Review Article

The narrow path to organized LDCT lung cancer screening programs in Europe

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Abstract: A recent position statement by a group of European experts reviewed the current evidence for low-dose computed tomography (LDCT) lung cancer screening, based on the outcomes and screening performance of the published randomized trials and identified actions needed for eventual future implementation. After the National Lung Screening Trial (NLST) outcome publication, guidelines changed in USA and Canada, but there are still problems in real-world screening practice. In Europe any decision was postponed to the publication of the European randomized trial outcomes and recommendations continue to discourage screening for lung cancer in all member countries. The NELSON randomized controlled trial (RCT), the largest one in Europe, outcome results are still waited, whereas the MILD, DANTE, DLSCT and ITALUNG (all with small sample size) RCTs have published mortality and incidence data with adequate follow up. The implementation of an organized screening in Europe is conditioned by a health technology assessment process at European level. According with the European policy, confirmed in the recent European Cancer Code [2015], screening is transferred in current public-health practice according with evidence-based recommendations and based on organized, usually population-based, programs. Guidelines, standard indicators of performance, training of dedicated radiologists and professionals and a comprehensive quality assurance system is requested in European countries to implement nationally a public health screening program. Waiting the NELSON randomized trial results, key issues as modality for selection of high risk subjects and recruitment, integration of screening and smoking cessation, optimal screening regimen and related research on biomarkers should be assessed, discussed and reviewed. Informed decision making, promotion of primary prevention and integration of screening and smoking cessation are all essential components of a comprehensive risk reduction policy. The path to an Evidence-based screening practice is narrow and, in the absence of a well-established decision-making process, the risk of a spontaneous, uncontrolled use of LDCT screening or, on the other side, an oversight of the screening opportunity is high.

Keywords: Lung cancer; low-dose computed tomography screening (LDCT screening); screening program

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Introduction

Lung cancer screening with low-dose computed tomography (LDCT) has been since the beginning controversial on methodology and international in perspective, with a harsh debate about the need of randomized versus one-arm trials to assess the screening efficacy and harms (1). The European Union/United States Collaborative Group, with the Liverpool Statement (2) signed in 2005 by scientists of experimental and observational studies, agreed to explore areas of interest for the harmonization of screening practices, awaiting the trial final outcomes. In 2011, the National Lung Screening Trial (NLST)-USA (3), the world's largest randomized controlled lung cancer screening trial (RCT), showed positive outcome results determining a rapid change of recommendations and guidelines in the

United States (and, more recently, in Canada) (4,5). In Europe, a decision on screening recommendations has been postponed to the publication of the outcomes of ongoing randomized screening trials (6).

A recent position statement by a group of European experts reviewed the current evidence for lung cancer screening, based on the outcomes and performance of the published screening randomized trials (7). Experimental European studies have substantially contributed to the knowledge of performance and possible harms of LDCT screening. The pooled DANTE and MILD data (8), DLCST (9), ITALUNG (10) have recently published outcomes with adequate follow up, but they were all underpowered. The LUSI (11) and UKLS RCTs (12) are still ongoing. The NELSON trial, the largest European RCT, has not yet published the final outcomes and the harm/benefit ratio estimate (13).

European policy on cancer screening has been confirmed in 2015 in the European Code against Cancer, where access to the organized programs was promoted for breast, uterus and colorectal cancer screening (14). Lung cancer screening is discouraged. A specific screening practice is endorsed by the EU to national states only if a cancer screening regimen is recommended on the basis of scientific evidence and monitored by means of updated systematic reviews, as is happening with the European Commission Initiative on Breast Cancer (15). A controlled strategy based on organized, possibly population-based, cancer screening programs with guidelines, standard indicators of performance, training of dedicated radiologists and professionals and a comprehensive quality assurance system is established in most European countries (16).

Long time passed since the NLST first results, and Europe is at risk of failure of any, future, lung cancer screening evidence-based policy. The group of experts (7) suggested to the European health institutions, awaiting the outcome results of the NELSON study, to start the health technology assessment of the lung cancer screening process. How to manage the critical aspects of LDCT screening and harmonize practice is still controversial. Recommendations by experts have already contributed to the innovation of diagnostic imaging and improvement of knowledge of the characteristics of non-calcific-nodule management and clinical early diagnosis practice (7,17). The NELSON study outcome results will influence the next technology assessment process in depth. However, in the presence of the favorable evidence-based recommendations in USA—backed by the NLST study results—the debate about lung cancer screening early diagnosis is expected to continue, whatever the final outcome of the Dutch-Belgian study.

Key issues

Target population and selection of high risk subjects

Lung cancer screening has limitations and should be integrated with other actions as primary prevention, smoking cessation and treatment innovation. However, in the eligible population the LDCT screening contribution is expected to be important to reduce mortality. Lung cancer screening randomized trials adopted similar criteria (age, smoking habit, sex) for the selection of subjects eligible for screening. Following the NLST criteria, the 50% of the subjects with incident lung cancer would have been selected as eligible to a screening program in a European population-based program with LDCT screening, based on the experience of German large EPIC cohort of volunteers (18).

In USA, after the publication of the NLST, guidelines have changed and screening made available to subjects at risk. Based on NLST, 77 years were considered the oldest age for LDCT screening. The extension to age 80 has been recommended by the USPSTF, but also criticized by other modelling results (4,19).

In an evaluation of nine risk prediction models, Ten Haaf *et al.* (20) concluded the use of an individual risk score is superior to the usual categories based on smoking habit and age. Comparing performances of risk models, they showed the best overall performance of PLCOm2012, Bach and Two-Stage Clonal Expansion prediction models. They estimated the risk thresholds for which the three risk prediction models had better positive net benefit in increasing lung cancer detection at 6 years since start, when applied to the LDCT arm of the NLST trial. Two prospective studies have adopted in screening practice a risk model for enrolment. In the Pan-Canadian study (21), a single arm study, 2,537 subjects aged 50–75 and eligible ever smokers were enrolled using PLCOm2012 model. Subjects without lung cancer at the end of the study had a median age of 62 years, the 62.6% current smokers and the mean number of pack-years was 54. After a median follow-up of 5.5 years, the cumulative incidence of lung cancer was statistically higher than that observed in NLST, and 77% of lung cancer screen detected cases were in early stage. The UKLS pilot study identified (2,028 invited) for enrolment the 50–75 age group and enrolled subjects with 5-year lung

cancer risk of ≥5% using the Liverpool Lung Project model (LLP_{v2}). The average, observed risk of enrollees was 8%. Follow-up time is still too short for a definite conclusion. The proportion of current smokers was 38.3% and asbestos exposed 36% (22). In the ITALUNG study (1,406 screened), where traditional recruitment was used, current smokers were 65.7% and asbestos exposed 6.6% (23).

The statement of the European experts did not recommend a specific risk model, and suggested the local performance of the model should be evaluated and monitored in pilot projects (7). Age at start must be defined in LDCT screening program, but individual smoking habit is certainly the most important risk factor, given the lower mortality rate of never smokers. Better selection of high risk subjects is the main objective of future applied research, given the screening costs and the benefit/harm ratio. Biological fluids should be bio-banked (with informed consent), according with standardized procedures, and analyzed to improve the risk model performance.

Recruitment population-based strategies and optimization

NELSON (13), ITALUNG (24) and UKLS (25) randomized trials had population-based strategies to recruit eligible subjects, with or without the cooperation of general practitioners (GP). Procedures for eligibility were different across Europe but all RCTs did not screen the control group with chest X-ray (as done in NLST). Letters were sent to a large number of population subjects; high risk individuals (according with the eligibility protocol) were selected according with study specific eligibility criteria and randomized. The number of letters of invitation, asking the individual interest in participating and to fill in questionnaires, was large in all these studies. In the NELSON study, the first letter was sent to 606,469 subjects, responders were 150,910 and after a second questionnaire 15,822 were randomized. The ITALUNG study made 71,232 invitations, with the cooperation of 269 GPs, who were supporting the subject individual decision to participate. Responders were 17,055, the enrollees 3,206. In the UKLST, 247,354 subjects were invited, the 30.7% responded and 8,729 were randomized. DLCST, DANTE and MILD were based on volunteers and their experience is not informative for a future population-based recruitment.

The population-based recruitment process is complex and expensive, it needs optimization. The best strategy of recruitment must be based on the local health care situation; individual population cancer and screening registries and cooperation with GPs and local preventive or chronic care services are essential. Best approaches should be investigated with the aim of decreasing inequality of access. In the recent Pan Canadian program, a promotional campaign with a national toll-free number and immediate web or interview based computerized recruit was shown to be an efficient tool to promote information (21).

Taking care of individual risk reduction

In almost all studies, LDCT screening has been offered to eligible smokers or ex-smokers. Across studies, comparing prospectively screened and control individuals, smoking cessation rates varied. A recent Editorial by Carreras & Gorini (26) reviewed the smoking cessation interventions in the context of lung cancer screening studies. The integration of smoking cessation and LDCT lung cancer screening needs further evaluation, but is a good option. Notably, there is no evidence of a harmful impact of LDCT screening on smoking habit and there is large agreement in the identification of screening for lung cancer as a teachable moment. Ongoing prospective studies are aimed to assess the impact of integrating risk reduction procedures and LDCT screening in health care centers (27).

The impact of the integration of smoking cessation and LDCT screening on lung cancer outcomes is not fully evaluated. Pastorino *et al.* investigated the reduction of overall mortality attributable to smoking cessation in the MILD active groups (N=3,381). They concluded for the independent, strong effect of stopping smoking both for former smokers at the enrolment and late quitters (smoking cessation after the enrolment) on overall mortality (28).

Any future LDCT screening program should consider the possible combined effect of smoking cessation on the overall and cause-specific mortality (especially smoking-related causes) as a research aim and assess best strategies of integration of anti-smoking policy and other preventive actions in the program. In a future European screening program an integrated offer of smoking cessation interventions is warranted and should be monitored to assess the impact on outcomes.

Performance indicators (detection and recall rate)

In LDCT screening, non-calcific nodules (NCN) are the main reason of recall for assessment at baseline or at repeated test, both immediately or after LDCT follow up, according with the specific study protocol. In the

NLST, DANTE, ITALUNG RCTs as in IELCAP (29) and COSMOS (30), diagnostic criteria were mainly based on visual nodule characteristics and measure of NCN diameter. The NCN was classified, at the end of the screening episode, as positive or negative. Negative recalls were considered as false positive results. Nodule diameter determined the type of assessment protocol: only a small proportion of subjects were followed up, eventually postponing the assessment after a varying time period.

A volumetric approach has been implemented in the NELSON, DLCST, MILD, UKLS and LUSI RCTs. NCN detected at LDCT screening were classified as negative, positive and indeterminate, based on nodule volume, as defined using a software. Volumetric reading approaches have been standardized and NCN classifications suggested. In the NELSON trial, a two-step approach allowed for an initial LDCT classification as negative, indeterminate or positive based on nodule presence and the volume estimated by software. The final screening test result of the indeterminate nodule follow-up was based on the nodule volume (50–500 mm^3), combined with a volume doubling time of 400–600 days (31). Indeterminate screening test results were not considered as positive screening tests, and are not included in the estimate of the recall rate. Final result of indeterminate nodules was classified as negative or positive after the follow-up, and the final result only was used for the measure of performance [sensitivity, specificity and positive predictive value (PPV)]. In NELSON study, PPV was estimated about the 40%, confirming the impact of the use of the different classification of recalls.

The high rate of recall both at prevalent and incident rounds is a reason of concern in traditional reading (in NLST, the 24% at prevalent screening). In a systematic review of lung cancer screening randomized and observational trials, including 63,372 prevalent (from 16 studies) and 79,302 incident screens (9 studies), recall rate for further diagnostic investigations or follow-up varied from 8.7% to 53.0%, detection rates from 0.4% to 3.3% and PPV ranged from 1.0% to 13.6%. The average prevalence recall rate for RCTs was 24.4%. The observed values were lower at incident screening. A strong reduction of the recall rate (and increase of the PPV) related to the cut-off size of the nodule and to the use of a volumetric approach was estimated (32).

IELCAP is the largest multi-centric, observational study carried out in about 20 years of LDCT screening with 65,374 participants at baseline test (29). Considering the high-risk subjects (comparable to the subjects enrolled in RCTs), 19,541 subjects had a baseline test, with a detection rate of 2.2%. In the same subgroup, the repeat tests were 31,303, and the DR was 0.41 (interval was usually 1 year, the rounds of repeated screening were cumulated).

Data were analyzed by screening test (first and repeat) and size. Consistency of the largest nodule was classified as solid or sub-solid, and then subdivided in non-solid or part-solid (ground glass opacities). At baseline, NCNs were solid in 84.3%, and at repeated screening new NCNs in 76.1%. Frequency and percentage of NCNs decreased at repeated rounds, as the proportion of nonsolid. However, they noted the proportion of adenocarcinomas in sub-solid nodules was the 35% (197/555) at baseline and the 24% at repeated. Only Adenocarcinomas were diagnosed in sub-solid nodules, and a high, long-term survival was estimated for this subgroup (as for typical carcinoids). A recent brief report of 60 new sub-solid nodules in the NELSON trial, diagnosed after baseline screening (0.7% of participants with one incidence screening), showed all (pre)malignancy lesions were adenocarcinoma (*in situ*) with favorable staging (stage I) (33). These results at baseline and repeated tests suggested the need of a continuous process of improvement of an optimal screening regimen, mainly related to the management and workout of NCNs.

In the European statement (7), the volumetric approach has been identified as the most innovative method and proposed for future screening practice. Implementation will depend on professional training and strict quality monitoring. Waited final outcomes of the NELSON RCT (and later UKLS and LUSI RCTs) will confirm if the volumetric approach had impact on outcomes. In any case, professional training and quality control, based on recent guidelines in nodule management, could avoid unnecessary recalls and improve measures of accuracy in screening practice.

The comparative evaluation of screening performance is complex, in the presence of a mix of screening practices. Harmonization of screening performance indicators is a high priority for the future European lung cancer screening initiative. A list of common, shared basic indicators is needed.

Inter-screening interval

In lung cancer screening RCTs the inter-screening interval was usually 1 year. In the NELSON study the inter-screening interval varied: 1, 2 and 2.5 years at first, second and third round, respectively. Yousaf-Khan

et al. (34) observed an increase of the interval cancer rate at subsequent rounds. In the last, longer, interval, they showed a higher proportion of advanced stages (the impact of the excess on lung cancer mortality is still unknown).

Lung cancer occurrence and LDCT screening performance can be evaluated considering a period of time since baseline screening, i.e., including 1 or more repeat rounds. In the NELSON trial, the total duration of the screening period was 5.5 years. Excluding the prevalent lung cancer cases, the proportion of interval cancers on the total number of cases in screened, i.e., the sum of screen detected at repeated screening plus interval cancers (circa the expected incidence) is a proxy measure of 1-screening sensitivity. The risk of interval cancers in the NELSON trial at first year was 8% (1-year interval), 20% at the second (2-year interval) and 39% at third round (2.5 years), suggesting a more than linear growth of the tumor. In the overall period the average interval was 22 months, with 52 interval cases and 178 screen detected (excluding prevalent cases), i.e., the 23% of the cases were occurring as interval cancers (52/230). About 80% anticipation of lung cancers with a 2-year interval was considered acceptable in other cancer screening programs, as breast cancer, in Europe. In the ITALUNG study, the number of screen detected lung cancer cases at repeated screening (T1–T3, 1-year interval) was 18, with 6 interval cancers (2 years since negative test): the 25% of the cases in the study period was detected in the annual interval [6/(18+6)] (35).

In the NELSON study, risk stratification after the baseline screening was suggested and based on the identification of subjects: (I) with exclusively negative results; (II) with ≥1 indeterminate result; (III) ≥1 positive for NCN results. At 3rd screening test, the risk for detecting lung cancer was 0.6% in ever negative subjects, compared to a 3.7% for those with indeterminate nodule. The conclusion was screening history might be useful to predict the risk of lung cancer at repeated test (36). Patz *et al.* looking at NLST subjects with a negative LDCT screening at baseline screening (T0), had less lung cancers and higher mortality reduction in comparison with the all intervention group. T0 negative subjects had a yield of lung cancer at first, annual, screening of 0.34%. The same proportion of lung cancers in all subjects was 1%. A longer inter-screening interval, based on their conclusions, might be warranted for subjects who were negative at baseline (37). In the COSMOS study, Maisonneuve *et al.* have stratified, after the baseline test, by emphysema, nodule type and size and showed these factors were modifiers of risk of being diagnosed with lung cancer at subsequent screening and good predictors of lung cancer detection at repeated screening test (38). Based on the NLST data, Schreuder *et al.* evaluated lung cancers diagnosed between first and second annual follow up using a polynomial model which considered patient characteristics and baseline scan morphology. They concluded a personalized risk estimate will enable many subjects to skip a subsequent annual screening (39).

Interval of 2 years is likely an acceptable choice for a lung cancer screening population-based program. Tailored screening interval approaches, based on risk stratification, must be tested in pilot studies with prospective cohorts.

Overdiagnosis and optimal screening regimen

The IELCAP authors estimated average lead time as the ratio between baseline and repeat screening test, showing a predominance of slow growing cancers at the first test (29). Their overall lead time estimate was 5.4 years (high risk subjects). The estimate was specific by nodule consistency and diameter. The relationship between sub-solid nodules and detection of cases with a low progression (possible reason of overdiagnosis) was confirmed. Implications of nodules consistency and tumor characteristics in relation to overdiagnosis are supported in a recent evaluation of a SEER-based early lung cancer series. Knowledge on consistency of NCNs and tumor aggressiveness might be used to inform treatment of screen detected cases (40,41). A better knowledge of nodules and tumor capacity of progression might modify the screening risk-benefit ratio, for example at older ages, favoring a less aggressive surveillance and/or tailored treatment.

The traditional estimate of lead time was based on the estimate of interval cancer occurrence, which weren't available in IELCAP. An optimal regimen of screening and diagnostic workup must be established in advance, but only consider nodule growth and consistency has limitations. Overdiagnosis is primarily an epidemiological concept, certainly related to cancer aggressiveness but not only, and should be measured, prospectively, by the excess of lung cancer cases in a screened population (versus an expected number of incident cases without diagnostic anticipation), and after the compensatory drop due to screening stop. Methodological issues have influenced the overdiagnosis quantification in RCT and observational screening trials (42), but in the future programs monitoring of this risk is needed. The NLST was stopped at 6.5 years (with a short follow up to observe a compensatory drop after

the screening end) showing an excess of incidence at 18.5%. The control incidence was influenced by the CXR screening of the control group, which could have reduced the overdiagnosis estimate. A recent CISNET model was finalized to assess the impact of extension to 80 years of age, as suggested by the USPSTF (19). The impact was modified by the screening stopping ages, with a model median range of overdiagnosis in NLST estimated in 3.9–10.7%, stopping at 75 years of age. The pooled analysis of the DANTE and MILD showed a 18.5% of excess of incidence (not considered as such as overdiagnosis) at 8 years of follow up (8). The ITALUNG study, with 9.5 years of follow up did not show excess of incidence between active and usual care groups (10). In conclusion, for the moment we do not have an agreed quantification of overdiagnosis risk attributable to LDCT screening.

Overdiagnosis is a serious harm of cancer screening, whereas difficult to measure. Screening regimen should contribute to improve diagnostic procedures and treatment, aimed to a greater effectiveness, with tailored treatment and surveillance regimens. Population-based quantification of the harms related to screening- and overdiagnosis and overtreatment are among the most important- is needed in screening programs to evaluate the impact of different strategies, as the age when is better to stop screening.

Biomarkers

Most of the lung cancer screening trials collected samples of biological fluids (usually blood and/or sputum) and stored samples in biobanks. Biomarkers in lung cancer screening have been considered with different purposes. First, combined with LDCT screening for risk prediction and screening of individuals at higher level of risk, second, as contributors in the nodule management and diagnostic process and third, in the follow up for nodules and recurrences of lung cancer cases. A growing list of biomarkers in biological fluid is today available, addressed to disease prediction and/or as screening tools. There is today a consensus on the insufficient evidence of the use of today available molecular biomarkers (43,44).

A screening biomarker should assess the risk of lung cancer within a short time window. The biomarker must have high sensitivity (identification of almost all subjects with lung cancer), but also a good specificity, i.e., the correct identification of negative subjects. A high negative predictive value is requested (i.e., negative subjects at biomarker should be without the disease, at least for the duration of the inter-screening time) and be cost effective in comparison with LDCT, the only screening test shown to be effective in reducing lung cancer mortality. Recall rate is high in LDCT screening with a PPV low in most RCTs with a traditional LDCT reading.

Most of the biomarkers tested for screening showed varying levels of accuracy, and usually low specificity. In a systematic review of blood and serum biomarkers, diagnostic performance was reviewed considering phase 3 studies on EarlyCDT-lung and microRNA based biomarkers concluding for the lack of high quality evidence to support the use in clinical practice (45). Recently, Santarpia *et al.* provided an overview on circulating biomarkers for lung cancer detection considering new techniques grouped under the title of "*Liquid biopsy for lung cancer early detection*". Cell free circulating tumor DNA (ctDNA), circulating tumor cells, exosomes and tumor-educated platelets might have a future role in screening practice, but are not considered suitable for current practice (46).

In the ITALUNG biomarker study, we combined the use of LDCT and the ITALUNG biomarker panel (microsatellite instability and plasma ctDNA measurement) for screening of high risk subjects, confirming a high sensitivity for lung cancer and the opportunity of biomarker use to increase the PPV of the program. Potentially, LDCT and biomarker combined screening might decrease the program costs. It's important to have good biomarkers, but a strategy for their use should be agreed and validation in controlled screening trials is needed (42,47).

A relevant area of new research development is radiomic, based on the features of LDCT images as predictive indicator. This evaluation is still preliminary and not yet available for clinical use (48).

Future research on biomarkers should be embedded in prospective pilot screening trials evaluating the contribution of different biomarkers for the selection of subjects and clinical management of nodules. The question is how they can be integrated in a combined lung cancer screening process, and their added value in the different phases of the screening process, from risk assessment to follow up.

Discussion

The population burden of lung cancer mortality is still high in Western countries. Smoking-related standardized mortality rates have been decreasing, at least in males, thanks to the decreasing smoking habit; however, the absolute number of deaths is decreasing slowly. Population-

based survival rates, in the presence of a high proportion of advanced stages, in Europe, are low and quite stable, waiting for the impact of new treatments.

Reducing the number of smokers and the risk due to carcinogens of selected groups is a priority in health care; smoking related diseases might be reduced with a policy combining preventive and screening approaches.

Primary prevention and screening for lung cancer should not be considered as stand-alone tools for the reduction of lung cancer mortality. Research and practice on lung cancer prevention, early diagnosis and treatment must be planned in a continuum, each of them offering new opportunities of reduction of the morbidity and mortality for lung cancer.

Lung cancer screening in Europe should be organized according with evidence-based recommendations, guidelines shared between professionals and stakeholders, and should be selective, i.e., addressed to high-risk subjects and controlled for possible harms. There are several reasons for all that: (I) both age and smoking habit are strong determinants of lung cancer risk; (II) screening harms can be important in false positive lesions (no cancer), especially in subjects with significant health problems; (III) quality assurance of the process of care can be critical; (IV) screen detection might anticipate in time consequences in terms of surgical and other side-effects which would have been delayed or not occurring in its absence (overdiagnosis/overtreatment); (V) screening is expensive. The risk of overdiagnosis (whereas in the absence of good estimates) might be relevant in older subjects. Tailored screening regimens can be recommended and evaluated considering the individual level of risk and individual preferences. Informed decision making and integration with smoking cessation policies are essential components of a comprehensive risk reduction policy.

The most important characteristic of an organized European cancer screening programs is the offer of a continuity of care, from prevention to early diagnosis and therapy. Lung cancer screening centers must be integrated with high-quality therapeutic centers, as happens for breast cancer in breast units, for pathology, surgery and oncological therapy. A selective, population-based lung cancer screening must be offered to eligible subjects with a continuous monitoring system of performance and outcomes and supported by imaging quality control. Information system is an essential component in the planning of a population-based screening program, where all eligible subjects at risk, whatever the personal socio-economic condition, might have access to early diagnosis. Information on each individual LDCT screening (including NCN characteristics), smoking cessation history, and the whole process of assessment should be registered in a national lung screening registry and evaluated to optimize the screening regimen. Cancer registry with adequate collection of lung cancer characteristics, must be a partner in the monitoring and outcome evaluation, improving reporting of the impact of new biological markers and therapies.

The implementation of LDCT screening in the US real world has arisen concerns about possible harms and low uptake. Incze & Redberg stated: "*the future depends on the ability to re-examine and refine the approach to patient selection and clearly communicate risks and benefit*" (49). Other problems, as the high rate of false positive, low detection rates and incidental findings were, among others, showed to be critical and not sufficiently addressed in current practice.

In Europe the path to an evidence-based screening practice is narrow and the risk of a spontaneous, uncontrolled use or, on the other side, the abandon of the lung cancer screening opportunity is increasing. The NELSON outcomes could modify the evidence-based decisions in Europe and, if negative, discourage the implementation of a public health program. Nonetheless, improvement of lung cancer primary prevention, early diagnosis, treatment and care must continue to be considered a top priority. The key issues discussed in this paper need to be supported by training of professionals, information system design, quality assurance and impact monitoring systems, all essential infrastructures for the continuous improvement of lung cancer care (50).

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Footnote

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