18,19} The vast majority of these nodules is benign. A nodule management protocol should be sensitive for lung cancer detection, with a false-positive rate as low as reasonably achievable. In the American lung cancer screening trials, as well as in the Lung CT Screening Reporting and Data System (LungRADS), used in routine lung cancer screening, nodule management is based on manually measured nodule diameters.^{1,20} In LungRADS, diameters are determined using electronic calipers, measuring average diameter rounded to the nearest whole number for nonround nodules and a single diameter for round nodules. Nodule growth is defined as an increase

in mean diameter of > 1.5 mm.²⁰ This assumes equal growth in all directions, similar to an expanding sphere. As pulmonary nodules are usually not perfectly geometrically shaped, errors in the estimation of nodule size may result.^{21,22}

The alternative method is to measure nodule volume using software for semiautomated measurements (Fig. 1). This software enables accurate estimation of nodule size after 3-dimensional reconstruction of thin slices (maximum 1 mm to create isometric voxels). The latter was applied in most European lung cancer screening trials and in recent guidelines from the British Thoracic Society and Fleischner society.^{23,24} They have chosen to adopt the volumetric measurement technique for its higher precision and smaller measurement bias, and higher reproducibility compared with manual diameter nodule measurements.^{25,26} This is especially relevant in nodule growth assessment.²⁷ Volume-based nodule management leads to up to 10 times less false-positive screen results compared with diameter-based nodule management.²⁸

Lung Cancer Probability in Solid Nodules Detected at Baseline

The most important predictor for lung cancer probability in baseline nodules is nodule size. In the NELSON study,¹⁸ it was shown that 2-year lung cancer probability for screenees without baseline nodules did not differ significantly from screenees with a baseline nodule <100 mm³ (or <5 mm, lung cancer probability 0.6%). Lung cancer probability rose with increasing nodule size, leading to the recommendation to directly refer screenees with a nodule > 300 mm³ (or > 10 mm, lung cancer probability > 16.9%) for further (invasive) workup. A comparable correlation between baseline nodule size and lung cancer probability is found in diameter-based lung cancer screening studies.²⁹

Lung Cancer Probability in Solid New Nodules at Incident Rounds

Lung nodules present at the baseline screening CT may have developed recently or might have been present for years. In contrast, nodules newly developed during screening represent a group of faster growing abnormalities. In a long-term screening program, new nodules are of special interest, as the incident screens will mainly determine the effectiveness of the

program in terms of early-lung cancer detection and thereby reduction in lung cancer mortality, as only one baseline screening is performed against up to 25 incident screens in individuals who start lung cancer screening at the age of 55 and continue to do so until the age of 80.

Annually, around 3% to 10% of screening participants develop a new noncalcified pulmonary nodule.^{30–32} Compared with baseline nodules, new nodules have a higher lung cancer probability already at a smaller volume.^{30–32} Therefore, newly CT-detected solid lung nodules should be followed-up more aggressively than nodules detected at baseline screening, for example, by using a lower size cut-off for a positive screen result and a shorter follow-up interval.³³

Lung Cancer Probability in Subsolid Nodules (SNN)

A nodule type known for its high lung cancer probability and nonaggressive behavior is the SSN. One of the concerns in lung cancer screening is overdiagnosis: some of the early-staged lung cancers may never become lethal. It was found that, although SSNs have a higher lung cancer probability than solid lung nodules, they rarely lead to lung cancer-related death.^{34–36} Therefore, 2 independent studies concluded that immediate resection of SSNs should be discouraged even in case of large SSNs; close follow-up of SSNs to identify possible growth or increase in attenuation by annual low-dose CT is sufficient because of the nonaggressiveness of subsolid lung cancers.^{34–36} Resection is advised only in case of evident growth or increase in density of the SSN.

EMPHYSEMA SCORE AS CT IMAGING BIOMARKER FOR COPD

Current Evidence of COPD Screening by Questionnaires or Spirometry

COPD is defined as a not-fully reversible airflow limitation. It can typically be diagnosed by detection of airflow limitation using spirometry and a decreased diffusion capacity. The disease severity can be determined by symptoms and the number of yearly exacerbations. Similar to lung cancer, patients with COPD usually have a history of smoking. Early stages of COPD might remain asymptomatic, and therefore underdiagnosed. Recently, the US Preventive Services Task Force concluded that early detection and treatment of COPD in asymptomatic subjects using spirometry does not alter the course of the disease. Until now, no evidence exists on the benefit of screening for COPD in asymptomatic adults using questionnaires or

spirometry on health-related quality of life, morbidity, or mortality.³⁷

Comorbidity of COPD may affect overall morbidity and mortality in patients with other coexisting diseases. By making an (early) diagnosis of COPD, patients at increased risk for premature mortality could potentially be identified. For instance, in patients with Rheumatoid Arthritis, an increased mortality risk was found for those with known COPD, as compared with those without COPD.³⁸ Furthermore, a decreased FEV1/FVC ratio at spirometry was an independent predictor for lung cancer, even in the absence of a diagnosis of COPD in the Genetic Epidemiology of COPD (COPDGene) population.³⁹ However, these studies did not evaluate the effects of screening for COPD. Hence, even though the benefit of diagnosing COPD may be expected in several patient populations, current evidence is lacking.

Screening for Emphysema by Imaging

A method for early detection of COPD is by quantifying emphysema, airway wall thickness, and air trapping on chest images. From these 3 measures, most experience has been gained with emphysema quantification; therefore, we will focus on this technique. Automated quantification of emphysema in chest CTs is more accurate than visual quantification or quantification of emphysema in chest radiography.⁴⁰ The presence of emphysema at chest CT and lung cancer diagnosis are strongly correlated, independently of a clinical diagnosis of COPD expressed as airflow limitation measured by pulmonary function tests.^{41–44} Evidence of the benefit of screening for emphysema at thoracic CT examinations for early detection and treatment of COPD in terms of health-related quality of life, morbidity, or mortality is lacking and needs to be investigated.

Emphysema Scoring Techniques

Currently, no reference standard for the quantification of emphysema at CT images is available. Emphysema can be quantified using automated densitometry software. Using this software, the percentage of voxels in the lungs at or below a certain attenuation level, usually $-910/-950$ to -970 HU,⁴⁵ is calculated (Fig. 2). In addition, the Perc15 method can be used, which identifies the HU value at the 15th percentile of the attenuation histogram of the lung parenchyma.⁴⁶ A lower Perc15, that is, more close to -1000 HU, reflects more severe emphysema.

In case both inspiratory and expiratory CT scans are available, parametric response mapping can be used to detect changes in attenuation between individual voxels at both

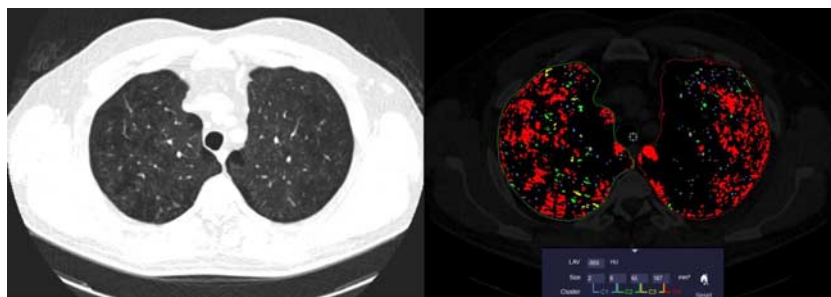


FIGURE 2. Screen capture of dedicated software to quantify emphysema automatically. The lung parenchyma with density below -950 HU is highlighted. Clusters of emphysema are color-coded according to volume. In this case, clusters sized 2 to 8 mm³ are blue, 8 to 65 mm³ green, 65 to 187 yellow, and > 187 mm³ red (volumes can be adjusted manually according to preferences). [full color online](#)

scans.⁴⁷ Using this method, the individual voxels are classified as normal lung, emphysema, or hyperinflation due to functional small airway disease. Thereby, a geographic map of the presence of COPD in the lungs can be created, and disease progression and response to bronchodilator therapy could be monitored at the level of the individual voxels.⁴⁸

Correlation of Emphysema Score With Lung Cancer Diagnosis and Mortality

As smoking is a risk factor for the development of both lung cancer and emphysema, the diseases are highly prevalent among heavy smokers. The question remains whether the presence of emphysema itself is a predictive factor for lung cancer development as well. There is indirect evidence to suggest this, as abnormal spirometry was an independent predictor of lung cancer in the COPD Gene population, as mentioned in the current evidence of COPD screening by questionnaires or spirometry section.³⁹ In a retrospective case-control study, COPD GOLD II or higher was more prevalent in patients with lung cancer (50%) compared with a randomly recruited community control group, matched for age, sex, and pack-years smoked but without lung cancer (8%).⁴⁹ In a subgroup of NLST participants, a strong linear relationship between increasing severity of airflow limitation and risk of lung cancer was shown. In both studies, diagnosis of COPD was based on spirometry. In the Danish Lung Cancer screening trial (DLCST), emphysema was both scored visually and quantified at the baseline screening CT. On the basis of the visual emphysema scoring, patients with baseline lung cancer had significantly more frequent and more extensive emphysema at baseline, compared with participants without baseline cancer. No difference was found using quantitative measurements.⁵⁰

The finding of emphysema on cardiac CT is related to both an increase in all-cause mortality and respiratory and lung cancer mortality in the general population, independent of age, sex, BMI, smoking status, and pack years.⁵¹ One study analyzed the correlation between CT-quantified emphysema and airway wall thickness and diagnosis of nonpulmonary cancer and lung cancer in 947 ever-smokers. In contrast to Wille and colleagues, they found that the baseline amount of quantitatively assessed emphysema was a significant predictor for both nonpulmonary cancer and lung cancer. Airway wall thickness did not predict cancer independently.⁵² Future (lung cancer screening) studies should confirm these findings and evaluate the value of using the presence of emphysema at the baseline CT quantified by software as an independent predictor of lung cancer in prediction models.

CAC SCORE AS CT IMAGING BIOMARKER FOR CVD

Current Evidence of CVD Screening by CAC Scan

CAC quantification by low-dose noncontrast cardiac CT has been used as a risk stratification tool for CVD over decades, with higher amounts of CAC associated with higher odds ratios for developing CVD.⁵³ While CAC indicates late to end-stage subclinical atherosclerosis, it correlates to the total coronary plaque burden, including vulnerable plaques that show a high risk for rupture or stenosis, leading to coronary heart disease.⁵⁴ Although various studies have shown the added value of CAC to classic CVD risk factors,^{53,55,56} the current level of evidence of CAC quantification is set at IIb (may be considered) by the American Heart Association and American College of Cardiology (AHA/ACC) and European

Society of Cardiology (ESC).^{54,57} In the Multi-Ethnic Study of Atherosclerosis (MESA), an algorithm was developed and validated that includes both traditional risk factors and CAC, to estimate 10-year coronary heart disease risk.⁵⁸ However, there is no evidence that treatment following CAC screening results in decreased CVD morbidity and mortality. In the upcoming 5 to 10 years, results from the population-based randomized controlled trial Risk Or Benefit in Screening for Cardiovascular disease (ROBINSICA) should provide evidence supporting or opposing the benefit of CAC screening.⁵⁹

CAC Scoring Techniques

The Agatston score for quantification of CAC on electron-beam CT was developed in 1990.⁶⁰ The score includes a total of measures of coronary calcifications, with each calcification score determined by the area (mm²) times a weight factor based on the maximum density (1 = 130 to 199 HU, 2 = 200 to 299 HU, 3 = 300 to 399 HU, 4 = 400 HU and greater) in that particular axial slice of the calcification. Summation of all slices of a calcification and all calcifications results in the total Agatston score (Fig. 3). Contrary to the Agatston score, the physical scores of calcifications like mass and volume can be used for ground truth comparison and quality assurance among different CT systems. Moreover, the mass score has shown lower inter-scanner and interreader variability compared with the Agatston score.⁶¹⁻⁶³ Nevertheless, the Agatston score remains the most used score because of the widespread use in large trials confirming the strong predictive value of the score, whereas such evidence is lacking for mass and volume scores.^{64,65}

Semiautomatic measurements of CAC are widely available in software packages from all major CT vendors and imaging analysis companies. In general, the software registers per coronary artery the number of lesions, volume, mass, and Agatston score and provides percentile rankings. Fully automatic CAC measurement software is emerging, but not yet commercially available.^{66,67}

CAC Risk Stratification

Many observational studies have been performed, which led to the following CVD risk stratification based on the Agatston score: very low: 0, mild: 1 to 99, moderate/high: 100 to 399, and very high: ≥ 400 .^{56,59} Some studies used slightly different cut-offs per category, that is, some differentiate also 1 to 10 as a separate risk category and highest risk category can start as low as ≥ 300 . The soon to be published CAC-RADS system (CAC equivalent to Lung-RADS) should give more uniformity and clarity about the risk categories to be used and corresponding potential treatment recommendations.⁶⁸ Nevertheless, future results of currently ongoing trials should provide the first evidence for such recommendations.

Besides risk stratification based on absolute Agatston values, percentile rankings are commonly used to describe the relative risk of an individual for his/her age, sex, and ethnicity, with a CAC score above the 75th percentile associated with increased CVD risk.⁵⁴ In most CAC analysis software, various percentile rankings can be chosen on the basis of different population studies. Percentile rankings should only be used to determine relative risk in individuals drawn from a comparable population as that of the study on which the specific ranking was based. Although the 2016 European Guidelines on CVD prevention reported "The value of the score can be further increased if the age and sex distribution within percentiles are taken into account," studies published in 2008-2009 showed that absolute

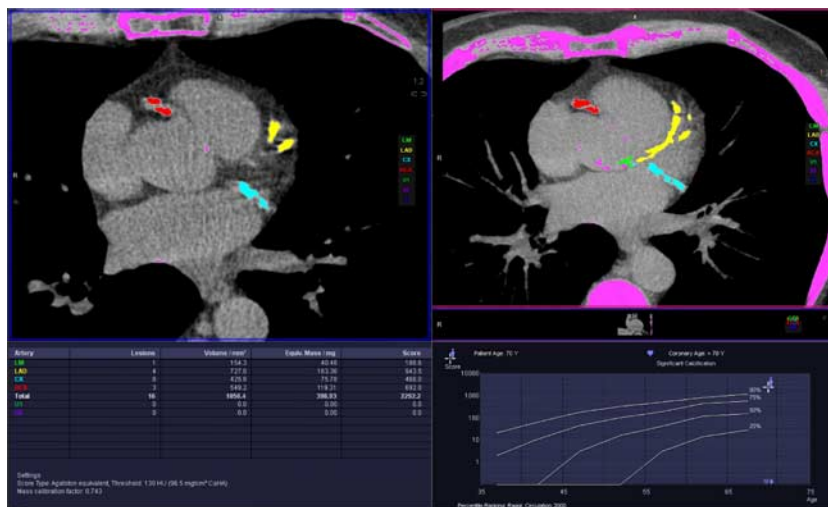


FIGURE 3. Coronary calcification scoring techniques: screen capture of semiautomatic coronary calcium scoring software. All voxels above the threshold of 130 HU are shown in pink. The coronary calcifications above the threshold can be assigned manually to a particular coronary artery, shown in red = RCA, green = LM, yellow = LAD, and in blue = LCx. As a result, a scoring table and percentile ranking graph and coronary age are calculated and depicted. LAD indicates left anterior descending; LCx, left circumflex artery; LM, left main coronary artery; RCA, right coronary artery.

Agatston values predict CHD events better than percentile ranking.^{69,70} These results are taken into account in the 2016 SCCT/STR guidelines for CVD risk assessment.⁶⁸

Instead of quantitative assessment like the Agatston score, qualitative assessment by visual estimation of the amount of CAC has been used to determine CVD risk determination in noncardiac scans. Such studies have shown that risk categorization, based on the visual assessment on chest CT, shows a high agreement with Agatston score-based categorization on dedicated cardiac CT.^{71,72} A disadvantage of qualitative assessment is the variation in interpretations of visual categories between radiologists, limiting uniform treatment management and CAC progression determination.

CAC Warranty Period and Progression

Studies have shown that the progression of CAC provides incremental value over baseline CAC scores and other CVD risk factors.⁷³ Follow-up CAC scanning to determine CAC progression may be considered in asymptomatic individuals at intermediate risk on the basis of CVD risk factors with a baseline CAC score of 0. The warranty period, defined as the duration in years in which cumulative CVD events rate remain within <1%, of individuals with a 0 score varies from ≥ 5 up to ≥ 15 years, depending on the study endpoints that were used (eg, nonfatal CVD events versus CVD mortality).^{74,75} As a fast increase of CAC (>100 Agatston points or >15% increase within 1 y) is predictive of CVD events, follow-up in individuals with a positive CAC score can be regarded as warranted after ≥ 1 year. However, follow-up is not recommended in the current guidelines.⁷⁶ In patients who are on statin therapy, increase of CAC score can represent plaque repair rather than continuing plaque expansion, as CVD events do not increase in these individuals.^{77,78}

COMBINATION OF THE CT IMAGING BIOMARKERS FOR SCREENING FOR THE BIG-3

Early detection and quantification of the Big-3 is possible with low-dose CT. On the basis of these low-dose CT

scans, lung nodule management based on nodule volume measurements can be performed, CVD risk stratification based on CAC score is feasible, and quantification of emphysema shows potential for early diagnosis of COPD. The next paragraphs give an overview of the 3 CT protocols with their current CT parameter settings, describe the technical considerations when combining the CT protocols, and highlight cost-effectiveness of such a screening method.

Technical Considerations

Currently, quantification of the different biomarkers is based on different scans optimized for that specific biomarker.^{59,79–83} Table 1 shows an overview of commonly used CT acquisition and reconstruction settings for the different biomarkers. The protocols used to acquire those scans could be combined in series by applying all of the protocols consecutively within one visit (Fig. 4, option 1). Although using validated conventional CT protocols for the 3 biomarkers is most convenient, the radiation dose may exceed the maximum allowed radiation dose of a screening examination (2.3 mSv, with a maximum dose of 5 mSv).⁸⁴ Nonetheless, combining all 3 dedicated protocols into a combined scan will be difficult without compromising on quality, reproducibility and robustness of the scans, and the accuracy and precision of biomarker quantification. Figure 4 shows different CT acquisition protocol options that might be feasible in screening the Big-3.

Combining CAC and Lung Nodule Scan Acquisition

Lung nodule quantification is based on chest CT acquisitions performed at variable tube voltages (eg, 70 to 140 kVp) depending on patient size, at a low tube current (eg, 20 mAs), and at a low pitch and no ECG gating.^{79,80} Prerequisites for adequate CAC quantification are CT scan acquisitions at a fixed tube voltage of 120 kVp with ECG gating and a high enough tube current to keep noise levels at an appropriate level (noise <23 HU for large patient size, measured in terms of SD).⁶⁴ Besides, preferably the entire heart is covered in one sequential acquisition or at a high

TABLE 1. Commonly Used CT Scan Parameter Settings Per Biomarker

	Lung Nodules	Emphysema Air Trapping	Coronary Artery Calcium
Acquisition parameter			
Patient instruction	Inspiration breath hold	Inspiration AND expiration breath hold scan	Inspiration breath hold
ECG gating	None	None	Prospective
Tube voltage	Variable (80-140 kVp) based on patient size	Fixed: 120 kVp 90-140 kVp	Fixed: 120 kVp
Tube current	Low tube current Fixed, or modulated based on patient size (20 mAs)	Low-medium tube current, fixed/modulated based on patient size (inspiratory: 80-150 mAs, expiratory: 50-90 mAs)	Low-medium tube current, modulated based on patient size (60-80 mAs)
Dose modulation	Tube voltage and tube current modulation	Tube current modulation to be determined	Tube current modulation
Scan mode	Low-pitch spiral	Low-pitch spiral	Sequential or high-pitch spiral
Reconstruction parameter			
Reconstruction algorithm	Filtered-back projection Iterative reconstruction	Filtered-back projection, use of iterative reconstruction has to be determined	Filtered-back projection, use of iterative reconstruction is discouraged
Kernel	Sharp lung kernels for detection of nodules Medium-smooth lung kernels for volume measurements	Medium/sharp lung kernels for emphysema measurement	Sharp cardiac/mediastinal kernel
Field-of-view	Variable, as long as the full chest is covered	To be determined whether fixed FOV is required, as long as the full chest is covered	Fixed, centered around the heart
Slice thickness/increment	Thin slices and increment, isotropic voxels ($\leq 1.0/0.7$ mm)	Very thin slices and increment, isotropic voxels (0.75-1/0.5-0.7 mm)	Thick slices and increment (3.0/3.0 or 3.0/1.5)
Estimated dose	< 4 mGy (0.9-1.6 mSv)	4.0-7.6 mGy	1.7-3.3 mGy (0.57-1.09 mSv)
Study examples	NLST ⁷⁹ /NELSON ⁸⁰ /UKLS ⁹	SPIROMICS ⁸¹ /MESA Lung study/SARP/ATLANTIS ⁸² /COPDGene	MESA ⁸³ /ROBINSCA ⁵⁹

pitch spiral acquisition within one heartbeat (Fig. 4, options 3 to 4).

CAC quantification has been performed on chest CT scans, on the basis of non-ECG-gated, variable tube voltages and low tube current acquisitions at a low scan pitch.^{72,85-87} Although CAC quantification based on chest CT shows a high agreement with dedicated CAC scans, CVD risk stratification on chest CT has not been validated, and reproducibility is low. Even if there is a high agreement ($k > 0.8$) present for a total population, a considerable number of individuals might have been reclassified to a higher or lower risk category. The clinical impact of reclassification should be determined before non-ECG-gated chest CT can be used for screening of CAC. Combining CAC and lung nodule scans would require a fixed tube voltage of 120 kVp, ECG gating, high pitch, and a medium tube current instead of a low tube current like that used in chest CT. However, scanning the entire lungs with a higher tube current will result in higher radiation. Instead, lower tube currents can be considered, but the impact on CAC score accurateness and reproducibility should be evaluated first.

Combining Lung Nodule and Emphysema Acquisition

For a more extensive evaluation of COPD, an additional expiratory scan could be acquired to determine air trapping, besides the inspiratory scan already acquired for emphysema and nodule quantification.^{81,82} Furthermore, the impact of tube voltage and tube current, iterative reconstruction, and/or spectral shaping on emphysema quantification should carefully be evaluated, and international consensus is still required to standardize CT for COPD quantification (Fig. 4, options 2, 4 to 6). For high reproducibility of mean lung density (HU) as a biomarker for emphysema, a fixed tube voltage and inspiration level may be necessary, but this remains to be proven. Patient

size-dependent dose modulation for tube current can be considered, but the optimal reference tube current setting has yet to be determined. A low tube current used in lung nodule quantification CTs might result in a low reproducibility and a noise level that is too high for proper segment-based or voxel-based parametric response mapping of emphysema. To overcome increased noise in low-dose CT, the common practice is to apply an iterative reconstruction algorithm to enhance image quality. One should be aware that iterative reconstruction on low-dose lung cancer screening CT can alter quantitative assessment of emphysema, as compared with filtered back projection.^{88,89} The same holds true for spectral shaping by use of a tin filter.⁹⁰

Combining Lung Nodule, Emphysema, and CAC Acquisition

Integrating all 3 acquisition protocols into one scan could be feasible. On the basis of preferences, either the CAC scan or the lung nodule scan can be used as a starting point in building the 3-in-1 protocol. However, the impact of using a low tube current and pitch on emphysema and CAC quantification should be determined first, before a 3-in-1 protocol can be implemented (Fig. 4, options 3,4).

Health Economic Consequences of Big-3 Screening

In the NLST, lung cancer screening was cost-effective, although it was noted that their figures could change merely by modest alterations in assumptions for the calculation.⁹¹ By identifying the most optimal population eligible for screening, for example, by limiting screening to those with substantially increased lung cancer risk (eg, stringent smoking eligibility criteria) and physically fit enough to undergo treatment for early-stage lung cancer, cost-effectiveness can be increased.⁹²

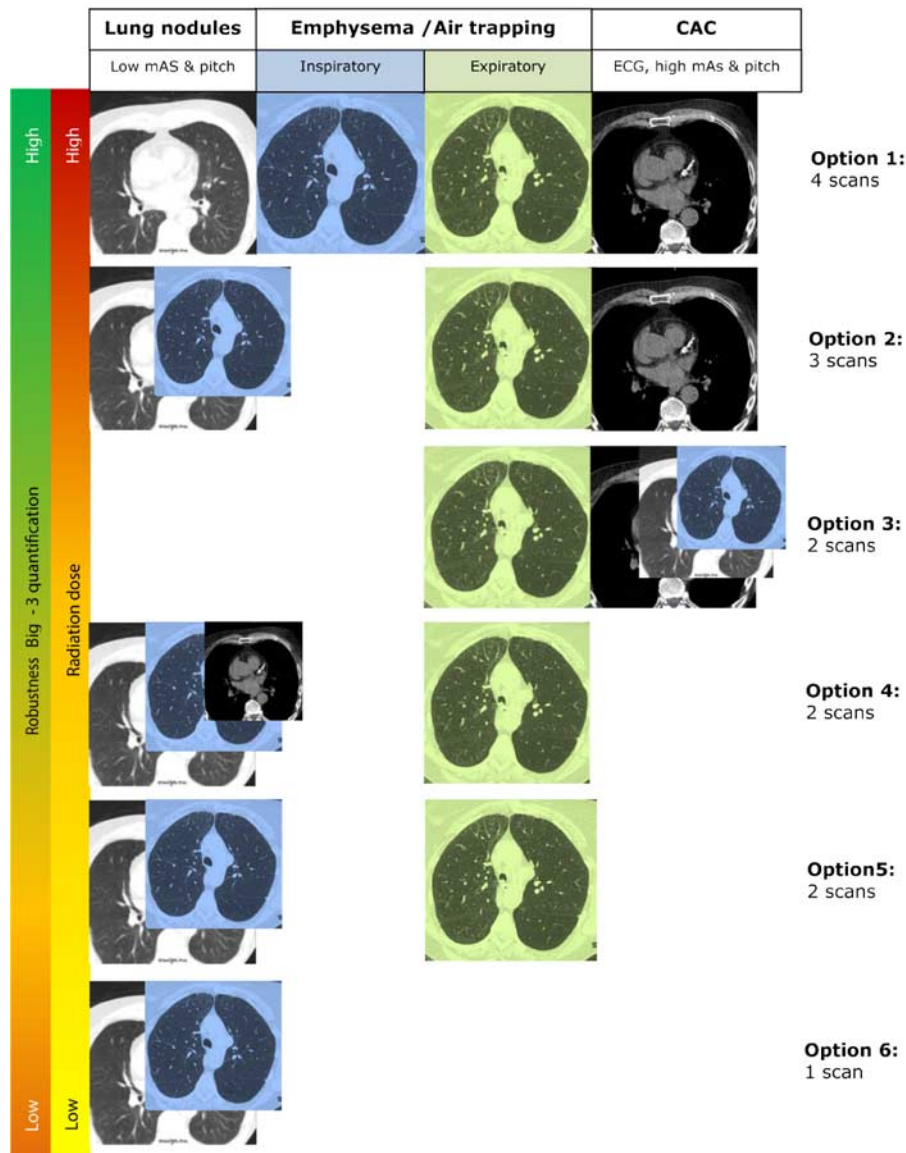


FIGURE 4. Overview of options (not extensive) for building an acquisition protocol for quantification of the Big-3: lung nodules, emphysema and air trapping, and coronary artery calcium. Option 1 includes separate acquisition for each biomarker. In option 2 the acquisition settings of the nodule scan and emphysema-inspiratory scan are combined into one new scan, with a separate air trapping-expiratory scan and CAC scan. Option 3 includes one combined acquisition of nodule, emphysema-inspiratory and CAC scan, and a separate air trapping-expiratory scan. The combined scan is optimized for CAC quantification: high pitch, high mAs, ECG gated. Option 4 is similar to option 3, but the combined scan is optimized for nodule/emphysema detection: low pitch, low mAs, and with ECG gating. Option 5 is optimized for nodule and emphysema quantification, CAC can be estimated based on the nodule/emphysema scan (without ECG gating, but with dedicated cardiac reconstruction). Option 6 is dedicated for nodules and partially for COPD (only emphysema quantification) (expiratory scan for air trapping evaluation not available); CAC quantification is similar to option 5. CAC indicates coronary artery calcium; COPD, chronic obstructive pulmonary disease. full color online

Trial-based cost-effectiveness models are required to inform health policy decisions on the implementation of screening.^{93,94} Typically, as the health effects of screening are only available at a sufficiently long follow-up period, decision analytic modeling techniques are used to extrapolate the long-term health and economic consequences. Potentially, Big-3 screening may offer health economic advantages, as the screened population is largely the same, and the costs of screening are comparable. However, additional costs due to prolonged survival in terms of additional diagnostic procedures, treatments, and other (indirect

medical costs) may diminish the potential beneficial economic effect of screening.

Early-stage health economic modeling is a known approach to analyze whether further technological development and implementation of new Big-3 screening would be useful.⁹⁵ A frequently applied method in early stages is the cost-effectiveness gap analysis or headroom.⁹⁶⁻⁹⁸ A cost-effectiveness gap analysis is performed to identify the maximum reimbursable price of a screening program by comparing the expectations about the cost-effectiveness against the prevailing willingness-to-pay threshold for one

unit of additional effectiveness (in this study QALYs). The population distribution over different disease stages and assumptions about the stage shifts that can be realized from screening have to be configured.

Lung cancer, COPD, and CVD are highly prevalent in the Netherlands (annual absolute incidences: lung cancer = 11,287, COPD = 53,300, and CVD = 82,100).^{99,100} Currently, a relatively large amount of patients present with stage IV disease at diagnosis in lung cancer (49.9% for non-small cell lung cancer and 69.0% for small cell lung cancer). In COPD and CVD also, many patients present with severe disease at diagnosis (24.2% and 65.5%, respectively). Survival in these advanced stages is worse than in earlier stages. If we assume that screening results in a stage shift, so that we anticipate less people presenting with stage IV disease, we can extrapolate survival and quality of life gains as if patients were detected in stage I or II disease. The resulting survival gain can then be aggregated on a population level. Initial analysis using the cost-effectiveness gap shows that screening for CVD potentially leads to considerable health gains followed by screening for lung cancer.

The cost-effectiveness of population screening depends on a number of factors, including the false-positive and false-negative findings, the health consequences of early detection, and the prevalence of the disease in the screened population. For this reason, implementation of population screening is usually limited to a high-risk population, as this implies a higher prevalence of disease and thus an increased predictive value of screening. Age and smoking are the most used risk factors for the identification of the high-risk screened population for lung cancer, and these risk factors also apply to emphysema and CVD. However, using solely these risk factors, some of the eligible screenees may have a too low lung cancer risk to benefit from screening; potential harms from exposure to CT might be higher. Instead, a high-risk population can be identified using risk prediction models that not only incorporate age and smoking status but other risk factors, that is, history of cancer and asbestos exposure, as well.^{101,102} In CT lung cancer screening programs, cost-effectiveness was driven primarily on the basis of non-lung cancer outcomes,¹⁰³ such as improvement in the quality of life. Smoking cessation is still regarded as the most effective measure for improvement of cost-effectiveness.

CONCLUSIONS

Imaging biomarkers for early stages of lung cancer, COPD, and CVD, gathered from combined screening with a (combined) low-dose CT might be used for early detection of all 3 diseases. Screening for COPD and CVD, in addition to lung cancer, may significantly improve the cost-effectiveness of low-dose lung cancer screening in the future. Studies are needed to confirm this hypothesis. Eventually, smoking cessation remains the most effective measure for decreasing disease burden from the Big-3 diseases.

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