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Hot Topic

Secondary prevention and treatment innovation of early stage non-small cell lung cancer: Impact on diagnostic-therapeutic pathway from a multidisciplinary perspective

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ABSTRACT

Lung cancer (LC) is the leading cause of cancer-related death worldwide, mostly because the lack of a screening program so far. Although smoking cessation has a central role in LC primary prevention, several trials on LC screening through low-dose computed tomography (LDCT) in a high risk population showed a significant reduction of LC related mortality. Most trials showed heterogeneity in terms of selection criteria, comparator arm, detection nodule method, timing and intervals of screening and duration of the follow-up.

LC screening programs currently active in Europe as well as around the world will lead to a higher number of early-stage Non Small Cell Lung Cancer (NSCLC) at the diagnosis.

Innovative drugs have been recently transposed from the metastatic to the perioperative setting, leading to improvements in terms of resection rates and pathological responses after induction chemoimmunotherapy, and disease free survival with targeted agents and immune checkpoint inhibitors.

The present review summarizes available evidence about LC screening, highlighting potential pitfalls and benefits and underlining the impact on the diagnostic therapeutic pathway of NSCLC from a multidisciplinary perspective. Future perspectives in terms of circulating biomarkers under evaluation for patients' risk stratification as well as a focus on recent clinical trials results and ongoing studies in the perioperative setting will be also presented.

Introduction

Lung cancer (LC) is the second incident solid tumor and the first cause of cancer-related death worldwide, with more than two million new cases and about 1.800.000 deaths in 2020 [1]. In Italy, more than 41.000 new cases have been estimated in 2020 with about 34.000 cancer-related deaths estimated in 2021 [2]. Five-year survival rate of LC patients is 15% to 22%, strictly correlated with histological subtype and stage at the diagnosis [1]. Although the detrimental effect of tobacco smoking on incidence and mortality of LC is well established, in Italy smokers amount to more than 14 million people (24.5% of the overall Italian population), with higher incidence in young males and females (25 to 49 years old)[3].

Unfortunately, the lack of a secondary prevention program so far, lead to a high prevalence of LC patients with a metastatic spread of the disease at the first clinical observation. The reduction of LC mortality recently observed may be considered as a direct consequence of systemic treatment improvement and innovative drugs introduction in the

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clinical practice[4]. Indeed, the approval of targeted agents in metastatic oncogene-addicted Non-Small Cell Lung Cancer (NSCLC) first, and of Immune Checkpoint Inhibitors (ICIs) as first or second line treatment more recently, improved median overall survival (OS) and quality of life of LC patients[4–8]. However, systemic treatments in the advanced/metastatic setting have mostly a palliative intent and almost all the patients still relapse and die; moreover, innovative anticancer drugs have been associated with increasing financial toxicity and have risen the issue about their economic sustainability underlining once again the importance of primary and secondary prevention[9].

The implementation of lung cancer screening as well as the introduction of targeted agents and ICIs in the therapeutic armamentarium of early stage NSCLC, will hopefully change the epidemiology of LC.

The present review includes a comprehensive description of potential benefits and critical issues emerging from the available evidence on LC screening with a multidisciplinary perspective; moreover, the impact of innovative systemic treatments in the perioperative setting on the diagnostic-therapeutic pathway of early stage NSCLC will be discussed.

Materials and methods

We reviewed the literature for both LC screening and LC early stage disease treatment. We performed an electronic double search of the literature using PubMed. For a search strategy optimization, we included the key terms “lung cancer AND screening” for the first search and “NSCLC AND early stage” for the second one. Based on the abstract, appropriate articles were selected. Based on full-text screening we excluded studies without relevant information or outside the scope of the present review. We also checked the reference lists of eligible studies, relevant systematic reviews and the abstracts from the European Lung Cancer Conference, European Society of Medical Oncology (ESMO) conference, World Conference on Lung Cancer (WCLC) and American Society for Clinical Oncology (ASCO) meeting. Finally, we looked for new upcoming treatments and ongoing clinical trials in the perioperative setting on ClinicalTrials.gov.

Lung cancer screening: Available evidence, pitfalls and pearls

The first LC screening trials enrolling participants to receive low-dose computed tomography (LDCT) was done in Japan[10]. In the 1990 s the Early Lung Cancer Action Project (ELCAP) conducted in North America showed a LC detection of 2.7% with LDCT and of 0.7% with chest X ray (CXR)[11]. Afterwards, several clinical trials investigating the benefit of LC early detection through LDCT have been published worldwide; these trials are characterized by high heterogeneity in terms of age and smoking status of the eligible population; control arm (no intervention or CXR); detection method of suspected nodules and screening positivity cut-off; timing and duration of the screening program in the experimental arm; duration of the follow-up[12]. Overall, all studies agree about the benefit of LDCT screening in terms of earlier diagnosis, increased resection rate and lung cancer related death risk reduction[13]. Currently, the US Preventive Services Task Force (USPTF) strongly recommends annual screening for LDCT in adults aged 50 to 80 years who have a 20 pack-year smoking history and currently smoke or have quit within the past 15 years[14], on the basis of the results from the larger clinical studies, the US NLST and the European NELSON trials[15,16]. The NLST trial is a randomised screening trial enrolling 53.454 participants with age between 55 and 74 years and a smoking history of at least 30 pack-years (or formers smokers quitting within the previous 15 years) to receive three annual LDCT or a single-view chest radiography (CXR). The study showed a reduction of mortality from LC with LDCT screening of 20% (95% CI, 6.8–26.7; $p = 0.004$). Also the rate of death from any cause was reduced in the LDCT group by 6.7% (95% CI, 1.2–13.6; $p = 0.02$)[15]. Differently from the NLST trial, the NELSON trial randomised 13.195 male participants to receive a LDCT at baseline, year 1, year 3 and year 5.5 or no radiological screening[16]. The selection criteria were quite different from NLST trial: participants were current or former smokers, quitting less than 10 years before, who had smoked more than 15 cigarettes a day for at least 25 years or more than 10 cigarettes a day for at least 30 years. This study showed a reduction in LC mortality of 24% in men group undergoing LDCT (95% CI, 0.61–0.94, $p = 0.01$). An interesting LC reduction was also seen among a small subset of women in screening group (HR 0.67; 95% CI, 0.38–1.14) at 10 years of follow-up.

Some differences were seen in screening results at baseline among the NELSON and NLST trial, with a percentage of patients with positive test of 2.1% vs 24% respectively, and a positive predictive value of 43.5% and 3.8% respectively; this was probably due to a difference in the nodule-management protocol based on volume in the NELSON trial and on diameter in the NLST. In both studies LC was more often diagnosed in stage IA or IB. On the basis of these two large studies, other trials have been conducted. These trials randomised participants to receive LDCT compared to CXR[17–19] or no interventions[20–24]. The Multi-centric Italian Lung Detection trial (MILD)[21] and the German Lung Cancer Screening Intervention Trial (LUSI)[23] confirmed the role of LDCT screening in reducing LC mortality. In particular, in the MILD trial a total of 4.099 high-risk participants were randomly assigned to receive annual LDCT, biennial LDCT or no screening. The screening with LDCT was associated with a significant reduction in LC related mortality (HR 0.61, 95% CI, 0.39–0.95; $p = 0.017$) and a non-significant decrease in all-cause mortality (HR 0.80, 95% CI, 0.62–1.03; $p = 0.069$). In the LUSI trial 4.052 long-term smokers were randomised to receive 5-annual LDCT screening or no intervention. After 8.8 years of follow-up, a reduced risk of 26% of LC related mortality was observed among the entire population (95% CI, 0.46–1.19; $p = 0.21$). However, a statistically significant reduction in LC mortality was seen among women (HR 0.31; 95% CI, 0.10–0.96, $p = 0.04$), but not among men (HR 0.94; 95% CI, 0.54–1.61, $p = 0.81$) receiving LDCT. Other studies showed only a trend in LC reduction, without statistical significance; these studies include: the Italian Lung Cancer Screening Trial (ITALUNG) in which 3.226 participants aged more than 49 years old and with smoking history of more than 20 pack/year were enrolled to receive 4 annual LDCT or no intervention (HR 0.83; 95% CI, 0.47–1.03)[20]; the Danish Lung Cancer Screening Trial (DLCST) including 4.104 50–70 years old smoker participants to receive 5 annual LDCT or observation (HR 1.03; 95% CI, 0.66–1.60)[22]; the Lung Screening Study (LSS) in which 1.660 participants with age between 55 and 74 years and smoking history of more than 30 pack/year showed a 1-year positivity rate of LC of 25.8% in the annual LDCT group vs 8.7% in the CXR one[25].. Other studies confirmed the effectiveness of screening with LDCT in reducing mortality from LC [17–24,26] (Table 1) and a large metanalysis conducted by the American College of Chest Physicians (CHEST) concluded with a statistical significant 19% relative reduction in LC deaths, on the basis of most relevant LC screening trials[27]. The SUMMIT trial showed also the role of LC screening in detecting thoracic and extra-thoracic incidental findings, such as coronary artery calcifications, emphysemas, aortic aneurysms, bronchiectasis, interstitial lung abnormalities, aortic valve calcifications, osteoporotic wedge fractures and so far[28].

Despite this evidence, in the last years data about how to prolong the screening period were lacking. The Italian trial MILD was the first trial to report a 10-years follow-up of the screening program. These long-term results of MILD trial showed a 39% reduction of LC mortality at 10 years in patients who underwent LDCT along with a non-significant 20% decrease of overall mortality, confirming that a prolonged intervention beyond 5 years can optimize the benefit of the screening program[21]. Similar data were reported in the COSMOS trial, in which the authors concluded suggesting to continue screening beyond to ten years[29].

In the perspective of worldwide LC screening programs, it is important to take into account that LC incidence is influenced also by geographical characteristics. For example in China the prevalence and incidence of LC is very high and an increase is expected in the next years [30]. Furthermore, in Asian countries LC is more frequent even in non-

Table 1
Most relevant lung cancer screening programs, their characteristics and outcomes. c = cigarettes; CXR = Chest x-ray; d = day; DLCST = Danish Lung Cancer Screening Trial; F = females; HR = Hazard Ratio; ITALUNG = Italian Lung Cancer Screening Trial; y = years; LDCT = Low-Dose Computer Tomography; LSS = Lung Screening Study; LUSI = German Lung Cancer Screening Intervention Trial; M = males; MILD = Multi-centric Italian Lung Detection trial; UK = United Kingdom; US = United States.

Study	Sample size	Age	Gender	Smoking status/risk factors	Screening interval	Comparison intervention	Outcome
NLST (US) [15]	53.454	55–75 y	M 15.770F 10.952	≥ 30 pack/y	3 annual LDCT	Annual CXR	Reduction of LC-related mortality (HR 0.80; [0.70–0.92])
NELSON (Netherlands) [16]	15.789	50–75 y	M 13.195 F 2.594	≥ 15c/d for ≥ 25 y or ≥ 10c/d for ≥ 30 y (current or < 10 y ex-smoker)	LDCT at baseline and the with interval of after 1, 2 and 2.5 y	No intervention	Reduction of LC-related mortality among men (HR 0.76; [0.61–0.94]) and women (HR 0.67; [0.38–1.14])
DANTE (Italy) [17]	2.811	60–74 y	M 2.811 F 0	≥ 20 pack/y	Basal CXR and LDCT followed by 4 annual LDCT	Basal CXR and then no intervention	No significant reduction of LC-related mortality (HR 0.99 [0.70–1.44])
ITALUNG (Italy) [20]	3.206	55–69 y	M 2.074 F 1.132	≥ 20 pack/y	4 annual LDCT	No intervention	Trend to reduction of LC-related mortality without statistical significance (HR 0.83 [0.47–1.03])
MILD (Italy)[21]	4.099	≥ 49 y	M 2.716 F 1.383	≥ 20 pack/y	Basal LDCT followed by annual or biennal LDCT for 5 y	No intervention	Reduction of risk of 10-y LC-related mortality (HR 0.61; [0.39–0.95])
DLCST (Denmark)[22]	4.104	50–70 y	M 2.267 F 1.837	≥ 20 pack/y	5 annual LDCT	No intervention	No significant reduction of LC-related mortality (HR 1.03 [0.66, 1.60]); high-risk subjects have a significantly increased risk of death due to LC, with non-significantly fewer deaths in the screening group
LUSI (Germany) [23]	4.052	50–69 y	M 2.622 F 1.430	≥ 15c/d for ≥ 25 y or ≥ 10c/d for ≥ 30 y	5 annual LDCT	No intervention	Reduction LC-related mortality only in women (HR 0.31 [0.10 – 0.96])
LSS (US)[18,25]	3.318	55–74 y	M 1.957 F 1.361	≥ 30 pack/y	Annual LDCT	Annual CXR	No significant reduction of LC-related mortality (HR 1.24 [0.74–2.08]); 1-y positivity rates were 25.8% vs 8.7%.
DEPISCAN (France)[19]	765	50–75 y	M 541 F 224	≥ 15c/d for ≥ 20 y	3 annual LDCT	Annual CXR	LC is 10 [6.36–17.07] times more often detected from LDCT than from CXR
UKLS (UK)[24]	4.055	50–75 y	M 3.036 F 1.019	Five-year LC risk ≥ 5% (based on LLP_{v2} risk prediction model	Single LDCT	No intervention	LC detected in 2.1% of patients
AME (China)[33]	6717	45–70 y	M 1625 F 1887	At least one between: ≥20 pack-y, family history of cancer, cancer history, exposure to carcinogenic agents, passive smoking, exposure to cooking oil fumes	Baseline LDCT followed by a LDCT after 2 y	No intervention	74.1% increase in detecting early-stage LC in LDCT group. Only 7.1% participant met NLST cristeria

smokers and, among non-smokers, females are more affected from LC than males[31]. In the last years some studies have been conducted both in Chinese populations[32,33] and other Asian participants. In particular, the Korean Lung Cancer Screening Project (K-LUCAS) was a single-arm cohort study enrolling 55–74 years old high-risk Korean population with a smoking history of 30 pack-year or more[34]; a Chinese study from the AME Thoracic Surgery Collaborative Group enrolled a total of 6.717 participant to receive LDCT or observation. LDCT led to a 74.1% increase in detecting early stage LC. In this study participants were enrolled on the basis of age (45–70 years old) and the presence of at least one of the following risk factors: smoking history of more than 20 pack-year (currently smoke or quit less than 15 years before); family history of cancer; cancer history of any kind; occupational exposure to carcinogenic agents; long history of passive smoking; long-term exposure to cooking oil fumes[33]. Interestingly only 7.1% participants met the NLST criteria, suggesting that population selection for LC screening programs might follow different criteria for Chinese population[33]; overall these studies provided the evidence supporting the implementation of LC screening in Asian population.

As already observed by Yang et al.[33], taking into account the geographic and ethnic heterogeneity and the different smoking status of the target population, criteria for defining high risk participants could potentially be different for the Chinese population compared with those commonly adopted in Europe or North America.

Recently, Li et al. conducted the largest multicentre, population-based, prospective cohort study in a Chinese population. This study enrolled patients with age between 40 and 74 years and showed that one-off LDCT screening was associated with a significant reduction in LC mortality and all-cause mortality for high-risk patients. Unexpectedly, despite the premises, no reduction of mortality was demonstrated in participants younger than 55 years and in non-smokers or smokers of less than 20 pack-year. Authors concluded that further studies powered for these subgroup are needed to better understand the role of LC screening on this populations among Asian individuals[35].

Furthermore, despite some studies as DANTE trial enrolled only male participants[17], gender difference in favour of women among LC screening programs have been observed. In particular in the NLST trial a trend towards a major benefit in reducing mortality was seen among women but without statistical significance[15]. Similar data was seen among female participants enrolled in NELSON trial, in which a post-hoc subgroup analysis showed reduction of LC related mortality in women (HR 0.67; 95% CI, 0.38–1.14)[16], and LUSI trial (HR 0.31; 95% CI, 0.10 – 0.96) [23]. These results could be explained by the increasing number of smokers among women, but the biological and epidemiological reason of this difference in sex performance on LC screening programs needs further evidence. An interesting topic of discussion could be whether this trend in a major benefit from screening in reducing LC mortality in women is due to sex-related factors, such as biological features including histology, or gender-related factors including cultural, social and psychological characteristics influencing also screening programs adherence, or both[36]. In addition, also racial disparities have been seen among patients undergoing screening for LC. Black individuals have higher age-adjusted LC incidence and mortality rates than White individuals and those from other racial groups. Thus, more data are needed to better select those patients with adapted eligibility screening criteria with the aim to reduce racial disparities[37].

On the balance of the demonstrated benefit of LC-related mortality reduction among screening programs, potential harms of LDCT screening have to be taken into account. Among these, the possibility of false positive findings and overdiagnosis and the risk of cumulative radiation exposure and low cost-effectiveness[27] (Table 2) should be mentioned. Recent evidences showed the importance of volume doubling times and optimal cut-offs of probability definition for lung nodules detected at LDCT[38,39], longer rounds interval, follow-up and screening duration[16,21] in order to minimize the risk of false positives and overdiagnosis. National Comprehensive Cancer Network (NCCN) guidelines on LC screening recommend to adopt the Lung-RADS protocol to standardize the reporting and management of LDCT lung examinations, with the aim to improve the detection of LC and to decrease the false-positive rate[40]. Lung-RADS is a tool designed for the development of a standard classification of nodules detected during LC screening and their management. Recently, Lung-RADS protocol has been updated at version 2022, with new classifications including atypical pulmonary cystis, juxtapleural nodules, inflammatory or infectious findings and airway nodules with their management. In this updated version also the nodules growth rate has been introduced and the management of nodule findings has been revised[41]. Other potential harms to take into account include also the physical and psychological consequences of identifying and evaluating lung nodules[27].

Table 2
pearls and pitfalls of lung cancer screening. LC = Lung Cancer.

PEARLS	PITFALLS
Reduction of LC related mortality	Risk of low-cost effectiveness
Diagnosis of other cardiac, pulmonary or extra-thoracic diseases	False positive findings and their psychological effects
Implementation of smoking cessation programs and adherence to them	Overdiagnosis
	Cumulative radiation exposure

Cost-effectiveness per quality-adjusted life-year and life-year gained seems to be favourable and the incremental cost-effectiveness has been shown lower than the accepted threshold thus suggesting that screening can be introduced at contained cost, saving the lives of many LC patients [42,43].

Patients' risk stratification

The benefit of LDCT screening among high-risk population is often heterogenous and many recommendations and position statements underline the need of a better patients' selection on the basis of risk stratification models[12,44]. For this reason, despite the large use of the $USPSTF_{2013}$ and the new $USPSTF_{2021}$[45] including criteria, several risk-prediction models have been developed up to date, in order to improve the selection of individuals for LC screening[46–50]. In the last years, a LC risk-prediction model from Prostate, Lung, Colorectal and Ovarian (PLCO) Cancer Screening Trial has been developed and validated. The model predictor included age, level of education, body-mass index (BMI), family history of LC, chronic obstructive pulmonary disease (COPD), CXR in the previous 3 years and smoking status. The use of the $PLCO_{M2012}$ model demonstrated to be more sensitive than the NLST criteria[51] and the $USPSTF_{2013}$ criteria[52] for LC detection. Other predictive risk models include the Liverpool Lung Project model (LLP_{v2}) from UK Lung Cancer Screening Trials (UKLS)[24,53]. The LLP_{v2} includes risk factors beyond age and smoking status, such as gender, family history of LC, prior malignancy, respiratory disease, and asbestos exposure. The LLP_{v2} has been used as risk prediction model in the United Kingdom Lung Screening Study (UKLS), showing a LC presence in 2.1% of participants with five-years LC risk more than 5% undergoing single LDCT.

LC incidence and mortality is influenced by geographic, ethnic and gender disparities and risk factors other than smoking, such as air pollution, has a role in LC incidence in younger and non-smoker patients [54].

For this reason, Luo et al. enrolled a larger cohort of patients not meeting USPSTF criteria in a LC screening program. The expansion of USPSTF criteria to those participants who quit smoking more than 15 years before or were up to 5 years younger than 55 years old could resulted in reduction of LC mortality also in these subgroups[55] and this expanded criteria of selection may be relevant in those populations highly exposed to air pollution in which LC incidence is elevated also in younger, non-smokers individuals[54].

Other risk-prediction models have been developed among selected geographic-based populations. For example Guo et al. developed both the first LC risk prediction model in a China screening subset[56] and a specific model for Chinese never-smokers participants. In particular this second model was based on demographic characteristics including age, gender, race, height, weight and level of education; dietary habit; living environment and exposure to cooking oil fume; physical activity; comorbidities including history of chronic respiratory disease, tuberculosis, chronic bronchitis, emphysema, asthma bronchiectasis and hyperlipidaemia; family history of lung cancer[57].

More recently, also molecular biomarkers have been evaluated in risk-stratification modelling and Guida et al. firstly demonstrated the role of circulating biomarkers on LC risk assessment[58]. Fahrmann et al. developed a risk stratification model based on a four-marker protein panel (4MP), consisting of the precursor form of surfactant protein B, cancer antigen 125, carcinoembryonic antigen and cytokeratin-19 fragment, in combination with the $PLCO_{m2012}$ compared with USPSTF screening criteria. The benefit of 4MP in the combined model was seen in sensitivity and specificity improvement. In particular, the 4MP in combination with $PLCO_{m2012}$ model yielded superior predictive performance and sensitivity and specificity for ruling individuals into LDCT screening compared with $USPSTF_{2013}$ or $USPSTF_{2021}$ eligibility criteria and with the $PLCO_{m2012}$ model alone[59]. Despite this landscape of available risk-models (Fig. 1), further investigations are needed to better select biomarkers for an integrated, more comprehensive risk-based model for LC screening.

Other important questions concern the right moment to start and stop screening and the best screening interval choice. Annual screening interval is nowadays the standard recommended worldwide. However, it has been seen that a sex-specific interval could be consider in the future, on the basis that the nodule growth is slower in women than in men[16]. As mentioned before, in the MILD trial, high-risk participants were randomly assigned to receive annual LDCT, biennial LDCT or no screening; this study showed no differences in biennial and annual screening, demonstrating the potential role of biennial screening on the balance of risk and benefit for LC screening[26].

To conclude, in this perspective the 4-IN-THE-LUNG-RUN (4-ITLR "Towards Individually tailored Invitations, screening Intervals, and Integrated comorbidity reducing strategies in lung cancer screening") is the first multicentre implementation trial on LDCT for LC screening across five European countries with the aim to assess the relative safety of a risk-based less intensive screening, considering health risk-factors, baseline CT scan and biomarkers for a personalized, tailored LC screening[36]. Thanks to this emergent considerations, in the future the possibility of intervals stratification by risk will have a central role il LC screening with the aim to improve the harms-benefit ratio[36] of screening programs.

Systemic treatment in the perioperative setting: More than chemotherapy

The diagnostic-therapeutic pathway of patients with stage I-III NSCLC must be discussed and defined within multidisciplinary teams after an adequate clinical and radiological staging. In addition, the endoscopic evaluation of the mediastinal lymph nodes is mandatory for the staging[60]. The early-stage and resectable locally advanced disease occurs at diagnosis in a lower percentage of patients[61]. Nowadays, the standard treatment for resectable disease consists in the integration of both surgery and perioperative systemic treatments to prolong survival by reducing the risk of relapse. The multidisciplinary teams have a central role in the assessment of the risk/benefit ratio of systemic treatments, on the basis of the stage of disease, the biological heterogeneity and the potential presence of circulating micrometastasis.

Platinum-based adjuvant chemotherapy should be offered to patients with resected stage IIB-III NSCLC (according to the 8th edition of TNM staging system) and can be considered in patients with stage IIA resected primary tumor greater than 4 cm (pT2bpN0)[60]. The standard adjuvant treatment is represented by a platinum-doublet chemotherapy, which demonstrated an absolute increase in 5-years survival of 4% to 5% compared with surgery alone[62,59]. In those patients with single station N2 stage III potentially resectable NSCLC documented in pre-surgery staging or in selected multi-station N2 disease, a neoadjuvant treatment could be considered before surgery[60]. Induction platinum-based doublets chemotherapy has shown to have the same impact on improving OS as adjuvant treatment[63]. In the last few years most innovative therapeutic innovations for advanced and metastatic NSCLC have been transposed also in early-stage and locally advanced disease.

Targeted therapies

The most innovative study of the last years in this setting is the ADAURA study. This study has been designed on the basis on the recent progresses in molecular classification of NSCLC, with the identification of *EGFR* mutations (exon 19 deletion and exon 21 L858R mutation) as a target for tyrosine kinase inhibitors (TKIs). ADAURA is a randomised phase III study that assessed the efficacy and safety of adjuvant

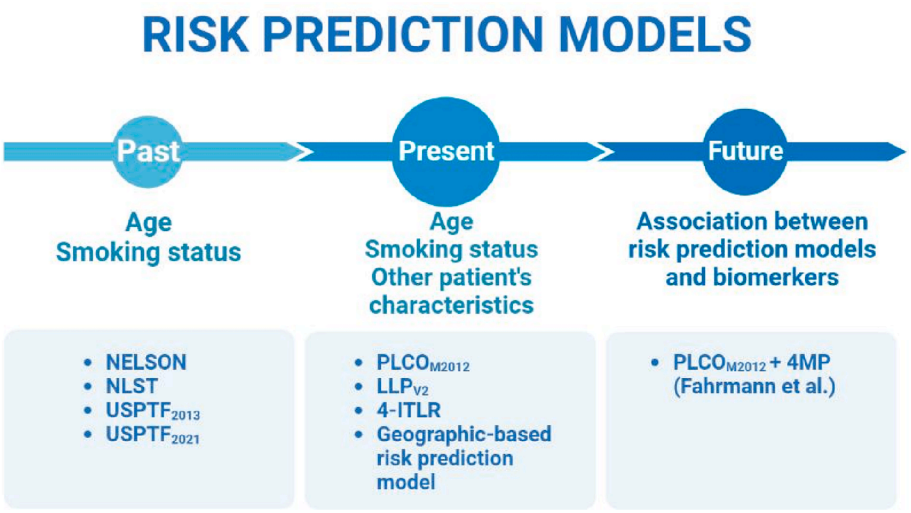

Fig. 1. Landscape of patients' selection risk-models evolution among lung cancer screening programs. PLCO = Prostate, Lung, Colorectal and Ovarian; USPTF = US Preventive Services Task Force. Created with BioRender.com.

osimertinib (a third generation *EGFR* TKI) versus placebo in patients with resected stage IB-IIIA *EGFR* mutation-positive (Ex19Del or L858R) NSCLC, with or without prior adjuvant chemotherapy as per clinician's choice; the primary endpoint was the Disease Free Survival (DFS). The study demonstrated a reduction in the risk of disease recurrence or death of 83% among patients in the osimertinib group[64]. At ESMO 2022 an updated analyses of ADAURA confirmed the efficacy of adjuvant osimertinib with a 3-year DFS of 65.8% vs 21.9% in the control group (HR 0.23; 95% CI, 0.18–0.30)[65]. The efficacy of osimertinib was confirmed also considering the stage according to TNM VIII edition criteria, despite the initial accrual following the TNM VII edition criteria. In addition, the curves of this updated analysis seem to show a possible initial osimertinib waning effect after treatment discontinuation, opening questions about the ideal duration of the adjuvant treatment. Thanks to these results, osimertinib has been approved in the adjuvant setting by European Medicines Agency (EMA) in June 2021 and by the Italian drug agency (AIFA) in September 2022. Several trials exploring other therapies targeting *EGFR* or *ALK* in both adjuvant and neoadjuvant setting are ongoing[66]. Probably in the future the choice of the appropriate treatment in early stage disease will be based on extended molecular analysis (such as Next Generation Sequencing – NGS) and subsequent multidisciplinary team discussion, as recently presented at ESMO 2022 Congress in the context of the PURPOSE trial [67].

Immune checkpoint inhibitors

ICIs are the standard up-front treatment for patients with advanced or metastatic non oncogene-addicted NSCLC and recently have been also introduced as consolidation therapy after concurrent chemoradiotherapy in locally unresectable stage III disease[68–71]. The PACIFIC study, a randomised phase III trial, changed the history of unresectable stage III disease by demonstrating a prolongation of the DFS and OS and a reduction of 28% in risk of death in patients treated with consolidative durvalumab, an anti-Program Death – Ligand 1 (PD-L1), or placebo, after concurrent chemoradiotherapy. Durvalumab, nowadays approved for NSCLC patients with PD-L1 expression $\geq$ 1% [72], is changing the multidisciplinary team approach to stage III disease, thanks to an always more precise staging of disease and an increase of patients receiving concurrent chemoradiotherapy instead of sequential treatment.

Immunotherapy with PD1 and PD-L1 inhibitors has been transferred from metastatic and locally advanced setting also to early stage, thanks to ongoing clinical trials evaluating their efficacy in adjuvant and neoadjuvant setting.

Atezolizumab, an anti PD-L1, has been approved by EMA in April 2022 for the adjuvant treatment after radical surgery and systemic treatment with platinum-based chemotherapy in stage II-IIIA NSCLC with PD-L1 expression $\geq$ 50%. This approval comes after the study IMpower010, a multicentre, phase III study that randomised completely resected stage IB-IIIA (according to the VII edition of TNM staging) NSCLC patients to receive atezolizumab up to 1 year versus best supportive care after adjuvant cisplatin-based chemotherapy. The primary endpoint was the DFS in stage II-IIIA population whose tumor expressed PD-L1 on 1% or more of tumor cells by the SP263 immunohistochemistry assay, in all patients with stage II-IIIA and in the intention-to-treat (ITT) population. The study met its primary endpoint and atezolizumab treatment improved DFS in patients with stage II-IIIA disease and PD-L1 positive (HR 0.66; 95% CI, 0.50–0.88) and in all patients in the stage II-IIIA (HR 0.79; 95% CI, 0.64–0.96). The survival benefit of adjuvant atezolizumab was particularly evident in the stage II-IIIA population with PD-L1 expression on 50% or more of tumor cells (HR 0.43; 95% CI, 0.27–0.68). In patients in the stage II–IIIA population whose tumours expressed PD-L1 on 1% or more of tumour cells, the 3-year disease-free survival rates were 60% in the atezolizumab group vs 48% in the control group[73].

Other ICIs have been explored in the adjuvant setting. Pembrolizumab, an anti PD-L1 has been studied in the PEARLS study, a randomised, triple-blind, phase III study, enrolling completely resected stage IB-IIIA NSCLC patients unselected for PD-L1 expression, to receive pembrolizumab or placebo for up to 18 cycles. Adjuvant chemotherapy administration was recommended but not mandatory. Primary endpoint was DFS in overall population and in the population with PD-L1 tumor proportion score (TPS) of 50% or greater. Chemotherapy was received in 86% of overall population and in 85% of patients with PD-L1 TPS $\geq$ 50%. A mDFS of 53.6 months has been observed in overall population treated with pembrolizumab versus 42.0 months in the placebo arm. In the subgroup analysis of patients with PD-L1 TPS $\geq$ 50% benefit in mDFS has unexpectedly not been seen[74]. Other subgroup analyses showed how pembrolizumab did not improve survival in patients previously untreated with adjuvant chemotherapy (HR 1.25; 95% CI, 0.76 – 2.05) and in squamous histology (HR 1.04; 95% CI, 0.75 – 1.45), whereas patients with *EGFR* mutations seem to benefit from adjuvant pembrolizumab (HR 0.44; 95% CI, 0.23 – 0.84)[75]. Survival data of PEARLS trial are still not mature and more investigations about the subgroup of *EGFR* mutant patients are needed: in particular, these data should be taken with caution, considering the known absence on survival benefit with ICIs in metastatic setting for this subgroup[76] and the small number of *EGFR* mutated patients included in the study.

The results of the PEARLS and IMpower010 trials differ, probably because of the different study design, heterogeneity of clinical population as regards the representation of stage III cases, different follow-up and the use of different assays to determine PD-L1 expression. Finally, the overperformance of the placebo group in the PD-L1 $\geq$ 50% population in the PEARLS trial, rises the issue of the prognostic and predictive value of PD-L1 in the earlies stages.

Adjuvant immunotherapy represents the future for non oncogene-addicted NSCLC, even though mature data about OS and DFS, as well as selection criteria are needed. Another issue to be taken into account is the use of DFS in adjuvant and neoadjuvant clinical trials: DFS may be considered as a valid surrogate endpoint for OS in studies of adjuvant chemotherapy and this is currently accepted by regulatory agencies for drugs approval, however further data and longer follow-up are needed with new treatments such as ICIs[77].

Immunotherapy showed promising data also in the neoadjuvant setting.

Nowadays, a neoadjuvant treatment can be considered in NSCLC patients with single station N2 disease documented in pre-surgery staging or in selected multi-station N2 disease[63]; a careful multidisciplinary discussion should consider that a worse survival has been observed with pneumonectomy after induction treatment, with particular reference to right-sided pneumonectomy[78]; moreover, low rates of pathological complete response (pCR) have been seen among patients receiving preoperative chemotherapy[79].

ICIs have a crucial role in the treatment and prevention of micrometastatic spread by reverting T-cell disfunction. In earlier stages, neoadjuvant immunotherapy may be particularly effective thanks to an intact immune system, the presence of neoantigens and a lower tumor heterogeneity and clonal resistance[80]. Neoadjuvant immunotherapy has also the advantage to be feasible and safe with less perioperative complications and a good patients' compliance. In the NEOSTAR trial, patients treated with neoadjuvant nivolumab with or without ipilimumab had a 80–96% resection rate, an R0 rate of 90–100% (vs 85–90% with neoadjuvant chemotherapy) and a lower 90-day perioperative mortality rate (1–4% vs 3–7% with neoadjuvant chemotherapy)[81].

Recently the CheckMate 816 trial explored the association between immunotherapy and chemotherapy as neoadjuvant approach for NSCLC, showing a median Event Free Survival (mEFS) of 31.6 months with nivolumab plus chemotherapy vs 20.8 months in patients treated with chemotherapy alone (HR 0.63, 97.38% IC 0.43–0.91). The rate of pCR was 24% and 2.2% respectively. As concerns the surgery outcomes, in the nivolumab plus chemotherapy group the median duration of surgery

was shorter, the use of minimally invasive approaches was more common, and pneumonectomies were less common than in the chemotherapy alone group, and these differences were more pronounced in patients with stage IIIA disease[82]. Besides, atezolizumab demonstrated to have a role in neoadjuvant setting; the LCMC3 trial was a phase II study of neoadjuvant atezolizumab in patients with resectable stage IB-IIIB NSCLC. In this study a Major Pathological Response (MPR) rate of 20% (6% pCR) was reached[83]. The role of neoadjuvant atezolizumab has been explored also in association with chemotherapy in a phase II study, showing a 57% rate of MPR (pCR 33%)[84]. Despite these encouraging results, more investigations are needed to confirm the role of atezolizumab in the neoadjuvant setting.

Other ongoing studies exploring the role of ICIs alone or in combination with chemotherapy in neoadjuvant and adjuvant setting are ongoing[66].

The role of immunotherapy seems to be very promising so far, although the introduction of this therapeutic strategy in the neoadjuvant setting leads to some innovation also in other steps of the diagnostic-therapeutic pathway. Indeed, the pathology report of MPR or pCR has been recently subjected to some improvements. An intertrial variability in MPR (a standard surrogate for neoadjuvant setting) has been seen among clinical trials with ICIs. This variability could be due to different sample size, tumor burden, tumor histologies, timing and type of neoadjuvant therapy[85]. Another point to be taken into account is the discrepancy between radiological and pathological response with neoadjuvant immunotherapy. This could be explained by a difference in the tumor bed after immunotherapy rather than chemotherapy, characterized by proliferative fibrosis, neovascularization, cholesterol clefts, higher rate of tumor-infiltrating lymphocytes and tertiary lymphoid structures. With these different features some authors proposed to change the definition “tumor bed” in “regression bed”, consisting in tissue replacing the tumor without a necessary reduction in the volume of tumor bed[85,86]. On this basis, an immune-related pathologic response criteria has been introduced, defined as the percentage of response calculated as a ratio of residual volume of tumor-to-tumor bed in which the tumor bed includes residual volume of tumor plus regression bed and necrosis[85]. However, more mature data and investigations are needed to better understand the different behaviour of ICIs in neoadjuvant response to therapy.

In the near future, the association between induction chemotherapy and immunotherapy could help to improve the rate of complete pathological response, with the hope of reducing the amount of pneumonectomies. Despite this, future biomarkers are needed in order to improve patients’ prognostic stratification and to identify patients potentially benefiting from perioperative therapy. Among these, circulating tumor DNA (ctDNA) seems to be promising[82].

Furthermore, the introduction of targeted therapies and ICIs in early stage disease led to the need of an appropriate molecular characterizations and PD-L1 expression analysis. A critical point in this landscape is the definition of the optimal tumor samples, biopsy or surgical specimen, to perform. A panel of international expert pathologists and molecular biologists recommends repeating the molecular analysis in both bioptic and surgical tissue samples if first cytological or histological specimen resulted negative and if initial biopsy has been performed more than 2 months before surgery. The analysis of PD-L1 should always be repeated considering its spatio-temporal heterogeneity[87]. Thus, an adequate bioptic sample remains essential for defining the biological characteristics of the disease and consequently for determining the opportune therapeutic approach.

Future perspectives in LC screening program and early stage lung cancer treatment

Thanks to the introduction of LC screening programs worldwide and the progresses reached in the treatment of early stage disease, the management of LC will change in the next years and a reduction of LC related mortality is expected. However, despite the recent innovations in the field of LC screening programs depicted before, several questions are still open and deserve further exploration (Fig. 2).

The epidemiology of LC in non-smoker patients will change in the next years; indeed, even though smoking is the most important risk factor for LC, about 10–25% of LC patients are non-smokers, with a variable proportion in some geographic areas such as East Asia[88]. Second or third-hand smoke, radon exposure, high fasting plasma glucose and some occupational exposures demonstrated to have a role in carcinogenesis for non-smokers LC patients[89].

Recently, at ESMO Congress 2022, Swanton C. et al. presented emerging data about the link between air pollution exposure and LC incidence in non-smoking individual with *EGFR* mutations. The pathway is driven by an influx of macrophages and an increase in the inflammatory mediator interleukin-1β. Lung cells have shown to be *EGFR* mutated in approximately 15% of normal lung samples; when lung cells are exposed to increasing concentration of 2.5um PM ($PM_{2.5}$) carcinogenesis is more quickly induced. These new findings open some questions about the extension of a program of LC screening in populations with high exposure to air pollution. A hypothetic strategy in the future could be the identification of non-smokers with *EGFR* mutations in their cells to be enrolled in LC screening programs with LDCT[90]. The TALENT study conducted in Taiwan enrolled 55–75 years old never-smoker patients, with an increased risk including family history of LC and passive smoking exposure. This study confirmed the effectiveness of LDCT screening in a pre-defined, never-smoker high-risk population [91]. The effectiveness of LC screening with LDCT was seen also among individuals living in unfavourable regions in terms of radon exposure [92]. Despite some preliminary data showed a prediction model of LC risk for non-smokers[57], further investigations are needed to explore how to extend LC screening programs to this subgroup of patients.

Future perspectives in LC screening programs are focused on the investigation of radiomics, functional, inflammatory and immunitary biomarkers of smoking-related damage as promising tools for risk prediction[93]. For example, ongoing studies are investigating the role of biomarkers such as the use of methylation profile in the circulating cell-free DNA (cfDNA) to predict the existence of LC. Other blood-based biomarkers have been studied, such as a panel including proteins pro-SFTPB, CA125, CYFRA 21–1 and CEA, that in combination with LDCT could help to reduce the number of false-positive screens[94,95]. Furthermore, serum levels of CEA, CYFRA21-1, IL-8 and VEGF have shown to be significantly higher in LC patients with radon exposure[95]. Also studies on urine samples and volatile organic compounds detected on breath analysis are ongoing, with interesting results[94].

Furthermore, circulating microRNAs (miRNAs) have emerged as potential bio-markers for cancer diagnosis and their use in LC screening resulted in reductions of LDCT false-positive rate[96–98]. miRNAs are released from cells into body fluids including plasma, whole blood, sputum and urine through exosomal or non exosomal pathway. Among these, miRNA-20a, miRNA-10b, miRNA-150 and miRNA-223, seem to be excellent diagnostic biomarkers for NSCLC, whereas miRNA-205 is specific for squamous cell carcinoma[97]. Other data suggested miRNA-142-3p, miRNA-148a-3p and miRNA-451a as signature improving LC risk when combined with pack-years or risk-factor based LC models[99]. The combination of LDCT and blood miRNAs demonstrated to predict individual LC incidence and mortality, with future important implications in personalizing screening intervals[100]. Despite this, no standard panel of miRNA is currently available for early detection of LC and further investigation for standardization are needed.

The development of artificial intelligence tools allowing the integration of clinical data from subjects undergoing screening programs with risk, predictive and diagnostic biomarkers from different biological samples and radiomics features from LDCT imaging, may be considered the next future in this settings[101,102] and translational studies ancillary to LC screening programs are encouraged by the scientific community (Fig. 3).

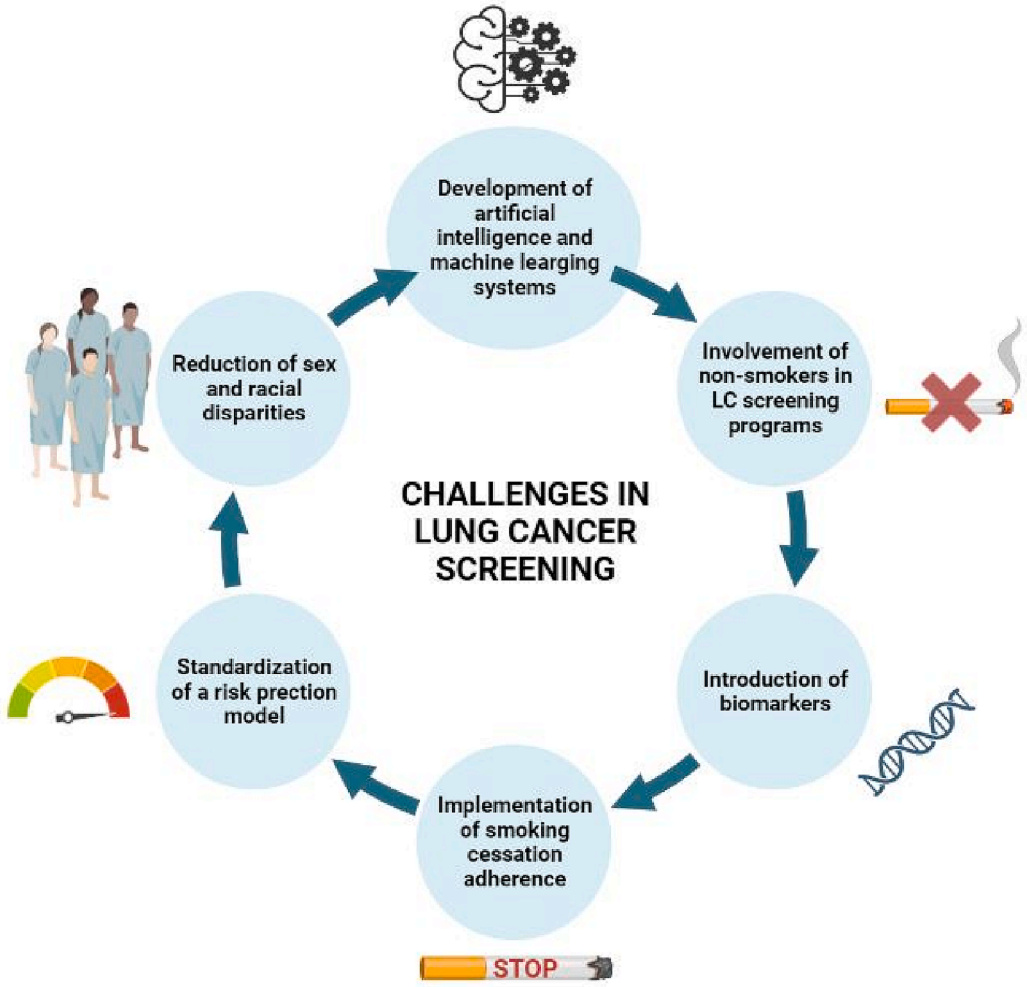

Fig. 2. Challenges and future perspective in lung cancer screening. LC = Lung Cancer; PLCO = Prostate, Lung, Colorectal and Ovarian, USPTF = US Preventive Services Task Force. Created with BioRender.com.

Although LC screening with LDCT represents the best secondary form of prevention with demonstrated mortality reduction, smoking cessation remains the most effective primary lung cancer prevention[103] and LC screening is not an alternative to quitting smoking. Programs of smoking cessation alongside with active radiological screening showed a reduction in LC mortality and for this reason have to be implemented [14,27,34,104]. LC screening programs are also a unique opportunity to motivate smoking cessation, in fact a cessation rate of 7–23% has been seen in screening participants. Besides, among LC screening programs the use of Cytisine, a partial agonist-binding nicotine acetylcholine receptor, seems to have a role in improving smoking cessation[98]. Out of screening programs, adherence to smoking cessation is not so high and amounts to 3–7% in general population[105]. Furthermore, the adherence to the screening trials is not always so optimal after enrolment and it seems to be influenced from geographic, ethnic and socio-economic reasons. Also emotional barriers could represent a central obstacle to screening participation for current smokers[12]. A metanalysis evaluated 13 of the largest LC screening studies and found out that overall second round non-adherence rate across the studies was 28%[106]. With the limit of a significant heterogeneity between studies, greater non-adherence was found in participants younger than 60 or older than 74, with longer travel distances to screening centers and having a low risk perception of LC. Furthermore, smokers were more likely to be nonadherent and White participants were less likely nonadherent. No differences were seen among male and female participants[106]. Quaife et al. showed in the Lung Screen Uptake Trial (LSUT) that participant in LDCT group did not have an increased adherence. In this study, regardless of trial arm, uptake was considerably higher than previous clinical and *real-world* studies, probably because of the prevalence of lower socioeconomic position smoker participants. Authors concluded that strategies including a Lung Health Check approach, could represent a standard for improving LC screening adherence[107].

With these premises and following the 4-iTLR project, the Italian network for LC screening, the Rete Italiana Screening Polmonare (RISP), involving 18 Italian oncological Centres, was established in 2020 to lead a randomised controlled study aiming to improve the efficacy of LC screening. This project has the purpose to compare the efficacy of two different LC screening strategies: a) standard arm performing a basal LDCT followed, if negative, by two annual CTs; b) risk-based arm performing a basal LDCT followed, if negative, by a single CT after two years[36]. Patients' risk-based stratification consider age, gender, ethnicity, smoking status and intensity, level of education, respiratory comorbidities such as COPD, family history of lung cancer and BMI[36].

The project has the purpose to include in Italy 10.000 high risk patients. The eligibility criteria include age between 55 and 75 years old, 30 pack/year smoking history, current smoker or ex-smoker less than 10 years, no previous other cancers in the last 5 years and absence of serious chronic comorbidities or psychiatric comorbidities Patients will be randomised 1:1 in two arms and will undergo to radiological assessment as previous mentioned. If LC will be detected, patient will be discussed in a multidisciplinary team of the referred oncological centre and then will receive the appropriate treatment according to European and Italian

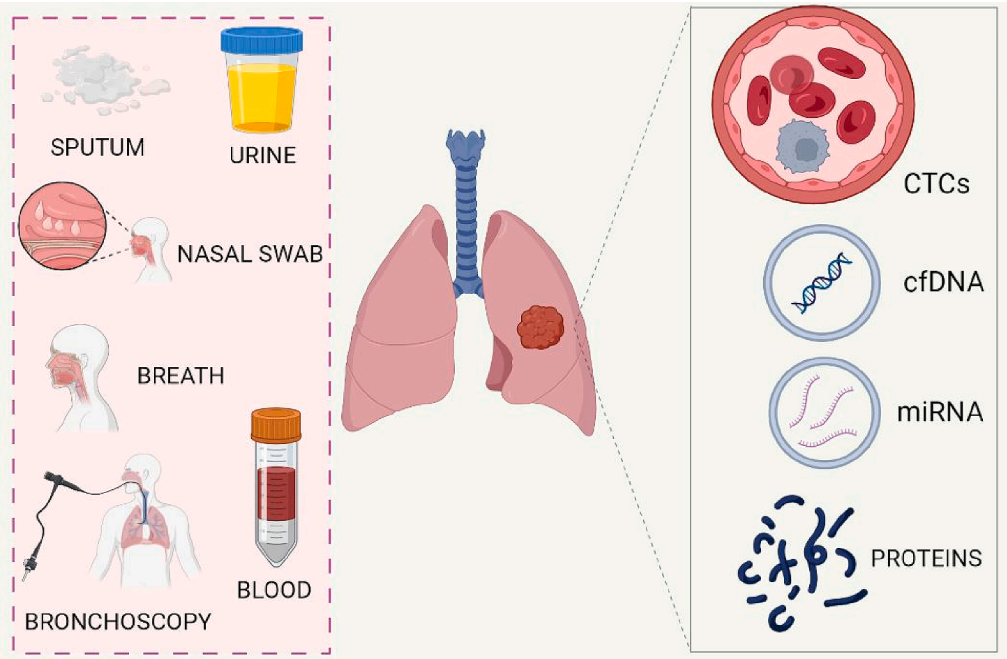

Fig. 3. Molecular biomarkers potentially applicable in lung cancer screening and their sources. cfDNA = circulating free DNA; CTCs = Circulating Tumor Cells; miRNA = microRNA. Created with BioRender.com.

guidelines.

General Practitioners have a central role in the selection of eligible subjects to the LC screening program.

Some grey areas have been shown in the definition of selection criteria of eligible subjects, with particular reference to the cancer risk management in never smoking patients.

The identification of reference centres and of dedicated multidisciplinary working groups at National and Regional level will clearly define the timing of LC screening program activation, identify the involved centres, and make available eligibility criteria for patients' selection and guidelines for the management of suspected nodules. The core team should include the radiologist and radiology technician in order to define strategies to reduce dose exposure as well as to allow a differential diagnosis of suspected nodules; experienced thoracic surgeon in order to perform mini-invasive surgery and to organize hybrid operating rooms allowing the pathological confirmation of small undefined nodules; finally, the pathologist and molecular technician for the set-up of standard operating procedures (SOPs) for the optimal sample fixation, tumor bed review according to the updated international guidelines and molecular analyses planning according to the available therapeutic options.

Finally, the communication of the screening results will require a counselling team, for the ethical and psychological consequences of such a program.

The implementation of screening programs will result in an increase of the early-stage LC diagnosis in the future. In the last years a lot of improvements has been seen in the treatment of early-stage disease. In particular, the introduction of immunotherapy in this landscape has changed the perspectives on the management of LC cancer, improving OS and reducing LC-related mortality.

Conclusion

To conclude, according to ESMO guidelines, nowadays LDCT screening can be performed outside a clinical trial if offered within a dedicated program with quality control, in a centre with experience in CT screening, a large volume of thoracic oncology activity and multidisciplinary management of positive findings. LC screening should be offer to 55–74 years current or former heavy smokers (30 pack-years or 15 years since smoking cessation) after appropriate information about potential benefits and risks and within a smoking cessation program [103].

The project of LC screening with LDCT starting in Italy for high-risk patients will allow to detect early-stage LC in a greater number of patients, with a probable changing in the survival of this disease. On one hand, the activation of a program of secondary prevention will require the definition of a specific organized pathway to attend in the regional reference centres, but on the other hand early-stage LC disease could nowadays benefit of several innovations in terms of locoregional approaches and systemic treatments with new drugs. This requires a good collaboration among the multidisciplinary teams in order to obtain the cure on patients affected from LC and for implementing, projects of translational and *real world* research.

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CRediT authorship contribution statement

Giulia Pasello: Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Project administration, Supervision, Validation, Visualization, Writing – original draft, Writing – review & editing. **Daniela Scattolin:** Data curation, Formal analysis, Investigation, Methodology, Project administration, Supervision, Validation, Visualization, Writing – original draft. **Laura Bonanno:** Validation, Visualization, Writing – original draft, Writing – review & editing. **Francesca Caumo:** . **Andrea Dell'Amore:** Validation, Visualization, Writing – original draft, Writing – review & editing. **Elena Scagliori:** Validation, Visualization, Writing – original draft, Writing – review & editing. **Mariaenrica Tinè:** Validation, Visualization, Writing – original draft, Writing – review & editing. **Fiorella Calabrese:** Supervision, Validation, Visualization, Writing – review & editing. **Gaetano Benati:** Supervision, Validation, Visualization, Writing – review & editing. **Matteo Sepulcri:** . **Cristina Baiocchi:** Validation, Visualization, Writing – original draft, Writing – review & editing. **Michele Milella:** Supervision, Validation, Visualization, Writing – review & editing.

Federico Rea: . **Valentina Guarneri:** Supervision, Validation, Visualization, Writing – review & editing.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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