cancer screening committee

Recommendation on low-dose CT screening for lung cancer

Appraisal report

November 2022

cancer screening committee

Impressum

Geschäftsstelle Cancer Screening Committee

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Cancer Screening Committee

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Executive Summary - English

Lung cancer is the leading cause of cancer-related death in Switzerland and worldwide. Around 3,300 people die of lung cancer in Switzerland every year. Cigarette smoking is by far the leading risk factor for lung cancer. It is estimated that 80% to 90% of lung cancer diagnoses are attributable to tobacco smoking. In view of the high burden of disease, there is a national and international debate on whether low-dose CT (LDCT) screening for lung cancer screening should be offered to people at risk, defined as current and former smokers aged 55 and older.

The Swiss Cancer Screening Committee commissioned an HTA LDCT screening for lung cancer in Switzerland. Based on this, it appraised the evidence on ethical issues in lung cancer screening, the clinical effectiveness as well as the cost-effectiveness and the budget impact. The appraisal has been made following the Evidence to Decision (EtD) framework. Based on this appraisal, the Committee issued the following recommendations:

The Cancer Screening Committee suggests offering LDCT lung cancer screening to people at risk in Switzerland.
(GRADE conditional recommendation).

The committee issued a conditional recommendation in favour of screening because LDCT lung cancer screening probably results in a relative reduction of lung cancer deaths by 20%, translating in an absolute reduction of 43 lung cancer deaths per 10,000 persons over a 10-year screening period (moderate evidence). The number of deaths overall may be reduced by 4%, translating in an absolute reduction of 36 deaths per 10,000 persons (low evidence). In addition, LDCT lung cancer screening may result an increase in lung cancer stage I or II diagnoses (low evidence) and a small reduction in lung cancer stage III or IV diagnoses (low evidence).

The scope of this recommendation is centred on the individual perspective of people considering screening, based on the current body of evidence on the potential benefits, harms and practical issues regarding screening. The conditional recommendation means that the committee thinks a majority of informed high-risk people would consider or opt for screening in this context. Shared decision making is critical to ensure everyone has the opportunity to make a decision consistent with their values, preferences, and situation, at a given time.

In order to make screening available, the committee ties its recommendation to key considerations regarding the choice of optimal implementation strategies: The preferences of the individuals must be accepted. It is important that to participate in screening is a free choice and that non-participation does not have negative consequences. Smoking cessation support according to the latest state of knowledge should always be offered to persons at risk, regardless of their decision to undergo screening or not. Stigmatisation and any (mis-)attribution to smokers or previous smokers of moral responsibility for their disease should be avoided.

The committee strongly recommends offering LDCT lung cancer screening within organised programmes, rather than relying on individual practitioners and stakeholders to offer screening on their own. Only an organised programme can ensure a broad, accessible, and equitable offer of screening. It can also ensure the quality and reproducibility of any indicated follow-up testing after a suspicious screening result and a structured and target-group oriented invitation of the at-risk population. A program would also allow exemption from the deductible according to the standard rules of the statutory health insurance, another important prerequisite for equity of access.

Reaching the population at risk is a central concern and a major challenge for which special recruitment strategies and implementation approaches are required. To prevent economically driven disparities in access to care, financial barriers for persons participating in the screening such as deductibles, should be abolished.

Executive Summary – German

Lungenkrebs ist die häufigste krebsbedingte Todesursache in der Schweiz und weltweit. Jährlich sterben in der Schweiz rund 3'300 Menschen an Lungenkrebs. Der mit Abstand wichtigste Risikofaktor für Lungenkrebs ist Tabakrauchen. Schätzungsweise rund 80 bis 90% der Lungenkrebsdiagnosen sind darauf zurückzuführen. Angesichts der hohen Krankheitslast wird national und international diskutiert, ob ein Lungenkrebsscreening mittels niedrigdosierter Computertomographie (low dose CT, LDCT) für Risikopersonen angeboten werden sollte. Als Risikopersonen gelten aktuelle und ehemalige Raucher:innen ab einem Alter von etwa 55 Jahren.

Das nationale Expertengremium Krebsfrüherkennung hat ein Health Technology Assessment (HTA) zum LDCT-Lungenkrebsscreening in der Schweiz in Auftrag gegeben. Auf dieser Grundlage bewertete es die Evidenz zu ethischen Fragen des Lungenkrebsscreenings, zur klinischen Wirksamkeit sowie zur Kosteneffektivität und den Kostenfolgen. Die Bewertung erfolgte nach dem Evidence to Decision Framework (EtD). Gestützt auf diese Überlegungen gab das Gremium die folgende Empfehlung ab:

Das Expertengremium Krebsfrüherkennung schlägt vor, in der Schweiz für Risikopersonen Lungenkrebsscreening mittels niedrigdosierter Computertomographie anzubieten.
(GRADE bedingte Empfehlung)

Das Komitee spricht eine bedingte Empfehlung für das Screening aus, weil das LDCT-Lungenkrebsscreening wahrscheinlich zu einer relativen Reduktion der Lungenkrebstodesfälle um 20% führt, was einer absoluten Reduktion um 43 Lungenkrebstodesfälle pro 10’000 Personen über einen Zeitraum von 10 Jahren entspricht (moderate Evidenz). Die Zahl der Todesfälle insgesamt kann um 4% verringert werden, was einer absoluten Reduktion um 36 Todesfälle pro 10’000 Personen im Screening entspräche (schwache Evidenz). Darüber hinaus kann das LDCT-Lungenkrebsscreening zu einer Zunahme der Diagnosen von Lungenkrebs im Stadium I oder II (schwache Evidenz) und zu einer geringen Abnahme der Diagnosen von Lungenkrebs im Stadium III oder IV führen (schwache Evidenz).

Die Empfehlung orientiert sich an der individuellen Perspektive von Personen, die ein Screening in Erwägung ziehen und basiert auf der aktuellen Evidenzlage zu potenziellem Nutzen, Schaden und praktischen Fragen des Screenings. Die bedingte Empfehlung bedeutet, dass das

Expertengremium davon ausgeht, dass eine Mehrheit der informierten Risikopersonen ein Lungenkrebsscreening in Betracht ziehen oder sich dafür entscheiden würde. Die gemeinsame Entscheidungsfindung ist von zentraler Bedeutung, um sicherzustellen, dass jede:r die Möglichkeit hat, zu einem bestimmten Zeitpunkt eine Entscheidung zu treffen, die seinen/ihren Werten, Präferenzen und der individuellen Situation entspricht.

Das Gremium knüpft seine Empfehlung an wichtige Überlegungen zur Wahl der optimalen Implementierungsstrategien: Die Präferenzen des Einzelnen müssen respektiert werden. Es ist wichtig, dass die Teilnahme am Screening eine freie Entscheidung ist und dass die Nichtteilnahme keine negativen Folgen hat. Unterstützung bei der Raucherentwöhnung nach dem neuesten Stand des Wissens sollte Risikopersonen immer angeboten werden, unabhängig davon, ob sie sich für oder gegen das Screening entscheiden. Eine Stigmatisierung von aktuellen oder ehemaligen Raucher:innen und eine (falsche) Zuschreibung der moralischen Verantwortung für eine Erkrankung sollte vermieden werden.

Das Expertengremium empfiehlt ausdrücklich, das LDCT-Lungenkrebsscreening im Rahmen organisierter Programme anzubieten und zu vermeiden, dass einzelne Ärzt:innen und Interessengruppen ein Screening in eigener Regie organisieren. Nur ein organisiertes Programm kann ein umfassendes, zugängliches und gerechtes Angebot gewährleisten. In einem Programm kann auch die Qualität und die Reproduzierbarkeit der angezeigten Folgeuntersuchungen nach einem verdächtigen Screening-Ergebnis und eine strukturierte und zielgruppenorientierte Einladung der Risikopopulation gewährleistet werden. Zudem wäre – bei entsprechender Anpassung der Krankenpflege-Leistungsverordnung – die Befreiung des Screenings von der Franchise möglich, eine weitere wichtige Voraussetzung, um einen gerechten Zugang zu garantieren.

Das Erreichen der Risikopopulation ist ein zentrales Anliegen und eine grosse Herausforderung, für die spezielle Rekrutierungsstrategien und Implementierungsansätze erforderlich sind. Um ökonomisch bedingte Ungleichheiten beim Zugang zur Versorgung zu vermeiden, sollten finanzielle Barrieren für die Teilnahme am Screening, wie z. B. Franchisen, abgeschafft werden.

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Executive Summary – French

Le cancer du poumon est la première cause de mortalité par cancer en Suisse et dans le monde. Chaque année, il entraîne quelque 3300 décès dans notre pays. Le tabagisme est de loin le principal facteur de risque ; il est à l'origine de 80 à 90 % des diagnostics de carcinome pulmonaire. Compte tenu de la charge de morbidité élevée, l'opportunité de proposer un dépistage par scanner thoracique à faible dose (*low dose CT,* LDCT) à la population à risque est discutée sur le plan national et international. Font partie de cette catégorie les personnes de plus de 55 ans environ qui fument ou ont fumé dans le passé.

Le comité d'experts du dépistage du cancer a mandaté une évaluation des technologies de la santé (*Health Technology Assessment*, HTA) pour le dépistage du cancer du poumon par LDCT en Suisse. Il a analysé sur cette base les données disponibles sur les aspects éthiques du dépistage du cancer du poumon, l'efficacité clinique, ainsi que le rapport coût-efficacité et l'impact financier. Cette analyse a été réalisée selon le cadre décisionnel « *Evidence to Decision Framework, EtD* ». À la suite de cette évaluation, le comité d'experts a formulé la recommandation suivante :

Le comité d'experts du dépistage du cancer suggère de proposer un dépistage du cancer du poumon par scanner thoracique à faible dose aux personnes à risque.
(force de la recommandation : conditionnelle selon l'approche GRADE)

Le comité formule une recommandation conditionnelle, car le dépistage par LDCT mène probablement à une réduction relative de la mortalité par cancer du poumon de 20 %, ce qui correspond, en chiffres absolus, à 43 décès en moins par carcinome pulmonaire par 10 000 personnes sur une période de dix ans (niveau de preuve intermédiaire). La mortalité générale peut être réduite de 4 %, ce qui correspond, en termes absolus, à 36 décès en moins par 10 000 personnes (niveau de preuve faible). En outre, le dépistage du cancer du poumon par LDCT peut conduire à une augmentation des diagnostics posés au stade I ou II (niveau de preuve faible) et à une légère baisse des diagnostics au stade III ou IV (niveau de preuve faible).

La recommandation prend en compte le point de vue individuel des personnes qui envisagent un dépistage ; elle repose sur le niveau de preuve actuel concernant les bénéfices potentiels, les risques et les aspects pratiques du dépistage. Elle est conditionnelle, ce qui signifie que le comité

d’experts estime qu’après avoir été informées, une majorité de personnes qui présentent un risque accru de cancer du poumon envisageraient un dépistage ou opteraient pour cette solution. La prise de décision partagée revêt une importance capitale pour garantir que chaque individu ait la possibilité de faire, à un moment donné, un choix en accord avec ses valeurs, ses préférences et sa situation personnelle.

Pour que le dépistage puisse être réalisé, le comité assortit sa recommandation de considérations importantes sur le choix des meilleures stratégies de mise en œuvre. Les préférences individuelles doivent être respectées. Il est important que la participation au dépistage soit une décision prise librement et que la non-participation n’ait pas de conséquences négatives. Un accompagnement à l’arrêt du tabac basé sur les connaissances scientifiques les plus récentes devrait systématiquement être proposé aux personnes à risque, qu’elles décident de se soumettre à un dépistage ou non. Enfin, il convient d’éviter de stigmatiser les personnes qui fument ou ont fumé et de s’abstenir de leur attribuer (à tort) la responsabilité morale de leur maladie.

Le comité d’experts recommande expressément de proposer le dépistage du cancer du poumon par LDCT dans le cadre d’un programme organisé et de ne pas le confier à des praticiens ou des acteurs individuels qui l’effectueraient d’eux-mêmes. Seul un programme organisé peut assurer une offre accessible et équitable à large échelle et assurer la qualité et la reproductibilité des examens complémentaires indiqués après un résultat suspect, de même qu’une invitation structurée et ciblée de la population à risque. Cela permettrait en outre — moyennant une adaptation de l’ordonnance sur les prestations de l’assurance des soins — d’exonérer l’examen de la franchise, une autre condition essentielle pour un accès équitable.

Accéder à la population à risque constitue une préoccupation centrale et un défi majeur. Pour ce faire, des stratégies de recrutement et de mise en œuvre spécifiques sont indispensables. Pour éviter des inégalités d’ordre économique dans l’accès aux soins, les barrières financières qui font obstacle à la participation au dépistage, comme la franchise, devraient être éliminées.

1. Mandate of the Cancer Screening Committee

The National Cancer Screening Committee was established within the framework of the National Strategy against Cancer in Switzerland. The Trusteeship Council is composed of Oncosuisse, the Federal Office of Public Health (FOPH), the Conference of Cantonal Directors of Public Health (GDK-CDS), and Public Health Schweiz. In February 2019, the executive board elected the members of the committee. One original member resigned at the end of 2021: Prof. Dr. med. Reto Auer. The Trusteeship Council unanimously elected Prof. Dr. med. Kevin Selby as his successor as expert for the field of Medicine (Clinical Practice and Prevention). Table 1 shows the composition of the committee in 2022.

The mandates entrusted to the committee are as follows:

- It operates as an independent advisory body.
- It addresses questions of cancer screening (population-based screening).
- It appraises the evidence previously assembled by third-party assessment teams and formulates recommendations for screening strategies.
- It takes into account medical, epidemiological, economic, legal, and ethical aspects from a societal and patient-centred perspective.
- It monitors and considers relevant developments in Switzerland and abroad.
- It prepares recommendations for relevant political and professional stakeholders involved in cancer screening.

The committee works in a scientifically rigorous, trustworthy, balanced, and independent manner.

The recommendations of the committee will aim to provide rigorous and independent guidance for evidence-based policy by political and professional stakeholders (Swiss Confederation, cantons, service providers, insurers, professional societies, patient organisations, and non-governmental organisations (NGOs)).

cancer screening committee

Table 1. Members of the Committee of Experts on Cancer Screening

Appraisal Committee of Experts on Cancer Screening

EXPERT	FIELD OF EXPERTISE
Prof. Dr. Marcel Zwahlen Institute for Social and Preventive Medicine, University of Bern (Chairman) **Prof. Dr. med. Thomas Agoritsas** Divisions of Internal Medicine & Clinical Epidemiology, Geneva University Hospitals	Epidemiology, Methodology, Statistics
Prof. Dr. med. Stefan Aebi Cancer Center, Division of Medical Oncology, Lucerne Cantonal Hospital **Prof. Dr. med. Kevin Selby** Center for Primary Care and Public Health (Unisanté), Lausanne **Dr. med. Reto Guetg**[1] Independent Medical Examiner, Medical Advisor Federal law on Health Insurance, Bern	Medicine (Clinical Practice and Prevention)
Dr. med. Jacques Fracheboud Retired, formerly Erasmus University Medical Center, Rotterdam, The Netherlands	Screening
Prof. Dr. Matthias Schwenkglenks Institute of Pharmaceutical Medicine (ECPM), University of Basel; Epidemiology, Biostatistics and Prevention Institute, University of Zurich	Health Economics
Prof. Dr. med. Samia Hurst-Majno Institute for Ethics, History and the Humanities, University of Geneva	Ethics
lic. iur. MAE Michelle Salathé Medicine Ethics Law, Basel	Law and Ethics
David U. Haerry Chairman, Positive Council, Zurich	Patient partner

For the recommendations presented here, there are no financial or other conflicts of interest among the members of the committee.

The health economic part of the assessment report was done at the Epidemiology, Biostatistics and Prevention Institute, University of Zurich, without any involvement of Matthias Schwenkglenks.

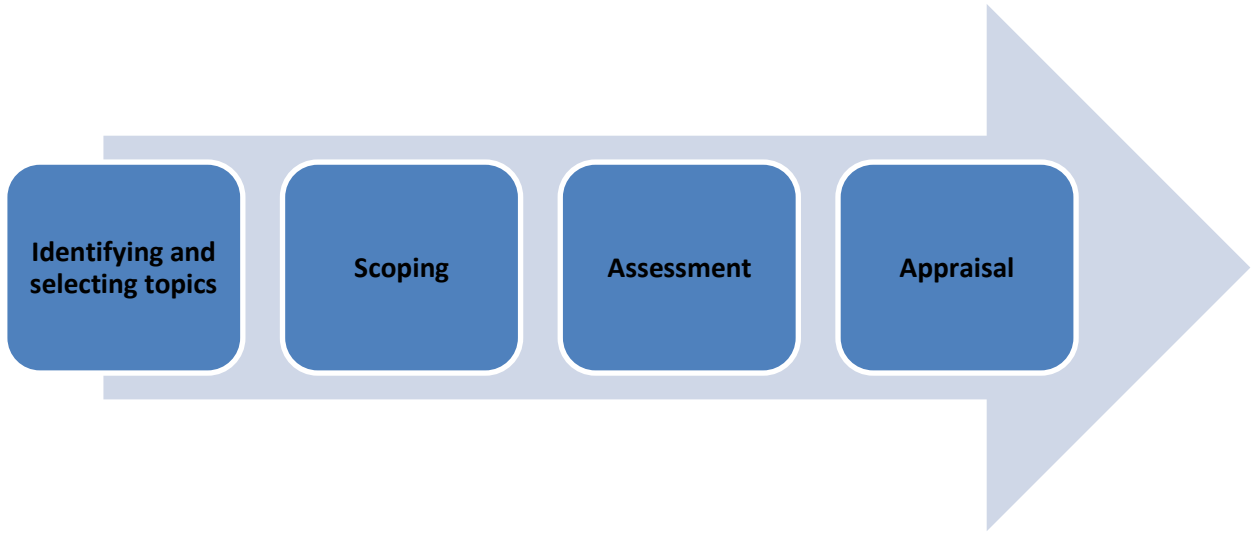
Kevin Selby is involved in the planning of a lung cancer screening pilot programme in the Canton of Vaud.

[1] Stepped down from committee in July 2022 due to personal reasons.

2. Methods

The Cancer Screening Committee follows nationally and internationally established guidance for the assessment of medical procedures (i.e. “health technology assessment”) [1,2]. The development of the present recommendations followed four steps (Figure 1).

Figure 1: Working process of the Cancer Screening Committee



a. Topic identification and selection

Based on a broad survey of interested parties, the Cancer Screening Committee prioritised specific topics considering the current body of evidence, burden of disease and screening (in terms of not only time and money invested but also unnecessary worries and further medical clarifications due to false-positive or unclear results), and presence of a current policy reason to address each issue. Based on the committee’s proposal, the Trusteeship Council identified the topic of low-dose CT (LDCT) screening for lung cancer as one of the first topics to be addressed.

Lung cancer is one of the five most common types of cancer in Switzerland, accounting for 4,700 new diagnoses per year. It is the most frequent cause of cancer-related death, estimated to be responsible for 3,300 deaths per year (2018). The high burden of disease justifies a review of lung cancer screening options in Switzerland.

LDCT has been used since the 1990s for the early detection of lung cancer foci. Several well-conducted randomised studies have investigated the benefits, down-stream consequences and harms of LDCT for lung cancer screening. The results of the large Dutch-Belgian NELSON study were published in January 2020.

LDCT lung cancer screening is currently being discussed intensively in national and international contexts. Various countries have been discussing whether to recommend LDCT screening for heavy smokers or ex-smokers with a long duration of cigarette smoking before quitting.

b. Scoping

The Cancer Screening Committee invited approximately 20 potential mandate holders to formulate a scoping report on LDCT screening for lung cancer in the Swiss context. The question addressed by the scoping report was '*What is the clinical effectiveness (and cost-effectiveness) of LDCT lung cancer screening compared to usual care or another screening test among high-risk adults?'.* The Institute for Clinical Epidemiology and Biostatistics, University Hospital Basel, Switzerland, submitted an offer according to its specifications. An evaluation team composed of Prof. Marcel Zwahlen, Chair Cancer Screening Committee; Aline Flatz, MD, MPH, Scientific Collaborator Swiss Cancer League, Scientific Office; Dr. rer. nat. Rolf Marti, Swiss Cancer League, Head of Research, Innovation and Development, Member of the Managing Board; and Yvonne Grendelmeier, lic. phil., Head Office of the Cancer Screening Committee, evaluated the offer in 2019 according to the award criteria. They inferred that the scoping review would help confirm the rigor and accuracy of the retrieved results. Upon recommendation of the evaluation team, the Cancer Screening Committee commissioned the Institute for Clinical Epidemiology and Biostatistics, University Hospital Basel, Switzerland, to conduct the scoping.

The drafted questions were refined in the scoping report [3] (Table 2, Population, Intervention, Comparator, Outcome [PICO] approach), and methods were defined to systematically assess the clinical effectiveness of lung cancer screening with LDCT, cost-effectiveness and potential budget impact, and ethical aspects raised by LDCT screening.

The population of interest was defined as any asymptomatic adult (≥18 years) at a high risk of lung cancer due to smoking.

LDCT-Screening was compared with no screening/usual care and chest radiography [CXR]. The number of screening rounds or the screening intervals were not taken into account as eligibility criteria. In terms of clinical review, the critical outcomes were as follows: lung cancer mortality (at least 5 years of follow-up), all-cause mortality (at least 5 years of follow-up), number of false-positive scans with invasive procedures (e.g. fine-needle biopsy, bronchoscopy or surgery), and number of false-positive scans with complications.

Medical societies and other stakeholders were invited to comment on the drafted questions, and changes were made accordingly (available at www.cancerscreeningcommittee.ch).

Table 2. Population, Intervention, Comparator, Outcome (PICO) defined in the scoping report

Population	Smokers and former smokers: Any asymptomatic adult population (≥18 years) at high risk of lung cancer due to smoking
Intervention	Low-dose computed tomography (LDCT): Any screening with LDCT irrespective of the number of screening rounds or screening intervals.
Comparator	No screening/ usual care and chest X-ray
Outcomes	Critical and important patient-relevant outcomes Critical outcomes: - Lung cancer mortality (at least 5 years follow-up) - All-cause mortality (at least 5 years follow-up) - Number of false-positive scans with invasive procedures (e.g. fine-needle biopsy, bronchoscopy or surgery) - Number of false-positive scans with complications Important outcomes: - Number of false-positive scans - Number of indeterminate scans - Number of follow-up assessment with LDCT - Number of lung cancer detected - The lung cancer stage is not patient-relevant; however, early detection facilitates less severe therapeutic measures - Interval of lung cancer detection (after negative screening result or undetermined screening result without follow-up CT scan - Psychological distress (depression, anxiety, stress, or other) - Overdiagnosis - Smoking cessation rate - Number and type of lung cancer treatment - Number of follow-up investigations (invasive and non-invasive) - Quality of life

A false-positive scan was defined as a positive scan result (leading to further testing or treatment) in the absence of lung cancer. The definition of false-positive scan was extracted for each trial as there might be variations between the trials.

Due to possible variations in the definitions of complications between the trials, the definition for complications following invasive and non-invasive diagnostic procedures were extracted for each trial.

An indeterminate scan was defined as a scan that did not allow to decide, if there was an abnormal finding / a suspicion of lung cancer or not. Indeterminate scans warranted further testing. Due to possible variations between trials regarding the definition of indeterminate scans, the definition of false-positive scans was extracted for each trial.

c. Assessment

Based on the scoping report, the Cancer Screening Committee appointed the Institute for Clinical Epidemiology and Biostatistics, University Hospital Basel, Switzerland, to undertake the systematic collection and assessment of the available evidence based on the scoping report.

Systematic searches using relevant databases were conducted to update the systematic review and economic evaluation by Snowsill [4] for the assessment of clinical effectiveness and cost-effectiveness. Empirical research on individual attitudes and analytical literature on ethical issues were identified using purposive sampling on PubMed and Google Scholar.

For the assessment of clinical effectiveness, trials with ≥5 years of follow-up and available critical binary outcomes in both trial arms were included for further assessment and meta-analysis using a random effects model. The certainty of evidence regarding patient-important clinical outcomes defined in the PICO was assessed using the Grading of Recommendations, Assessment, Development, and Evaluation (GRADE) approach [5]. In a sensitivity analysis of the critical outcomes of lung cancer mortality and overall mortality an indirect comparison of trials comparing LDCT screening versus no screening, LDCT screening versus CXR screening, and CXR screening versus no screening was conducted.

For the assessment of cost-effectiveness and budget impact, data extraction and quality assessment of all eligible articles were conducted according to the Consensus on Health Economic Criteria (CHEC) check list for economic evaluations. The population demographics, study characteristics, and main results are summarised and briefly described. A de novo cost-effectiveness analysis was based on a newly programmed version of the 'MIcrosimulation SCreening ANalysis (MISCAN)' Lung model (a stochastic microsimulation model) [6]. Effectiveness data from the Dutch–Belgian lung cancer screening trial (NELSON) were used to calibrate the model. Different inclusion criteria were modelled. Costs included those for LDCT screening and invitation, risk assessment, LDCT follow-up, biopsy, and treatment (divided by care phase and including immunotherapy costs as part of the terminal care costs). Cost-effectiveness was expressed as cost per life-year gained (LYG) and cost per quality-adjusted life year (QALY) gained. The analyses were conducted using a healthcare perspective, lifetime horizon, and discount rate of 3% (for both costs and effects).

Budget impact analysis was based on the results of cost-effectiveness analysis. The undiscounted costs of the selected screening scenarios were compared to those of no screening.

Ethics

Eligible articles on ethical issues were identified and categorised. After identification of issues, ethical issues were categorised into two main groups – clinical ethical issues concerning screening, and wider issues concerning justice and discrimination. Each issue was subjected to normative analysis via application of key ethical principles and available arguments in the ethical literature.

The assessment report was completed in March 2022. Stakeholders were invited to provide comments on the report in writing until May 2022. The full assessment report is published on the committee website [7].

d. Appraisal

The Cancer Screening Committee appraised the synthesised evidence in four meetings as per the Evidence to Decision (EtD) framework [8,9] considering the following: (1) ethical issues in lung cancer screening, (2) balance of the estimated clinical benefits and harms, (3) certainty of these estimates (i.e. quality of the evidence), (4) resource considerations, (5) health equity, (6) acceptability, and (7) feasibility of implementing screening. In addition to the assessment report, the committee considered the feedback received from stakeholders and guidelines from other countries. In one appraisal meeting, external experts from the Swiss Lung Cancer Screening Implementation Group (CH-LSIG)[2] were present during parts of the meeting to answer technical and practical questions from the committee. The experts provided information on the aspects of feasibility in the Swiss context.

After four appraisal meetings, the first version of the recommendation report was drafted by the scientific office. The draft was then revised by the committee members and finalised in the fifth meeting. The committee issued recommendations based on ethical considerations, clinical

[2] Representatives of the Swiss Lung Cancer Screening Implementation Group (CH-LSIG):
Prof. Christoph von Garnier, Head of Department, Department of Pneumology, CHUV
Prof. Thomas Frauenfelder, Deputy Director Institute for Diagnostic and Interventional Radiology, USZ
Prof. Milo Puhan, Director Epidemiology, Biostatistics and Prevention Institute, UZH

effectiveness, harms, cost-effectiveness, and budget impact of LDCT screening for lung cancer. Health equity, acceptability, and feasibility were also considered. The committee followed the GRADE approach, in which recommendations can be strong or weak/conditional. The key determinants of the strength of a recommendation are based on the EtD framework, which provides a basis for balancing the desirable and undesirable consequences of alternative management strategies. The committee used the GRADE wording ‘we recommend’ for strong recommendations and ‘we suggest’ for weak recommendations, with either ‘weak/conditional recommendation’ or ‘strong recommendation’ mentioned in brackets at the end of each given statement for further clarity.

3. Background on lung cancer

a. Epidemiology of lung cancer

Lung cancer, one of the most common types of cancers, is responsible for 1.8 million deaths worldwide every year [10]. In Switzerland, approximately 4,700 people are diagnosed with lung cancer every year, and 3,300 die from it [11]. Lung cancer in those under age 50 is rare. Then the incidence increases steadily until the age of 75 to 84, after which it decreases again (Figure 1). In the last 30 years, the age-standardised incidence per year decreased for men from 73.2 to 48.8 per 100,000 individuals, and almost doubled for women from 16.7 to 30.3 per 100,000 individuals [11] (Figure 2). Additionally, from 1989 to 2018, mortality decreased in men, from 65.2 to 34.4 per 100,000 individuals, whereas it increased in women from 11.7 to 18.9 per 100,000 individuals [11] (Figure 2). In 2018, the 5-year and 10-year survival probabilities were approximately 23% and 16% in men and 31% and 22% in women, respectively [11].

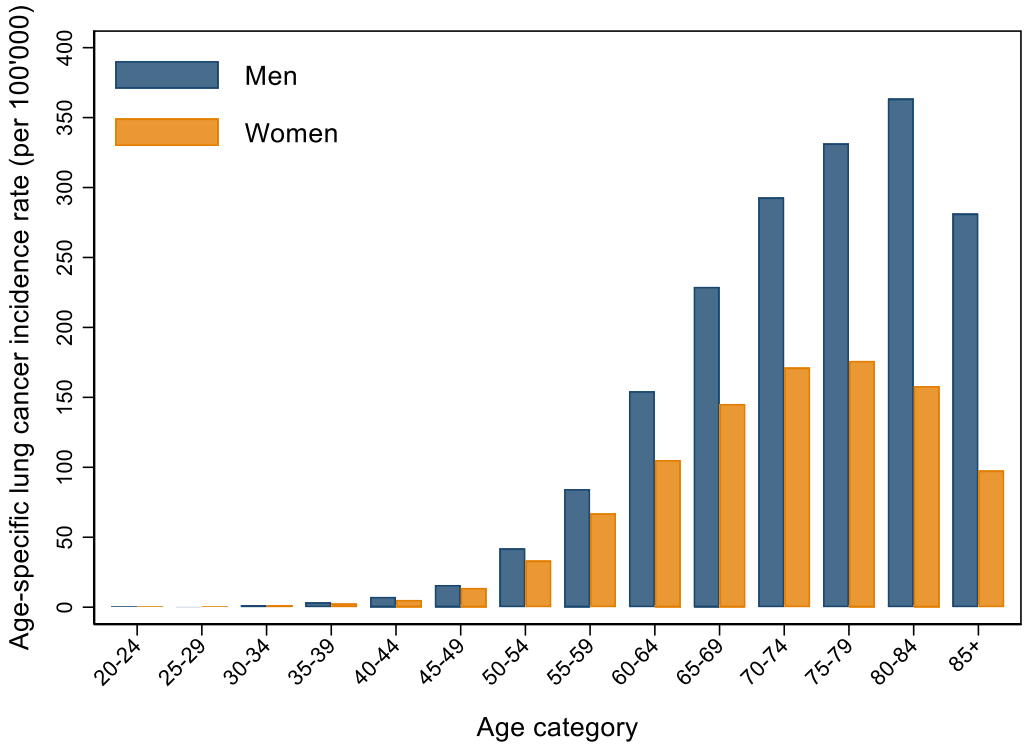


Figure 1. Age-specific lung cancer incidence rates in Switzerland 2014-2018 (Source: BFS/NRKS, 2022)

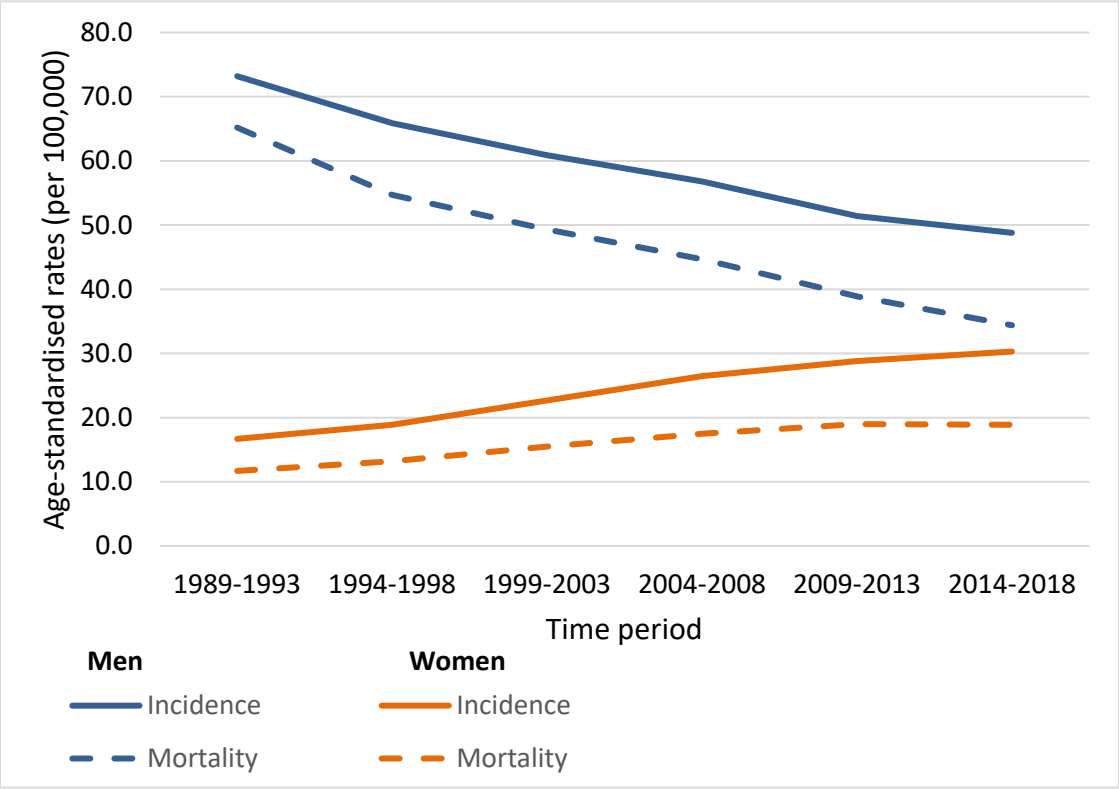


Figure 2. Age-standardised lung cancer incidence and mortality rates for men and women over time in Switzerland (Source: BFS/NRKS, 2022)

b. Risk factors for lung cancer

Cigarette smoking is the leading risk factor for lung cancer. It is estimated that 80% to 90% of lung cancer diagnoses are attributable to tobacco smoking [12]. People who smoke cigarettes are 15 to 30 times more likely to develop lung cancer or die from it than those who never smoked cigarettes [13]. The risk of lung cancer increases with the number of cigarettes smoked per day and years of smoking [14–16]. People who quit smoking have a lower risk of lung cancer than those who continue to smoke, but they have a higher risk than people who never smoked [14,15]. Second-hand smoking increases the risk of lung cancer [14,17]. The increase in the risk of lung cancer for persons smoking the new e-cigarettes are yet to be consistently quantified and will be an important area for research with increasing use of such products [16].

In addition to smoking, the other known risk factors for lung cancer include: exposure to radon and asbestos, air pollution, radiation therapy to the chest and a personal or family history of lung cancer.

c. Symptoms, diagnosis and treatment

Lung cancer is often asymptomatic in the early stages, or with non-specific symptoms involving mostly cough, coughing up phlegm with blood, ache or pain in the chest or shoulder, persistent or repeated chest infections, loss of appetite, fatigue and weight loss.

Several examinations are usually necessary to diagnose lung cancer, including physical examination, X-ray, lung endoscopy (bronchoscopy) with tissue sampling, CT, magnetic resonance imaging (MRI) and positron emission computed tomography (PET-CT). At the individual level, not all examinations described here may be carried out.

There are different types of primary lung cancer. The two main types are small cell lung cancer and non-small cell lung cancer (NSCLC). Most lung cancers (80-85 %) are NSCLC, which often can be surgically removed at the early stage. Patients with more advanced disease stages require additional treatments (see below). The three main types of NSCLC are adenocarcinomas, squamous cell carcinomas and large cell carcinomas.

Small cell lung cancer is rarer and more aggressive, grows rapidly, and spreads to other organs early. Therefore, its prognosis is less favourable. Surgery is rarely indicated, and patients are treated with systemic and radiation therapy.

The treatment options for lung cancer include surgery, drug therapy and radiotherapy. Immunotherapy has emerged as an additional option for patients with advanced lung cancer in recent years. These treatments are used either individually or in combination (simultaneously or sequentially). Successful curative treatment is possible if lung cancer can be completely removed or eliminated by radiotherapy or/and chemotherapy.

A cure is usually impossible at the advanced stage (already spread in the lungs or to other organs). In these cases, palliative treatments aim to inhibit disease progression, alleviate symptoms and maintain quality of life.

d. Current screening situation abroad and in Switzerland

Owing to promising results from individual trials, lung cancer screening is a topic in many industrialised countries.

In September 2022, the European Commission made a proposal to update the Council Recommendation on cancer screening [18]. The update includes among other things the recommendation for lung cancer screening for current heavy and ex-smokers aged 50-75 years. Once adopted by the Council, the Recommendation will replace the current Recommendation on cancer screening from 2003.

The U.S. Preventive Services Task Force (USPSTF) had made a Grade B (moderate) recommendation for annual LDCT screening for lung cancer in 2013 [19]. In 2021, the Grade B recommendation was maintained, and the eligibility was expanded: age range was expanded to 50 to 80 years (previously, 55 to 80 years), and pack-year history was reduced to 20 pack-years of smoking (previously, 30 pack-years) [20]. A recently published study showed a stage shift towards stage I in NSCLC after the first recommendation of the USPSTF in 2013 [21]. The recommendation for lung cancer screening is also supported in principle by US professional societies such as the American Association for Thoracic Surgery and American Cancer Society, and the National Comprehensive Cancer Network [22–24].

In 2016, the Canadian Task Force on Preventive Health Care made a weak recommendation for lung cancer screening [25]. In Australia, the independent Medical Services Advisory Committee (MSAC) advised the Australian Minister for Health and Aged Care to create a national lung cancer screening programme for asymptomatic high-risk Australians in October 2022 [26].

At the country level, numerous projects were launched in recent years at national and regional levels, such as the development of official recommendations and, implementation of a programme, pilot project, or study. In a survey of 23 European countries in 2022, half of the countries reported ongoing feasibility projects, piloting the implementation of LDCT lung cancer screening [27].

Table 3 summarises the main parameters of the US-recommendation and some ongoing European pilot programmes or large studies.

Lung cancer screening is currently not covered by compulsory health insurance (OKP) in Switzerland. To change this, lung cancer screening would have to be explicitly included in the

Ordinance on Health Care Services (KLV) Art 12e on measures for the early detection of diseases in the general population. Under this condition, it would also be possible for the service to be exempted from the deductibles within cantonal programmes. To include lung cancer screening in the KLV, an application that demonstrates the effectiveness, appropriateness, and economic efficiency of the service is required.

The interdisciplinary CH-LSIG, funded by the Swiss Lung League, has been studying the feasibility of this project for several years [28]. A project was initiated to investigate unanswered questions regarding a possible implementation.

The private Foundation for Lung Diagnostics has been offering lung cancer screening for several years; these services are not reimbursed by the OKP [29].

Table 3. Main parameters of the US recommendations for lung cancer screening and a selection of ongoing European projects

Country	Recommendation/ Programme/Study	Age group	Smoking history	Screening interval
U.S. Preventive Services Task Force	Recommendation	50-80 years	20 pack-years	Annual
Croatia	National Programme	50-75	30 pack-years	Annual
Poland [30]	National Pilot	50-75	20 pack-years	Annual
Czech Republic [31]	Population based Study	55-74	30 pack-years	Annual
UK	Regional pilots	55-74	Risk score	Annual

4. Evidence from the assessment report

The Cancer Screening Committee commissioned an assessment report to update the relative effectiveness and cost-effectiveness of LCDT screening for lung cancer in Switzerland, and address ethical issues related to LDCT screening [8]. The main results and corresponding conclusions of the Committee are summarised below.

a. Ethical issues in lung cancer screening

Ethical issues in lung cancer screening were described and analysed using relevant literature. The identified ethical issues were categorised into two main groups.

- Ethical issues raised by the use of screening, such as public attitudes towards screening and possibility of stigmatisation, shared decision-making and risk communication, screening modalities that might influence an individual's decisions to participate, and smoking cessation in conjunction with screening offer.

- Wider issues concerning justice and fairness, such as those related to cost-effectiveness and ethical resource use, issues of social justice and health equity, or issues of fairness arising from eligibility criteria.

Each issue was subjected to normative analysis via the application of key ethical principles and available arguments in the ethical literature.

Possibly, the most important point in terms of ethics is that any value must be articulated to facilitate transparency in decisions about implementing lung cancer screening at the individual, societal and the health system levels. Any underlying moral values regarding justice or harm-benefit considerations must be shared. Despite promising results reported in several trials, the benefits of screening were occasionally overstated and inadvertently miscommunicated. This could be due to unconscious conflict of interest.

By their nature, all decisions based on cost-effectiveness remain contentious. It is unclear whether screening represents a fair distribution of resources given the relatively low number of lung cancer deaths prevented, at best small effect on overall mortality and burdens imposed on the screened population.

Weaker socioeconomic groups could benefit from the implementation of screening to a greater extent than other population groups. Perceptions of lung cancer as a 'self-inflicted' disease are held by some citizens, although not prevalent, and screening is perceived positively by most citizens.

If screening is implemented, individual attitudes and barriers to involvement in screening must be considered. Discussion with a potential participant in screening must adhere to best practice in terms of shared decision-making and risk communication, including consideration of different screening modalities and smoking cessation and how they relate to individual preferences.

b. Evidence on clinical effectiveness and harm

For clinical assessment, 13 trials comparing LDCT to no screening or CXR were identified; of these, seven trials included more than 5 years of follow-up. The trials included 88,006 participants, which contributed to the primary critical outcome analyses. There were considerable variations in the screening intensity (most trials conducted three to five screening rounds), definition of a positive node, and the necessary work-up investigations.

Two trials, the NELSON [32] and NLST trial [33], had a weight of approximately 75% in the pooled summary of all mortality outcome data.

For the critical mortality outcomes, the risk of bias in the trials was judged as moderate.

Clinical effectiveness outcomes

Table 4 presents the main meta-analysis results regarding clinical effectiveness. In the control group, 207 per 10,000 individuals died of lung cancer within at least 5 years of follow-up. In the screening group, the number of lung cancer deaths was 43 per 10,000 individuals lower (95%CI 20 to 58 lower). The number of deaths from all causes was 878 per 10,000 individuals in the control group, 36 more (95%CI 0 to 71 more) than in the screening group. The results of the additional network meta-analysis were consistent with these results.

More lung cancers were detected with LDCT. Compared with the control participants, individuals who underwent LDCT screening were more likely to be diagnosed with lung cancers at earlier stages I and II (risk ratio 2.69, 95% CI 1.94-3.74).

Table 4 Summary of the main results on clinical effectiveness

Outcome	Quality of Evidence	RR (95%CI)	Anticipated absolute effects (per 10,000 individuals)	
			Risk control group	Risk difference (95% CI)
Lung cancer deaths	Moderate	0.80 (0.72-0.88)	207	43 less (20 to 58 less)
Overall mortality	Low	0.96 (0.92-1.00)	878	36 less (0 to 71 less)
Lung cancer stage I or II at diagnosis	Low	2.69 (1.94-3.74)	120	202 more (112 to 328 more)
Lung cancer stage III or IV at diagnosis	Low	0.79 (0.72-0.86)	140	45 less (32 to 67 less)

No uniform picture in terms of psychological consequences from screening with LDCT can be drawn as only a few trials investigated them, and all these trials had validity issues due to the relative subjectivity of outcomes assessment, lack of blinding and losses to follow-up.

Two trials evaluating changes in smoking behaviour failed to show differences in smoking cessation rates between the LDCT screening and control groups.

Due to the large variation in definition of positive nodes LDCT findings, the range of any found thorax abnormality in the screening arms of the trials was wide, between 4.5% and 47.5%. The range of occurrence of false-positive scans was also large between trials, and varied between 0.6% and 45.3%. Trials with defined workup algorithms had considerably lower false-positive rates.

c. Health economic assessment

A total of 43 cost-effectiveness analyses were included in the systematic review. The quality of reporting differed substantially between studies. The included studies showed high heterogeneity in the interventions (e.g. single, annual, biennial, triennial LDCT screening), comparators (no screening or CXR), main source of effectiveness assumptions, perspective (e.g. healthcare, payer, insurer, societal), and time horizon. In general, a common theme in the study results was that

LDCT screening was costlier and more effective than no screening or CXR. In most cases, the incremental cost-effectiveness ratios (ICERs) were below USD/EUR 100,000 per LYG or per QALY gained. Studies based on the recently published NELSON [32] trial seemed to lead to improved ICERs for LDCT screening compared to those based on the NLST [33] or other trials. Many studies have emphasised that the screening strategy, cost of LDCT scans, effectiveness of screening and incidence/prevalence of lung cancer are key factors affecting the cost-effectiveness of screening.

In addition, de novo cost-effectiveness modelling was performed. To compare previously published analyses based on the effectiveness reported in the NLST with the new estimations based on the effectiveness reported in NELSON, 2,972 scenarios were modelled. The results showed that scenarios based on the effectiveness reported in NELSON led to more LYG compared to the original scenarios based on the effectiveness reported in the NLST. In the models based on the effectiveness reported in the NELSON trial, the average cost-effectiveness ratios (ACERs) comparing each scenario with no screening ranged from CHF 14,452 to CHF 37,959 per QALY gained.

In the budget impact analysis, the yearly total costs related to lung cancer treatment in Switzerland in the absence of screening are estimated to increase from CHF 474 million in 2023 to CHF 724 million in 2037. The total costs of all screening scenarios are higher than those for no screening. Over a period of 15 years, the total cost of lung cancer in the no screening scenario is estimated to reach CHF 9,400 million, while the cost for three selected scenarios on the efficiency frontier of the cost-effectiveness plane range between CHF 10,200 million and CHF 12,600 million (i.e. budget impact between +9% and +34% compared to no screening, respectively). All calculated scenarios assumed an uptake of 100%. Limited data from other countries and screening programmes suggest that uptake is likely to be much lower. Consequently, investigation costs are expected to be substantially lower. However, the total programme costs for the recruitment and decision-making process would not be reduced to the same extent.

5. Statements of the Committee

Statements on ethical issues based on the HTA and discussions of the Committee

- Values and priorities used to inform the recommendation must be explicit to ensure transparency for all stakeholders for the implementation of lung cancer screening at the individual, the societal and the health system levels. Any underlying moral values regarding justice or harm-benefit considerations must be transparent.
- Good information and communication are crucial; thus, shared decision-making is very important.
- The challenges are different for different segments of the at-risk population eligible for screening. Equal access is an important objective.
- Reaching the at-risk population is a central concern and a major challenge for which special recruitment strategies and implementation approaches are required.
- Smoking is more prevalent among socially disadvantaged populations. Therefore, screening can potentially reduce social disparities.
- There is a risk of stigmatisation and misattribution to smokers or previous smokers regarding moral responsibility for their disease.
- Smoking cessation support and screening are public health interventions aimed at reducing the damaging health consequences of cigarette smoking. In principle, they are complementary and should not be discussed as exclusive options.
- Lung cancer screening could be cost-effective in Switzerland. However, given the relatively low number of lung cancer deaths prevented, small effect on overall mortality, burdens imposed on the screened population, and the fact that money spent on screening could be spent on other healthcare interventions and public health campaigns, it can be questioned whether screening represents a fair distribution of resources.
- The use of resources for LDCT screening seems justified compared to that for other accepted screenings because its clinical effect of reducing cancer-specific and overall mortality is similar of magnitude or even better than that of other cancer screenings. The number needed to screen to prevent one cancer-specific death is lower in lung

cancer screening with LDCT than in mammography screening for breast cancer in 50-69-year-old women.

- Lung cancer caused by smoking is a consequence of a legal tobacco industry and trade. It could be argued that this implies a responsibility of the society to mitigate the health consequences of this industry by providing appropriate mitigation interventions.

Statements on clinical effectiveness based on the HTA

- LDCT lung cancer screening in an at-risk population probably reduces lung cancer deaths from 207 per 10,000 individuals by 43 (95% CI: 20 - 58 less) per 10,000 individuals over approximately 10 years. (moderate evidence)
- LDCT lung cancer screening in an at-risk population may reduce the number of overall deaths from 878 per 10,000 individuals by 36 (95% CI: 0-71 less) per 10,000 individuals over approximately 10 years. (low evidence)
- LDCT lung cancer screening in an at-risk population may increase the number of lung cancer stage I or II diagnoses from 120 per 10,000 individuals by 202 (95% CI: 112-328 more) per 10,000 individuals over approximately 10 years. (low evidence)
- LDCT lung cancer screening in an at-risk population may decrease the number of lung cancer stage III or IV diagnoses from 140 per 10,000 individuals by 45 (95% CI: 32-67 less) per 10,000 individuals over approximately 10 years. (low evidence)
- The trials showed a wide range of false-positive rates, likely due to the methods used. In an LDCT lung cancer screening trial with volume-based definitions for lung nodes and strict protocols for interval scans and diagnostic work-up (NELSON), up to 5% of scans were false positives. In trials that used definitions other than volume-based, the proportion of false-positive scans was higher.
- Overdiagnosis is an important potential drawback in cancer screening. The extent of overdiagnosis during LDCT lung cancer screening is unclear. In the trials included in the HTA, overdiagnosis was estimated based on the difference in cumulative incidence of lung cancer between the LDCT and control arms. The rates of overdiagnosis were less than 5-10% for follow-up times of more than 10 years.
- There is no conclusive evidence regarding the negative or positive psychosocial consequences of LDCT lung cancer screening.

- There is no evidence that lung cancer screening leads to an increased rate of smoking cessation. The limited evidence available from trials shows that in both the screening and the control arms, 10% to 25% of initial smokers were non-smokers 2-5 years after the intervention of a smoking cessation programme. Nonetheless, the offer of screening may be a good opportunity to help smokers quit smoking.
- Appropriate and stringent eligibility criteria are crucial when making a recommendation in favour of LDCT lung cancer screening to avoid screening low-risk individuals with little benefit.

Statements on health economics based on the HTA

- A review of international literature shows that lung cancer screening is cost-effective. Many scenarios were modelled for Switzerland, and all of these scenarios were cost-effective compared with no screening.
- The cost-effectiveness of different screening strategies is not highly dependent on the choice of screening age and screening interval. Therefore, fine-tuning of the screening design to be implemented should be guided by the preferences of the screened persons as well as feasibility, practicability, and affordability.
- The budget impact depends on the population invited for screening and screening modalities and intervals. The overall costs of all screening scenarios were higher than those of no screening. Over a period of 15 years and assuming an uptake of 100%, the costs of possible screening scenarios were 11% to 39% or 1.4 to 3,700 million CHF more expensive than the costs of non-screening.
- The costs were higher at the beginning and lower when the programme ran longer.
- Depending on the inclusion criteria (age, smoking history) and screening interval, 100,000 to 320,000 people would be eligible for screening in 2023.

6. Recommendation

The Cancer Screening Committee suggests offering lung cancer screening to at-risk people in Switzerland.

(GRADE conditional recommendation)

a. Scope of the recommendation:

The scope of this recommendation is centred on the individual perspective of people considering screening, based on the current body of evidence on the potential benefits, harms and practical issues regarding screening.

However, to make screening available to high-risk persons who would opt for it, this recommendation also has implications for the Swiss health-care system. Therefore, the committee ties the recommendation to key considerations regarding the choice of optimal implementation strategies (see Section d.)

b. Justification

The committee issued a conditional recommendation in favour of screening because it probably results in a small reduction in lung cancer deaths (moderate evidence), a small reduction of overall deaths (low evidence), an increase in lung cancer stage I or II diagnoses (low evidence) and a small reduction in lung cancer stage III or IV diagnoses (low evidence).
Conditional recommendation means that the committee thinks that a majority of informed high-risk people would consider or opt for screening in this context.

People who are more likely to opt for screening are those at higher risk and therefore more likely to benefit from screening, and those who place a high value on minimising their risk of dying from lung cancer and being able to receive early treatment.

Therefore, shared decision-making is critical to ensure that each individual makes the decision most in line with their values, preferences, and context at a given time.

c. Smoking cessation support and prevention of stigmatisation

Smoking cessation – according to the current state of knowledge – should always be offered to persons at risk, regardless of their decision to undergo screening or not.

Stigmatisation and any misattribution to smokers or previous smokers regarding moral responsibility for their disease should be avoided. The view that lung cancer is a self-inflicted disease should be combated. All individuals in Switzerland should have access to health care services and care according to their needs.

The preferences of individuals must be accepted, and paternalism should be avoided. It is important that participation in screening is a free choice and non-participation does not result in negative consequences such as stigmatisation or exclusion from health care services.

d. Implications for the health care system

The committee strongly recommends offering lung cancer screening within organised programmes rather than relying on individual practitioners and stakeholders to offer screening on their own. Only an organised programme can ensure broad, accessible, and equitable screening. It can also ensure the quality and reproducibility of any indicated follow-up testing (after a suspicious screening result), a structured and target-group oriented invitation of the at-risk population, and efficient monitoring and evaluation of the programme(s). A programme would also allow exemption from the deductible according to the standard rules of Swiss statutory health insurance, which is another important prerequisite for equity of access.

For optimal and rapid implementation, health care authorities and key stakeholders should work towards the development and implementation of an organised screening programme. Key stakeholders are also better placed to define optimal diagnostic pathways, processes, and screening intervals adapted to the Swiss context as well as regional and local specificities. Stakeholders need to clarify the high risk population that will be offered screening with regard to age ranges and smoking history, and need to decide on the feasible screening interval.

Cost-effectiveness analysis does not identify obvious thresholds. Different combinations of characteristics can lead to similar cost-effectiveness results, but have quite different meanings in terms of the size of the population invited, intensity of screening, and budget impact. This leads to different practical, equity, and fairness implications that should be considered.

Regarding the optimal age range, the committee does not provide strong recommendations, but suggests that the choice of age range could favour somewhat younger populations over older populations (e.g. 55 to 80 years rather than 60 to 85 years). Similarly, the committee suggests the choice of a moderate smoking history cut-off rather than heavy smoking history cut-off (e.g. starting at a lower cut-off of 20 pack-years and including ex-smokers). Alternatively, stakeholders may choose to implement stratification scores, that are properly calibrated to the Swiss context. The committee also believes that for practical reasons, a biennial screening interval rather than an annual screening interval provides advantages in terms of the burden of screening and feasibility of implementation, although this may result in differences in clinical effectiveness. Similar considerations may have resulted in the large variability in the screening modalities implemented across countries (Table 3).

In contrast, the committee feels strongly about the need for process standardisation. To minimise the number of false-positive lung cancer screening scans, volume-based definitions for lung nodes with adherence to strict protocols for interval scans and diagnostic work-up are clearly preferable to non-standardised procedures.

In addition, the following ethical, legal and social considerations must be considered during implementation:

Reaching the at-risk population is a central concern and a major challenge for which special recruitment strategies and implementation approaches are required. Smoking and lung cancer are more prevalent in population segments with a lower socio-economic status. It is important to reach these population segments with the screening offer.

Communication challenges should be identified, and the problems should be mitigated. Shared decision-making must be appropriately developed and conducted by trained health

care professionals, with roles clearly defined between the structured program and front-line practitioners.

Measures should be taken to ensure equal access. Coverage of the screening cost by statutory health insurance is a prerequisite to guarantee access to screening for all individuals entitled to it. To prevent economically driven disparities in access to care, financial barriers for persons participating in screening, such as deductibles, should be eliminated.

cancer screening committee

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