Lung Cancer Screening by Low-Dose Computed Tomography: Part 2 – Key Elements for Programmatic Implementation of Lung Cancer Screening

Lungenkrebs-Screening mittels Niedrigdosis-Computertomografie Teil 2 – Essenzielle Elemente für eine Implementierung eines Lungenkrebs-Screening-Programms

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ZUSAMMENFASSUNG

Ziel In einem erfolgreichen Lungenkrebs-Screening mit Niedrigdosis-CT (Low-Dose-CT, LDCT) müssen die Vorteile für die Teilnehmer die möglichen Risiken überwiegen. Die Senkung der Lungenkrebsmortalität in großen Screening-Studien betrug ca. 20 %. Um dies zu erzielen, müssen bei der Umsetzung eine Vielzahl organisatorischer Voraussetzungen erfüllt werden.

Material und Methoden Wichtigste Elemente sind ein effektives Einladungsverfahren, einheitliche und qualitätsgesicherte Kriterien und computergestützte Auswertungsverfahren zur Etablierung eines algorithmischen Verfahrens, das jedem Herdbefund die angemessene Intensität des Abklärungsverfahrens zuweist. Für Patienten mit nachgewiesenem Lungenkrebs ist die Verfügbarkeit unmittelbarer Beratung und leitliniengerechter Therapie in eng eingebunden Referenzzentren unabdingbar. Pneumologische Einrichtungen für Erstkontakt und klinische Betreuung der Teilnehmer sowie CT-Einrichtungen müssen wohnortnah verfügbar sein. Weitere Anforderungen sind IT-Infrastruktur, Anbindung an klinische Krebsregister, Qualitätsmanagement und epidemiologische Überwachung.

Ergebnisse Eine effektive Organisation des Screenings gewährleistet eine verzahnte Struktur aus wohnortnahen pneumologischen Einrichtungen als primäre Kontakte für die Teilnehmer und Referenzzentren, denen neben der Supervision der Screening-Aktivitäten die individuelle Abklärungsdiagnostik suspekter Befunde und die Behandlung nachgewiesener Bronchialkarzinome obliegt.

Schlussfolgerungen Um zu gewährleisten, dass der Nutzen des Screenings dessen möglichen ungünstigen Auswirkungen überwiegt, und damit es akzeptiert wird, ist eine dicht organisierte Struktur erforderlich, die zugleich eine breite Verfügbarkeit von pneumologischen Kontakten und CT-Einrichtungen und in Zentren integrierte Expertise und moderne Medizintechnik gewährleistet.

Kernaussagen:

- Lungenkrebs-Screening erfordert optimal funktionierende und eng abgestimmte Abläufe.
- Lungenkrebs-Screening erfordert eine Netzwerkstruktur aus Expertenzentren und kooperierenden Einrichtungen.
- IT-Infrastruktur, QM, epidemiologische Überwachung und Anbindung an Krebsregister sind essenziell.

ABSTRACT

Purpose For screening with low-dose CT (LDCT) to be effective, the benefits must outweigh the potential risks. In large lung cancer screening studies, a mortality reduction of approx. 20 % has been reported, which requires several organizational elements to be achieved in practice.

Materials and Methods The elements to be set up are an effective invitation strategy, uniform and quality-assured assessment criteria, and computer-assisted evaluation tools resulting in a nodule management algorithm to assign each nodule the needed workup intensity. For patients with confirmed lung cancer, immediate counseling and guideline-compliant treatment in tightly integrated regional expert centers with expert skills are required. First, pulmonology contacts as well as CT facilities should be available in the participant's neighborhood. IT infrastructure, linkage to clinical cancer registries, quality management as well as epidemiologic surveillance are also required.

Results An effective organization of screening will result in an articulated structure of both widely distributed pulmonology offices as the participants' primary contacts and CT facilities as well as central expert facilities for supervision of screening activities, individual clarification of suspicious findings, and treatment of proven cancer.

Conclusion In order to ensure that the benefits of screening more than outweigh the potential harms and that it will be accepted by the public, a tightly organized structure is needed to ensure wide availability of pulmonologists as first contacts and CT facilities with expert skills and high-level equipment concentrated in central facilities.

Key Points:

- For lung cancer screening, elements must function optimally and be tightly organized.
- Lung cancer screening requires a network of expert centers and collaborating facilities.
- IT infrastructure, QM, epidemiological surveillance, and linkage to cancer registries are essential.

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Background

The US National Lung Cancer Screening Trial (NLST [1, 2]), the Dutch-Belgian NELSON Study [3], and a number of smaller European trials [4–9] have provided conclusive evidence that low-dose CT screening can significantly reduce lung cancer mortality among heavy smokers. In Germany, recent years have witnessed screening occurring in a grey zone, usually for worried individuals with a long history of smoking, often motivated by nonspecific or even pretended symptoms. Such practice is not only illegal, but can actually be harmful in the absence of proper ascertainment of an individual's actual lung cancer risk, appropriate standardized workup for unclear findings, and backup by an interdisciplinary team to ensure appropriate treatment in case of true-positive findings. Apart from risks related to radiation exposure, major potential harms include invasive investigations triggered by false-positive screening tests and overdiagnosis. For screening to be successful, its benefits – a gain in high-quality life years by reducing lung cancer mortality – must outweigh the risks of these potential harms.

The mortality reduction reported so far has been hard to achieve: A screening program constitutes a chain of components, each of which has to function optimally and in a well-integrated fashion to ensure that a maximal net benefit for the population is achieved. The target group needs to be informed and motivated to participate, should have easy access close to where they live, and be properly selected according to their personal risk for lung cancer and the potential to gain a meaningful number of life years through early cancer detection. They must also be informed about the possible advantages and risks of screening as well as the benefits of smoking cessation, even after long exposure. A logistic infrastructure is needed to ensure that participants are included according to uniform criteria, with systematic (re)invitation of screening participants at regular and optimized intervals. The acquisition, reading, and interpretation of CT images must follow well-defined and standardized protocols, also when using machines from different vendors. Image archives should be set up to allow an evaluation of changes over time in an individual's CT images as an essential component of early tumor detection, while allowing screening participants to switch screening provider. High technical and medical standards must also be maintained for confirmatory diagnostic workup beyond CT screening and for optimal treatment of confirmed malignancy. Finally, screening should be supported by streamlined structures for systematic data collection – e. g. in the form of regional screening registries and image archives, with linkage to epidemiologic and clinical cancer registries – to allow rigorous radiologic, clinical, and epidemiologic quality control and surveillance, and to generate a "learning" system open to modifications to benefit from future gains in knowledge.

Part 1 of this review [10] reports on the epidemiologic backgrounds of lung cancer screening, the effects on lung cancer mortality in recent screening trials, the potential harms of screening, and how to identify persons who may benefit from taking part. In this second part, based on experiences and lessons learned from the German Lung Cancer Screening Intervention trial (LUSI) [8, 11] as well as

other screening trials in Europe and North America, we outline a number of organizational requirements for the successful programmatic implementation of high-quality cancer screening on a local level, including organized invitations and eligibility checks, systematic and quality-controlled performance of screening tests, and optimized oncologic treatment and structures for quality monitoring.

Local organizational structures

Population-based screening requires an organizational framework with an articulated architecture, to reconcile two circumstances: On the one hand, screening for lung cancer has to be delivered on a broad basis to a large cohort, sufficiently close to where the participants live. On the other hand, it is crucial that screening centers offer multidisciplinary capabilities not only for the inclusion of screening participants and radiologic imaging, but also for the differentiated diagnostic workup of individuals with positive screening tests and treatment of lung cancer cases. On a local or regional level, lung cancer screening centers should thus be set up as a multi-disciplinary program, built around a recognized center for lung cancer treatment in cooperation with remote partners. This should involve the specialized expertise of pulmonologists, radiologists, thoracic surgeons, pathologists, and medical and radiation oncologists. Establishing a first personal contact, eligibility checks, and shared decision making for screening participation in view of possible risks and benefits are tasks that can also be performed peripherally by cooperating pulmonology practices. Likewise, the LDCT examinations can be technically standardized and be carried out in partnered radiological practices, provided a suitable scanner is available, and images can be digitally transferred for reading and analysis. In addition to regional coordination, typical tasks for interdisciplinary institutions (e. g. a hospital or a collaborative group of differently located parties, as was the case for LUSI [8, 11]) would be image reading, computer-based image analysis, and nodule management.

This overall, multidisciplinary structure is also characteristic for screening trials, especially those in Europe, which generally were performed either at, or in close cooperation with larger university hospitals, including one active lung cancer screening program with low-dose CT in Germany for asbestos-exposed workers who were also heavy smokers ("Erweitertes Vorsorgeangebot zur Früherkennung von Lungenkrebs", https://gvs.bgetem.de/redaktion/informationen-zum-ld-hrct-vorsorgeangebot-der-gvs). A future lung cancer screening program for "only smokers" might take into account experience gained from that ongoing program including workflow, technical standards, reporting algorithms, etc.

Those involved (e. g., pulmonologists, radiologists, multidisciplinary tumor boards) each had a clear definition of their roles, ranging from contacting and informing screening participants to assigning participants to required measures, with clear documentation of decisions, systematic feedback on histologic and surgical results, as well as continuous storage of imaging data for observation of findings over time. A major benefit of the trials was that not only could the effects of applied criteria (regarding, e. g., eligibility or indication for biopsy) be analyzed and assessed as beneficial or detrimental, but also that, once sufficient data were available, epidemiologic modeling was possible to estimate a possible impact of modifying them.

Recruitment process

Adequate targeting of those who may benefit from screening (eligibility criteria)

As discussed in the first part of our review [10], in view of the potential harms of overdiagnosis, screening should be offered only to individuals with sufficiently high residual life expectancy. At the same time, their risk of having lung cancer should be sufficiently high for the expected screening benefit (life years gained) to outweigh risks related to radiation exposure and invasive medical investigations triggered by false-positive screening tests. The eligibility criteria used in the NLST or European trials were variable. Besides sufficient lifetime duration of intense smoking, the participants in LUSI were required to be 50 to 69 years of age [11], whereas NELSON and NLST included participants up to the age 75. Current evidence suggests that, on average, screening up to the age of 75 may be more appropriate than up to the age 80 in view of the expected balance between potential gain in life years vs. risk of overdiagnosis [12–14]. With the maximum age of screening eligibility set at 74 years (i. e., stopping age of 75), the criteria such as those used in NLST (corresponding to about 3.0 million eligible ever-smokers in Germany, and covering about 38 % of all incident lung cancer cases) or NELSON (about 5.5 million eligible, covering about 46 % of incident cases) can be used, where the overall breadth of inclusion criteria may further depend on cost-efficiency and acceptance by health insurances [15]. Within broadly defined criteria, such as those of NELSON or NLST, the complementary use of more precise risk models based on age, sex, and lifetime smoking history [16–19] may further help ensure that each single screening participant will have a sufficiently elevated LC risk to anticipate positive net benefit from screening [10].

Effective invitation of those who may benefit from screening

There are several ways of motivating persons at risk to participate in screening, the weakest tool being an information campaign via media, leaflets provided via mail or in doctors' offices or pharmacies, the internet, and/or social media. Additional incentives may be given by health insurance companies. A possibly more effective way of contacting individuals for screening would be their systematic invitation through local population registries ("Einwohnermelderegister"), which would supply data on age, sex, and postal address. This is the strategy that has been chosen for the German mammography screening program and has yielded good results in terms of overall screening participation. Whether or not a person in question possibly fulfills the inclusion criteria in terms of lifetime smoking history, and possibly further risk factors, should be determined from short questionnaires to be mailed back or filled in online, although in a subsequent step screening eligibility should be checked further by a trained clinician (see below). Such an invitation process has proven to be logistically feasible in LUSI [11] and other European trials, although response rates to questionnaires were not always optimal and accompanying measures to increase screening participation rates may be required.

Adequate information to participants on benefits and risks; informed consent

Potential participants must be informed that screening comes with risks. While the radiation risks are well known to almost everyone, possible harms resulting from false-positive follow-up examinations or overdiagnosis are more difficult to understand. It is of utmost importance that possible participants be fully informed about both the risks and benefits via several channels, including flyers, an official website and informed consent materials, with additional explanation by physicians. If the program is to be publicly accepted, possible participants should understand why they are either accepted to participate or not, and the eligibility criteria should be clearly explained. While age and smoking history as criteria will be easy to understand, results obtained with more complex risk models may not be and will thus require good communication skills on the part of the physician in charge of the first interview.

Screening participation should be accompanied by well-documented and signed informed consent, acknowledging that such information has been provided. Screening participants should also provide their explicit consent for being actively re-invited by their screening center for LC screening at regular intervals and, in view of systematic quality control, be asked to provide consent for the use of their data for systematic quality control of the screening process, through systematic archiving of these (pseudonymized) data at regional screening registries. This should include the permission to conduct record linkage with clinical and epidemiological cancer registries, as well as with registries for vital status and causes of death, in view of post-hoc epidemiologic evaluations of the screening effectiveness in the population.

Smoking cessation counseling

For active smokers, screening participation is a suitable occasion to propose counseling for smoking cessation [20, 21], and offering such counseling should be a compulsory element of a screening program. Even in long-term heavy smokers, quitting is an effective measure to lower lung cancer risk [22, 23], and smokers should be informed that it is never too late to quit. In screening trials, taking part in screening generally seems to have promoted cessation [24], irrespective of being in the screening or the control arm, dissipating concerns that negative screening results might encourage smoking continuation [25].

Standards for acquisition and reading of CT images, follow-up diagnostics, and reporting of findings

Well-defined protocols and standards for the acquisition and reading of CT images

There is broad agreement that lung cancer screening will be carried out using low-dose computed tomography (LDCT), with at least one radiologist reading the images, accompanied by a dedicated nodule detection software as a “second reader” and as a tool for determining a nodule’s volume. Scan parameters need to be clearly defined that can be applied to the scanners being used in the respective region. Interpreting focal findings on LDCT scans is a delicate task, especially when it comes to judging borderline values for size or growth, or for unclear morphologic features. Therefore, the readers must be trained and also submit to regular monitoring of their results.

The use of standardized assessment criteria for nodule malignancy, applied identically in all involved radiology practices, and irrespective of the exact type of scanner used (vendor), is crucial for maintaining a similar level of sensitivity and specificity of the organized screening program. As volumetric measurements will play a pivotal role, particularly when determining VDT, nodule detection software must be uniformly calibrated to achieve reproducible results. If different software is used, measurements would need to be calibrated using test datasets. Executing quality control and software calibration should be the responsibility of the local coordinating cancer center with which radiology practices are associated.

Well-specified criteria for screening detection and further diagnostic workup

The high prevalence of indeterminate pulmonary nodules, the majority of which are usually benign, is a major challenge. To avoid performing invasive diagnostic investigations of benign nodules in large numbers of screening participants, while maintaining sensitivity for detecting lung cancer, criteria and decision algorithms have been developed to identify nodules more likely to be malignant and for which biopsy is indicated, based on nodule size, growth over time, and morphological features. The criteria according to which a nodule will fall into one or the other category need to be carefully determined, since they may heavily influence the sensitivity and specificity of a screening program. Recommendations have been made, e. g. by the Fleischner Society [26], originally dedicated to the management of incidental pulmonary nodules, or the American College of Radiology (ACR) in their Lung-RADS categories (https://www.acr.org/Clinical-Resources/Reporting-and-Data-Systems/Lung-Rads). The main criteria are

- Size: Without a lower limit, image analysis might be cluttered with innumerable findings. Therefore, according to current recommendations, nodules < 5 mm (I-ELCAP [27] or < 6 mm [28]) will be counted as negative. Recommended size limits for a positive screening test are in the range of 8 mm or above for solid, and 6 mm or above for part-solid nodules [28], or 300 mm^3 [27], triggering immediate workup. Nodules meeting neither criterion will, as indeterminate lesions, be followed up by interim follow-up LDCT, and so will be non-solid lesions. Minimal size limits for follow-up examinations diverge widely in the published recommendations (see also [29]).
- Growth rate: When two or more examinations over time are available for comparison, nodule growth rates or volume doubling times (VDT) can be calculated. There is consensus that a VDT of > 600 days strongly argues against, and a VDT < 400 days in favor of malignancy. Where exactly to draw the line is not yet clear, and possibly the likelihood of cancer may be addressed by scheduling short-term follow-up scans. Extremely short VDTs in turn indicate inflammation rather than cancer.

- Morphological features are unreliable as primary criteria but may, with sound criticism, modify the assessment of a nodule. A triangular shape may, e. g., indicate a perifissural lymph node, or low-density values may be typical of hamartoma. Conversely, a ground-glass halo or a cavitation are rather worrisome features.

The criteria should be chosen so that every true lung cancer surrounded by ventilated parenchyma will eventually be diagnosed either in the present or, for smaller nodules, in a subsequent screening round. Additionally, the screening intervals should be short enough that a lung carcinoma that is still too small to warrant further measures in one round will not have progressed to a stage with an unfavorable prognosis by the subsequent round.

Due to its rapid growth and early metastatic spread, small cell lung cancer is not a target of lung cancer screening. Two other types of lung cancer need to be specifically mentioned. Lepidic carcinoma typically presents as a ground-glass or semi-solid lesion and, although malignant, may grow more slowly than solid cancers [30]. Furthermore, they are often less aggressive, and the recommendations on how to handle them may be different, e. g., by active surveillance [31], but so far, the appropriate way of handling them is controversial. Furthermore, LDCT can only be expected to detect nodules that are surrounded by ventilated lung parenchyma and is therefore insensitive to carcinomas arising from the central bronchi. In fact, at present, there is no noninvasive method to detect them, and this factor is one possible explanation why, e. g., in all studies the histologic spectrum of screening-detected lung cancers differed from that of those that have become clinically symptomatic.

Whereas an "algorithmic" workup along the above criteria will be sufficient for first triage within the settings of routine screening, further diagnostic investigation of suspicious nodules warrants more individualized evaluations as indicated by an interdisciplinary board of radiologists, pulmonologists, and possibly thoracic surgeons, and may range from antibiotic treatment to resolve possible infectious lesions or diagnostic chest CT or PET/CT to immediate biopsy. This more differentiated diagnostic workup no longer falls in the domain of routine screening but takes place in the context of expert clinical care at the regional cancer center. It is crucial to have well-structured and rapid feedback communication and reporting of clinical findings between clinical cancer and cooperating radiology practices. In LUSI, as well as in other previous lung cancer screening studies, the process of differentiated diagnostic workup often extended over several months. While this prolonged and stepwise process may appear worrisome at first glance, it is currently the only reasonable approach to buffer the shortcomings of the screening algorithm due to the high prevalence of benign nodules, and to minimize the probability of biopsies for benign findings.

Availability of immediate advice and state-of-the-art treatment for participants with suspicious findings

An important lesson learned in LUSI is that a person should never be confronted with the possibility of having cancer through a standard letter, or even be left alone in this situation, even if the professionals feel that there is ample probability that malignancy will eventually be ruled out. The fact that something has been detected that could be serious must be explained personally, which is a genuine medical task. Appointments to explain things and recommend what to do next have to be offered as immediately as possible. If the screening program is to achieve its goal, i. e., to reduce mortality due to lung cancer, the entire diagnostic and therapeutic chain must fully comply with what is the current medical standard at its highest level.

Archiving of screening scans

Screening studies have shown that recall rates during the first round ("prevalence screening") will be in the 30 % range, as it cannot be determined whether a given lesion has newly arisen, grown, or been constant for a long time. In subsequent screening rounds ("incidence screening"), with previous scans available, recall rates will drop by additionally taking into account whether a pulmonary nodule is newly observed or has grown since the previous screening. Thus, it is vital that all of an individual's previous scans be systematically archived and available for future comparisons. Since participants may move or change radiological practices, central access to image repositories needs to be established for the region where screening is being organized with each patient's informed consent to have their images stored there. Besides the need for being able to evaluate an individual's CT images over time, images obtained during screening may also provide important indications of an individual's risk of developing detectable lung cancer in the next few years [32–34], and may become an important component of risk algorithms to determine individually optimized screening intervals, e. g. with one-year intervals only for those at highest risk and longer (e. g. two-year) intervals for others. Finally, in view of improving the specificity of nodule detection, the archiving of screening scans is also important for monitoring the quality of the radiologic screening process, and for further research into possible improvements of algorithms for the radiologic detection of pulmonary malignancies [35–37]. As the program starts, artificial intelligence (AI) will not play a role in nodule management, since high-quality annotated and/or segmented datasets are not widely enough available. However, the screening archive will be an excellent resource for obtaining them, in order to train machine learning algorithms that in future may assist in (1) identifying patients who have cancer in some location, (2) locating malignant tumors, and (3) differentiating given nodules as either benign or malignant.

Epidemiologic surveillance and quality assurance

As described above, lung cancer screening and follow-up care constitute a complex, multi-step, and inter-disciplinary process, including many steps and variables that may affect overall effectiveness. It is thus of utmost importance to set up a data registration system that allows monitoring of key steps in this overall process (▶ **Table 1**). Key aspects to be monitored include data on screening participation (response rates to invitations for initial and follow-up screenings, and reasons for stopping participation), basic information on demographics and lung cancer risk factors of

▶ **Table 1** Registration of key data for quality control.

▶ **Tab. 1** Registrierung von Schlüsseldaten für die Qualitätskontrolle.

- **Screening (re-)participation:** invitations/responses
- **Registration of informed consent**
  In view of data linkage to image archives and cancer registries
- **Risk factors:**
  Age, sex, smoking history, medical history
  To evaluate lung cancer risk distributions (model-based)
- **Image archive:**
  Documentation of suspicious/indeterminate nodules
  Nodule characteristics, numbers, location
  Evaluation and development of diagnostic/predictive algorithms for malignancy (imaging + risk factors)
- **Outcome of every screen & diagnostic decision:**
  Screening outcomes; no suspicious findings; 3- or 6-month re-examinations
  Performance and outcomes of invasive interventions (bronchoscopy, biopsy, surgery)
  Estimation of false-positive rates of screening tests and follow-up diagnoses, and identification of possible causes
- **Characteristics of screen-detected tumors**
  Stage, histology, anatomical location
- **Linkage to epidemiologic & clinical cancer registries**
  Identification of interval cases (linkage to cancer registries) to estimate screening sensitivity
  Estimation and comparison of lung cancer survival among screened and non-screened individuals
  Modeling of sojourn times/test sensitivity

screening participants (age, sex, lifetime smoking history recorded through a brief and standardized questionnaire, postal code), the eventual outcome of every screening (referral to follow-up screening after regular or modified intervals), noninvasive and/or invasive clinical follow-up examinations performed, and their diagnostic outcomes (true- vs. false-positive screening detections and follow-up diagnoses; information on tumor stage, histology and location). Provided informed consent has been given, the information from the screening registry can then be further linked to screening imaging archives, as well as to epidemiologic and clinical cancer registries for data on lung cancer incidence and their treatments, and to registries for vital status and causes of death. Just as in LUSI and other screening trials performed so far, the population of screening participants can thus be followed as a prospective cohort with accumulating data on screening interventions, diagnostic outcomes and overall and cancer-specific survival data, for detailed radiologic, clinical, and epidemiologic monitoring of the screening process as its overall effectiveness.

Outlook

Although the studies published so far indicate that low-dose CT screening is capable of reducing lung cancer mortality, the reduction in lung cancer mortality that can be achieved lies in the 15 % to20 % range, which is modest, and screening can also cause major harm. Clearly, numerous factors must be taken into account to ensure that the benefit of screening will outweigh the risks of potential harms. European [29, 38, 39] and German [40] medical societies and expert panels have recommended that screening should be performed exclusively in context of a systematically organized and quality-assured program, regionally organized around expert oncological centers, similar to the key elements outlined above. The German Federal Office for Radiation Protection (*Bundesamt für Strahlenschutz*, BfS) is currently performing a scientific evaluation of LDCT screening for the reduction of lung cancer mortality, including the systematic modalities required for it to be sufficiently safe and overall beneficial. Provided this overall evaluation will be positive, an ensuing ministerial decree (*Bundesministerium für Umwelt, Naturschutz und nukleare Sicherheit*) will stipulate whether, and under which conditions LDCT screening for early lung cancer detection may be permitted. How exactly a screening program will be set up remains open so far, and so is the issue of funding: For LUSI, a total of approx. 4 fulltime equivalents (FTE) (doctors, technicians, case managers, pulmonologists, psychologists, data administrator, epidemiologist) were involved in scanning 10 to 20 participants after the clinical routine on normal working days. Additional, but only occasionally needed resources included pulmonologists in their own practice seeing those needing individual workup, as well as hospital personnel in case of scheduled thoracoscopic biopsy during a 3–4-day stay at a hospital for chest diseases. When compared to standard clinical care, screening comes at considerable costs, even when balanced against possibly reduced expenses for, e. g., additional radiotherapy or expensive drug treatment [41–44]. Whether or not society is willing to bear these costs is a pending discussion. This, as is often the case for lifestyle-associated conditions, may be controversial, and the authors hope that related objections will not contaminate the decision process.

Conflict of Interest

The authors declare that they have no conflict of interest.

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