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Lung cancer screening in Brazil: recommendations from the Brazilian Society of Thoracic Surgery, Brazilian Thoracic Association, and Brazilian College of Radiology and Diagnostic Imaging

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ABSTRACT

Although lung cancer (LC) is one of the most common and lethal tumors, only 15% of patients are diagnosed at an early stage. Smoking is still responsible for more than 85% of cases. Lung cancer screening (LCS) with low-dose CT (LDCT) reduces LC-related mortality by 20%, and that reduction reaches 38% when LCS by LDCT is combined with smoking cessation. In the last decade, a number of countries have adopted population-based LCS as a public health recommendation. Albeit still incipient, discussion on this topic in Brazil is becoming increasingly broad and necessary. With the aim of increasing knowledge and stimulating debate on LCS, the Brazilian Society of Thoracic Surgery, the Brazilian Thoracic Association, and the Brazilian College of Radiology and Diagnostic Imaging convened a panel of experts to prepare recommendations for LCS in Brazil. The recommendations presented here were based on a narrative review of the literature, with an emphasis on large population-based studies, systematic reviews, and the recommendations of international guidelines, and were developed after extensive discussion by the panel of experts. The following topics were reviewed: reasons for screening; general considerations about smoking; epidemiology of LC; eligibility criteria; incidental findings; granulomatous lesions; probabilistic models; minimum requirements for LDCT; volumetric acquisition; risks of screening; minimum structure and role of the multidisciplinary team; practice according to the Lung CT Screening Reporting and Data System; costs versus benefits of screening; and future perspectives for LCS.

Keywords: Lung neoplasms; Early detection of cancer; Tomography, X-ray computed; Tobacco use disorder.

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INTRODUCTION

Lung cancer screening (LCS) using low-dose CT (LDCT) of the chest has become the gold standard in the preventive approach to the population at high risk for lung cancer (LC). Over the last decade, various countries have adopted periodic population screening with LDCT as a public health recommendation, following the guidelines of specialized medical societies.

In Brazil, albeit still incipient, discussion on this topic is increasingly broad and necessary. To expand the knowledge of and stimulate debate regarding LCS, the *Sociedade Brasileira de Cirurgia Torácica* (SBCT, Brazilian Society of Thoracic Surgery), the *Sociedade Brasileira de Pneumologia e Tisiologia* (SBPT, Brazilian Thoracic Association), and the *Colégio Brasileiro de Radiologia e Diagnóstico por Imagem* (CBR, Brazilian College of Radiology and Diagnostic Imaging) convened a panel of experts to prepare these initial recommendations.

These recommendations are intended for all medical professionals involved in caring for patients with risk factors for LC. The group that conceived and coordinated the recommendations, including members from the SBCT, SBPT, and CBR, presented questions and general themes to the panel of 21 experts, who, in virtual meetings, defined the most relevant topics to be covered.

Each theme or question was written by two or three of the authors, on the basis of a narrative review of the current, most relevant evidence in the literature and internationally accepted guidelines. That was followed by two phases of text harmonization. In the first, four experts discussed and restructured the texts sent by the others, and, in the second, all of the experts reviewed, discussed, and validated the final text.

CONCEPTS ABOUT SCREENING AND WHY TO SCREEN

- Diagnosing LC at an early stage reduces mortality and healthcare costs.
- In organized screening, the target population is invited and monitored at a defined periodicity, within an examination quality program and decision flowcharts.
- These are challenges for implementing screening programs in Brazil:
  - Budgetary limitations
  - Heterogeneity in the distribution of human resources and equipment
  - Sociocultural barriers
  - Lack of public health policies appropriate to the levels of prevention

Despite the growing number of advances in the diagnosis and treatment of LC, there are an estimated 2.2 million new cases and more than 2 million deaths each year worldwide, with an estimated 31,270 new cases and 27,000 deaths in Brazil.[1,2] Of the new cases in Brazil, only 15% are diagnosed in stage I, which is potentially curable[3]; that translates to an overall five-year survival rate of less than 20%.

The clinical results in LC are directly related to the stage of cancer at the time of diagnosis. Screening and early detection significantly reduces the mortality associated with the disease. The impact can go beyond that, including lower public health expenditures, because the cost of treatment is lower for patients with early-stage LC than for those with advanced-stage LC.[4]

Screening is characterized by the application of tests in asymptomatic individuals, in a defined target population, with the aim of reducing the morbidity and mortality attributed to a specific disease.[5] The WHO classifies screening as one of two types:

1. Opportunistic—Examinations are carried out on the basis of patient demand or are offered by the health care professional during a health care visit.
2. Organized—The target population is invited and monitored at a defined frequency, within a quality program for examinations and following decision flow charts.

Screening for various cancers, such as prostate, skin, breast, uterine, and colorectal cancer, has been a reality for decades. Combining LCS with multidisciplinary management can also be cost-effective and is one of the best alternatives to minimize the consequences. However, it remains a major challenge in various countries, including high-income countries, where it is still limited in comparison with the screening for other neoplasms.

To diagnosis LC early and reduce mortality, a number of studies conducted in recent decades have evaluated LCS strategies. Initial protocols based on sputum smear cytology and chest X-ray proved to be innocuous.[6] Studies based on the Early Lung Cancer Action Project[7] and International Early Lung Cancer Action Project trials,[8] designated the ELCAP and IELCAP trials, respectively, have shown LDCT to be a method that is sensitive, safe, and feasible for early diagnosis. That was confirmed in 2011 by studies employing data from the National Lung Screening Trial (NLST),[9,10] which evaluated 53,454 high-risk volunteers, demonstrating a rate of positivity (positive nodule ≥ 4 mm) on LDCT of 39%, with confirmation of LC in 1% and a 20% reduction in cancer mortality.[9,10]

Some studies of LCS in Europe, with smaller sample sizes, did not show significant differences in LC mortality or overall mortality.[11-14] In Brazil, a prospective study, designated the First Brazilian Lung Cancer Screening Trial (BRELT1),[15] evaluated 790 volunteers with eligibility criteria similar to those of the NLST and showed the occurrence of positive findings to be 46% higher than in the NLST, with biopsies performed in 3.1% of the patients and cancer diagnosed in approximately 1.3%. The BRELT1[15] demonstrated that, despite there being a greater number of nodules > 4 mm, the prevalence of neoplasia was similar to that reported in the NLST.[9,10]

In 2020, the results of a study conducted in the Netherlands and Belgium, designated the NELSON trial (Registration no. NL580),[16] with a sample of 15,792 volunteers, showed a rate of positivity on LDCT (positive nodule: 500 mm^3, approximately 10 mm) of 6.5%, and LC was confirmed in 2.1% of the cases evaluated. The NELSON trial also showed that, over a period of 10 years, there were reductions in the risk of death from cancer of 24% in men and more than 60% in women.[16]

A systematic review of data from 84,558 volunteers up to 2020, showed a 17% reduction in the risk of death from LC, albeit without evidence of a reduction in overall mortality.[17]

A more recent study, designated the BRELT2,[18] evaluated 3,470 individuals undergoing screening with LDCT at six different centers in Brazil. In that study sample, the prevalence of LC was 2.1%. It is noteworthy that, in 51% of those cases, LC was diagnosed at an early stage. The data confirm that, despite the obstacles, LCS is feasible in Brazil, with results similar to those reported for other countries.

Based on this evidence, international societies and expert panels began to recommend performing LCS with LDCT, although questions regarding feasibility, cost-effectiveness, and access still stand between the recommendations and the practical implementation of this strategy, especially in public health care systems.[19,20]

The use of LCS assumes that symptomatic disease is preceded by a period of presymptomatic disease detectable by LDCT. The interval of time between detection by screening and the time at which the neoplasm would be detected by the onset of its clinical manifestations is called the lead time (LT). According to most estimates, LT values for LC detection by LDCT range from 0.9 years to 3.5 years. Real-world studies that report mortality after LC diagnosis are subject to the so-called LT bias, although adjustments to the methods, aimed at minimizing that bias, have been proposed.[21]

A more adequate assessment of NLST data should also consider overdiagnosis and LT bias. The magnitude of overdiagnosis depends critically on the duration of follow-up after final screening.[21] In the NLST, the maximum follow-up period was initially 7 years but was later extended to 11.3 years.[9,10] After that extension, the overdiagnosis rate during the entire NLST period, originally predicted to be zero, was 3%. Using life expectancy gain instead of adjusting (for LT bias) for the expected number of lives saved overestimated the efficacy of life expectancy gain in the NLST by 38%.[21]

There are still a number of challenges to overcome before screening programs can be implemented in Brazil, such challenges including budgetary limitations, as well as the heterogeneous distribution of human resources and equipment in the public and private health care systems. In addition, cultural barriers, between patients and between physicians, indicate the need to construct health policies that encompass approaches aimed at each level of prevention.[22,23]

GENERAL CONSIDERATIONS ABOUT SMOKING

- In Brazil, 9.3% of adults are smokers.
- Smoking cessation increases the efficacy of screening programs.
- Stopping smoking reduces the risk of complications and mortality from chronic diseases, including cancer, as well as increasing life expectancy and quality of life.
- The foundations of smoking cessation are determination, behavioral support, and pharmacological treatment.

Smoking is the leading cause of chronic noncommunicable diseases and causes dozens of types of cancer, being responsible for more than 85% of all cases of LC.[24,25]

Tobacco can be consumed without combustion, by using *snus* or snuff, or with combustion and smoke inhalation, by using cigars, pipes, cigarettes, or hookahs.[26,27] In recent years, the use of electronic smoking devices (ESDs) has skyrocketed in many countries, including Brazil.[28-34] Although they release fewer substances harmful to health, new generations of ESDs release aerosols with greater amounts of nicotine, heavy metals, and fine particulate matter than do regular cigarettes, with cardiovascular and respiratory risks, as well as risks of cancer and death.[29,35] One recent study detected nearly 2,000 substances in ESDs,[36] and another showed that ESD users are at a three times greater risk of becoming smokers of regular cigarettes than are individuals who have never used an ESD.[37]

The proportion of individuals who consume tobacco products worldwide is trending downward for the first time in decades; it was 23.6% in 2020.[38] Tobacco control policies instituted in Brazil a few decades ago helped to substantially reduce tobacco consumption rates, according to the Telephone-based System for the Surveillance of Risk and Protective Factors for Chronic Diseases, from 35% in the 1980s to 9.3% in 2023.[34,39-41]

In 2015, cigarette smoking in Brazil resulted in the expenditure, in Brazilian reals (R$), of R$56.9 billion related to health care, disability, and deaths, whereas only R$12.9 billion were collected in the form of taxes on the manufacture and sale of tobacco products.[42]

Quitting smoking increases life expectancy, improves quality of life, and reduces the risks/complications associated with dozens of diseases, as well as reducing health care costs.[43,44] Smoking cessation also reduces LC mortality by a magnitude comparable to that of screening (20%), and the reduction is even greater (38%) when both strategies are implemented.[45] In addition, survival after surgical treatment for early-stage LC is better among patients who have

quit smoking than among those who have not.[46] Therefore, it is essential to identify smokers and incorporate smoking cessation strategies into LCS protocols.

Quitting smoking is not an easy task, because of the combination of physical dependence, psychological dependence, and conditioning.[44,47-50] Smoking cessation treatment is based on the decisiveness/determination and motivation of the smoker, together with behavioral counseling and support (BCS) and the use of first-line medications.[43,44,47-50]

The foundations of BCS are the identification of situations that create a risk of relapse and the development of coping strategies through skills training. That support can be provided through a brief/minimal approach, in just a few minutes, by any and all health care professionals during routine care, and consists in interviewing, evaluating, and advising smokers in order to prepare them to quit smoking, comprising a basic approach, in which patients are monitored for the first few weeks after quitting smoking, and an intensive approach, in which at least seven sessions, each lasting at least 10 min, are held at specialized facilities.[43,44,47-50]

First-line medications are divided into two groups[43,44,48-50]: nicotinic medications, collectively known as nicotine replacement therapy (NRT), including nicotine patches, gum, and lozenges; and non-nicotinic medications, including bupropion, antidepressants, and varenicline, the last being a nicotinic receptor inhibitor that is temporarily unavailable in several countries, including Brazil.

The success rate of treatment with bupropion is similar to that of NRT, and both have success rates lower than that achieved through treatment with varenicline.[51-54] The choice of medications is individualized, monotherapy is generally sufficient, and the usual duration of treatment is 3 months. Combining more than one medication can increase the success rate in patients who have greater difficulty in quitting smoking.[48-53,55] Recently issued guidelines recommend the use of varenicline or the combination of two NRTs as the first option to initiate treatment for patients with heart disease, lung disease, or cancer.[56-58]

Because ESDs are not medications for smoking cessation, first-line medications should be preferred,[55,59] and the majority of smokers who stop smoking by switching to an ESD continue to use ESDs, which perpetuates their dependence on nicotine and increases the health risks they face.[60]

In Brazil, intensive smoking cessation treatment can be provided via the *Sistema Único de Saúde* (SUS, Unified Health Care System), free of charge, at primary health care clinics in municipalities; via some supplementary health care networks; and via private physician offices and clinics.

BASIC ASPECTS AND EPIDEMIOLOGY OF LC

- Smoking continues to be the main cause of LC.
- LC is one of the most common and lethal types of tumor.
- Only 15% of LCs are diagnosed at an early stage, when they are potentially curable.

For decades, smoking has been the most relevant risk factor for LC. Therefore, some of the most effective tobacco control measures are counseling to avoid taking up the habit of smoking, especially for young people, and advising current smokers to stop smoking as soon as possible.

There are two main types of LC: small-cell lung cancer and non-small-cell lung cancer (NSCLC). More than 80% of all cases of LC are NSCLC, which is divided into three subtypes[61]: adenocarcinoma, squamous-cell carcinoma, and large-cell carcinoma.

A retrospective cohort study in Brazil showed a 30% decrease in the proportion of cases of small-cell lung cancer between the 1997-2002 and 2002-2008 periods.[62] Another nationwide epidemiological study involving more than 35,000 cases of NSCLC reported a change among the NSCLC subtypes in Brazil from 2003 onwards—adenocarcinomas accounting for 43.3% of cases and squamous-cell carcinomas accounting for 36.5%.[63]

Worldwide, LC is the leading cancer in men and the third leading cancer in women; in Brazil, it is the third leading cancer in men and the fourth leading cancer in women, with the exception of non-melanoma skin cancer.[64] In Brazil, 31,270 new cases of LC and approximately 27,000 LC-related deaths are recorded annually.[2] Only 15% of patients with LC are diagnosed at an early stage, when the disease is potentially curable, which translates to an overall five-year survival rate

Table 1. Stages of lung cancer at diagnosis in studies carried out in Brazil.

Authors	N	Type of institution	NSCLC	Early stage (I/II)
Ismael et al.[62]	1,887	Public	89%	16%
Younes et al.[66]	737	Public	100%	22.5%
Costa et al.[67]	3,167	Public	90.8%	13.3%
Westphal et al.[68]	352	Public	91%	19%
Barros et al.[69]	263	Public	87%	6%
Novaes et al.[70]	240	Public	80%	28.2%
Araujo et al.[71]	566	Private	100%	20.4%
Mascarenhas et al.[72]	338	Private	83%	21.8%

NSCLC: non-small-cell lung cancer.

of less than 20% (Table 1).[62,65-72] Therefore, despite advances in diagnosis and staging—mainly in clinical treatment (targeted therapies and immunotherapy) and surgical treatment (video-assisted surgery and robotics)—the morbidity and mortality associated with LC remains high, as do its personal, family, public health, and supplementary health costs.

One of the reasons for a tumor being diagnosed at an advanced stage is the delay in diagnostic procedures via the SUS, such as CT and PET/CT, which are difficult to access in some regions of Brazil.[61]

In 2006, Barros et al.[69] reported that only 20% of patients with suspected LC had access to diagnostic CT. Nearly 90% of the patients in their cohort were diagnosed by chest X-ray.[69] Another study conducted in Brazil estimated that the median time from the onset of symptoms to diagnosis is 3 months.[73] That situation becomes even more complicated because few public health care facilities provide diagnostic procedures such as bronchoscopy and transthoracic biopsy.[61] The implementation of screening programs in the SUS will facilitate the development of regional LC diagnostic services in Brazil.

SCREENING ELIGIBILITY CRITERIA

- Eligibility criteria
  - Being a smokers/former smoker, being ≥ 50 years of age, and having a smoking history > 20 pack-years
- Exclusion criteria
  - Being > 80 years age
  - Having quit smoking > 15 years prior
  - Having symptoms suggestive of or a history of LC
  - Having a functional status or comorbidity that precludes curative treatment

The most important benefit of LCS is the increase in the number of cases diagnosed at an early stage (stage I or II) and the consequent reduction in that of those diagnosed at an advanced stage (stage III or IV).[74]

Studies using NLST data have demonstrated that LC-related mortality, in three annual rounds, was significantly lower when LCS employed LDCT than when it employed chest X-ray.[9,10] The incidence rate was 0.85, and the number needed to screen (NNS) to prevent one death was 323 over 6.5 years of follow-up.[10] Another study demonstrated a reduction in LC-related mortality in four rounds of follow-up, with an incidence rate of 0.75, and the NNS to prevent one death was 130 over 10 years of follow-up.[75]

Although there are variations in the inclusion criteria for LCS, the main international recommendations are based on the two largest trials (the NLST and the NELSON trial),[7,9,14-16,76-82] as detailed in Table 2.

On the basis of previous studies and microsimulation models, the U.S. Preventive Services Task Force (USPSTF) established, in 2013, guidelines for "real life" screening in the United States,[74,75] with the following inclusion criteria: being 55-74 years of age; having a smoking history of at least 30 pack-years; and having quit smoking less than 15 years prior.

At that time, the USPSTF guidelines did not take into account interracial differences in smoking patterns and LC risk, as had previously been demonstrated.[83,84] A few years after the screening program had been implemented in real-life scenarios (outside of clinical studies), it became obvious that there was a need to take such differences into account.

Aldrich et al.[85] found that the proportion of individuals diagnosed with LC who would not have been eligible for screening in the United States was higher among African-American smokers than among White smokers. That is because African-Americans typically develop LC with a smoking history of less than 30 pack-years and before 55 years of age. Therefore, it has been suggested that the smoking history criterion be reduced to 20 pack-years and that the age criterion be reduced to 50 years. Those new criteria were promptly adopted by the USPSTF and the National Comprehensive Cancer Network.[86,87]

Given such evidence, this panel of experts recommends that the inclusion criteria for LDCT screening consist of the following:

- Being a smoker or former smoker, ≥ 50 years of age
- Having a smoking history of more than 20 pack-years or having quit smoking less than 15 years prior

Screening should be discontinued when the volunteer is over 80 years of age or has been smoke-free for more than 15 years.

The exclusion criteria for screening are as follows[85-87]:

- The presence of symptoms highly suggestive of LC
- A history of LC
- Functional status or comorbidity that would prevent treatment with curative intent, given that the patient must be fit to undergo lung resection

It is recommended that the decision to start the screening program be shared between the individual and the multidisciplinary team, and that all smokers be encouraged to participate in BCS programs to quit smoking. That should permeate all consultations; it should be borne in mind that screening is not a substitute for smoking cessation.

The greatest challenge is still establishing the definition of a high-risk patient and, therefore, determining the inclusion criteria so that annual screening is even more cost-effective. In brief, it is necessary to improve the criteria for selecting asymptomatic individuals exposed to the main risk factors for LC, given that the relative risk of developing the disease increases in parallel with advancing age.

It is worth highlighting, however, that the recommendations above were based on population-level data from other countries. There is a need for studies on the appropriateness of these positivity criteria for use in the population of Brazil.

Table 2. National and international studies of lung cancer screening.

Authors	Study acronym	Participants*	Inclusion criteria	Positivity n (%)**	Biopsy n (%)	LC n (%)
National Lung Screening Trial Research Team et al.[9]	NLST	26,722	A 55-74 y; CS or FS (SF ≤ 15 y); SH ≥ 30 p-y	7,191 (27)	758 (2.8)	270 (1.0)
de Koning et al.[16]	NELSON	6,583	A 50-74 y; CS or FS (SF ≤ 12 y); SH ≥ 30 p-y	467 (2.1)	-	203 (0.9)
Henschke et al.[7]	ELCAP	1,000	A ≥ 60 y; SH ≥ 10 p-y; no previous cancer; clinically fit for thoracic surgery	233 (23)	28 (2.8)	27 (2.7)
Gohagan et al.[76]	LSS	1,586	A 55-74 y; CS or FS (SF ≤ 10 y); and SH ≥ 30 p-y	325 (21)	57 (3.6)	30 (1.9)
Wilson et al.[77]	PLuSS	3,642	A 50-79 y; CS or FS (SF ≤ 15 y); smoked ≥ 25 y and ≥ 10 cig/day; and body weight < 180 kg	1,477 (41)	90 (2.5)	36 (1.0)
Infante et al.[14]	DANTE	1,276	Male; A 60-74 y; CS or FS (SF < 10 y); and SH ≥ 20 p-y	199 (15)	52 (4.1)	28 (2.2)
Lopes Pegna et al.[78]	ITA LUNG	1,406	A 55-69 y; CS or FS (SF ≤ 10 y); and SH ≥ 20 p-y	426 (30)	22 (1.6)	21 (1.5)
Saghir et al.[79]	DLCST	2,052	A 50-70 y; CS or FS (SF < 10 y and > 50 y of A); SH ≥ 20 p-y; able to climb 36 steps without stopping	594 (29)	25 (1.2)	17 (0.8)
Becker et al.[80]	LUSI	2,029	A 50-69 y; CS or FS (SF ≤ 10 y); smoked ≥ 25 y and ≥ 15 cig/day or ≥ 30 y and ≥10 cig/day	540 (27)	31 (1.5)	22 (1.1)
Santos et al.[15]	BRELT1	790	A 55-74 y; CS or FS (SF ≤ 15 y); and SH ≥ 30 p-y	312 (39.5)	25 (3.1)	10 (1.3)
Hochhegger et al.[18]	BRELT2	3,470	A 55-74 y; CS or FS (SF ≤ 15 y); and SH ≥ 30 p-y	218 (6.3)	122 (3.1)	74 (2.1)
Chiarantano et al.[81]	--	233	A 55-74 y; CS or FS (SF ≤ 15 y); and SH ≥ 30 p-y	38 (16.3)	3 (1.3)	3 (1.3)
Svartman et al.[82]	--	712	A 55-80 y; CS or FS (SF ≤ 15 y); and SH ≥ 30 p-y		-	11 (1.5)

LC: lung cancer; A: age; y: years; CS: current smoker; FS: former smoker; SF: smoke-free; cig/day: cigarettes/day; SH: smoking history; and p-y: pack-years. *CT-arm patients only. **Refers to tests considered positive according to the methodology used in each study. The disparity between the proportions is due to variations in the positivity criteria over the years and the number of rounds of tests carried out in each study.

The criteria for indicating LCS are summarized in Figure 1.

INCIDENTAL FINDINGS ON LDCT AND THEIR IMPLICATIONS

- Incidental findings on LDCT that are unrelated to LC are mostly irrelevant.
- When the incidental findings are relevant and interpreted correctly, they can improve the cost-effectiveness of the examination, as well as the quality of life and life expectancy of those screened.

Incidental findings (IFs) are those that are unrelated to LC but can be identified on screening with LDCT (Chart 1). Most IFs are clinically insignificant and do not need to be reported, others require referral to specialists and further evaluation, and some require immediate medical intervention.[88,89]

Relevant findings, when interpreted correctly, can increase the benefits and cost-effectiveness of screening. However, findings without clinical significance identified through screening programs can lead to unnecessary investigations and additional costs.[90-92]

The prevalence of IFs in the chest or adjacent regions (the neck and abdomen) differs significantly between screening programs, with rates ranging from 41% to 94%, and their incidence is higher in the first LDCT. In the NLST, the IFs most commonly identified were related to the cardiovascular system (8.5%), followed by the kidneys (2.4%), liver/biliary tract (2.1%), adrenal glands (1.2%), and thyroid (0.6%).[93]

Among the cases in which there are IFs, additional investigation, including the use of other imaging methods, is required in 9-15%.[90] Of all of the deaths in the LDCT arm of the NLST, 10% were due to diseases other than LC.[10]

In the NLST, overall mortality was 6.7% lower in the group undergoing LDCT.[10] Therefore, it is possible that there is an advantage to LDCT in that it can identify other diseases, such as cardiovascular diseases (coronary arteriosclerosis, aortic aneurysm, pericardial thickening, and calcifications), COPD (emphysema

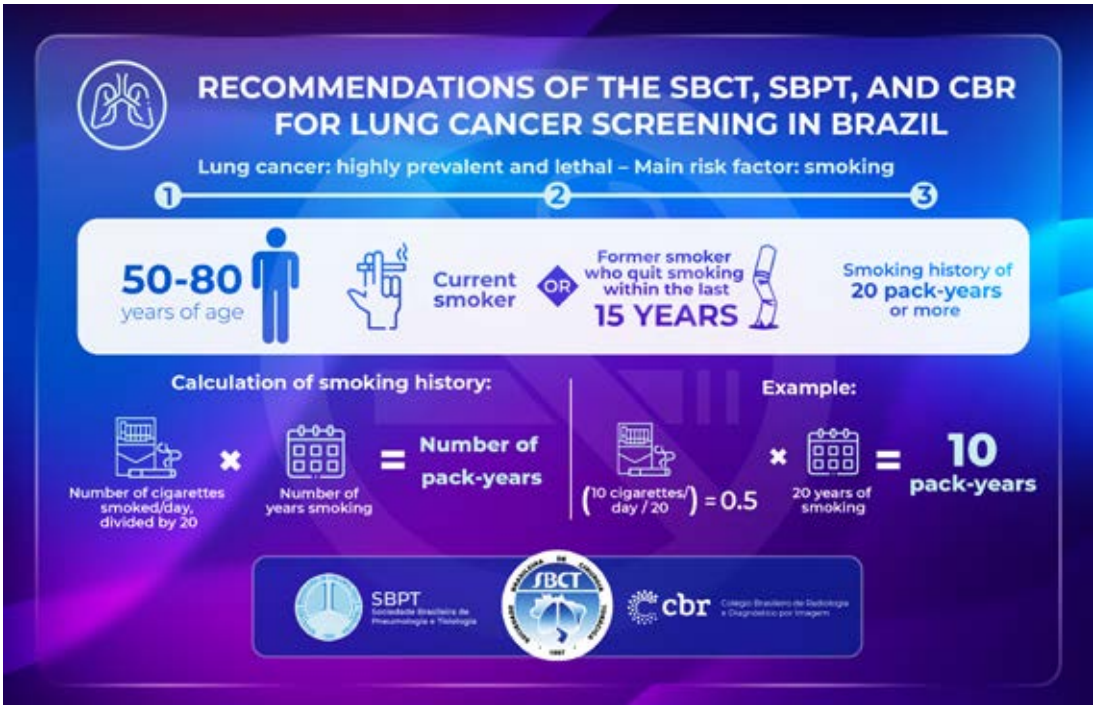

Figure 1. Eligibility criteria for lung cancer screening. SBCT: *Sociedade Brasileira de Cirurgia Torácica* (Brazilian Society of Thoracic Surgery); SBPT: *Sociedade Brasileira de Pneumologia e Tisiologia* (Brazilian Thoracic Association); and CBR: *Colégio Brasileiro de Radiologia e Diagnóstico por Imagem* (Brazilian College of Radiology and Diagnostic Imaging).

and thickening of bronchial walls), and other diseases related or unrelated to smoking (e.g., interstitial lung lesions, sarcopenia, osteopenia, diaphragmatic hernias, neck cancer, and tracheal neoplasia).[88,94] The main IFs are described in Table 2.[91,92,94]

CHANGES CONSISTENT WITH GRANULOMATOUS LESIONS

- The high prevalence of granulomatous diseases in Brazil is a challenge for the implementation and cost-effectiveness of LCS in the country.
- The need for adjustments to the nodule management algorithms for use in the population of Brazil should be taken into consideration.
- Algorithm-based assessment and multidisciplinary management can reduce the rates of positivity, false-positives, and unnecessary procedures, as well as bringing our rates of invasive procedures closer to those reported for high-income countries.

Chief among the various challenges for implementing LCS programs in low- and middle-income countries is the high prevalence of granulomatous diseases, which could increase the proportion of false-positive results, consequently increasing the number of diagnostic/surgical procedures and associated complications.[15,22,95,96] In recent data, the incidence of tuberculosis in Brazil was 45 cases/100,000 population, significantly higher than the 2 cases/100,000 population reported for the United States.[97]

In a study of LCS conducted in South Korea—the Korean Lung Cancer Screening Project (K-LUCAS), which used the Lung CT Screening Reporting and Data System (Lung-RADS) version 1.0—the proportion of positive results was higher among the patients with evidence of tuberculosis sequelae than among those without (21% vs. 16%) and a reported history of tuberculosis was associated with a positive screening result.[96] The authors also reported that the specificity and accuracy of LCS were lower for patients with tuberculosis sequelae than for those without (80% for both vs. 85% for both, respectively), indicating that false-positive results are associated with a history of infection. In addition, they detected no association between tuberculosis sequelae and a diagnosis of neoplasia at screening.[96]

In the first round of screening in the BRELT1, the positivity rate was 39.5%, significantly higher than that reported for other screening programs.[15] Although the biopsy rate in the BRELT1 (3.1%) was comparable to those of the largest screening studies, it is still difficult to extrapolate these results to Brazil as a whole because of the great epidemiological heterogeneity in the country.[98]

To implement LCS with LDCT in Brazil, it is possible that adjustments in nodule management are needed in order to reduce the rates of positive and false-positive results, thereby reducing the number of unnecessary procedures.

In the BRELT2,[18] which involved more than 3,000 patients from various regions of Brazil, the patients in whom the findings were characteristic of residual granulomatous inflammation, findings classified as

Chart 1. Categories of incidental findings on low-dose CT.

Incidental findings	Category	Recommendation	Incidence
Mild/moderate CAC; COPD*; mild/moderate aortic dilation; emphysema; bronchial wall thickening; degenerative skeletal changes; cysts (hepatic, renal, pancreatic, or splenic); hiatal hernia; other diaphragmatic hernias; pleural plaques; minimal pulmonary fibrosis; bronchiectasis; adrenal lesions < 10 HU; low-risk thyroid nodules (< 1.5 cm)	Low clinical relevance	*A priori* investigation not recommended	50%
Marked CAC; mediastinal adenopathy > 1 cm; adrenal lesions > 10 HU; compression fractures; breast nodules; suspicious thyroid nodules; aortic aneurysm 4.0-5.5 cm	Possible clinical relevance	Recommended investigation	10%
Opacities suggestive of pneumonia; aortic aneurysm ≥ 5.5 cm; lobar or segmental atelectasis; lesion suspected of being cancer; large pleural or pericardial effusions	Clinically relevant	Recommended therapeutic intervention	< 1%

Adapted from Mazzone et al.[90,91] CAC: coronary artery calcification. *Depending on the stage of the disease.

Lung-RADS category 3 or 4, were followed clinically. That same trend of clinical follow-up was observed in the K-LUCAS protocol.[18,96] The authors of that study proposed a separate category to indicate lesions with a benign appearance that were classified as Lung-RADS category 3 or 4, considering a downgrade in the classification of these lesions from the baseline examinations. For example, noncalcified nodules measuring at least 8 mm, adjacent to scarring/calcified nodules, are to be reclassified to a new category—category 2b (b = benign). For category 2b, follow-up examinations would be still be annual, rather than every 3 months.[96] Given that the epidemiological situation of granulomatous diseases in Brazil is closer to that seen in South Korea than to that seen in high-income countries, a national screening program in Brazil could benefit from that adjustment.

DO PROBABILISTIC MODELS REDUCE THE NUMBER OF FALSE POSITIVES?

- Yes, prediction models can improve clinical interventions, population care development and resource optimization
- However, it is necessary to validate such models for use in heterogeneous populations and to define the cutoff score for practices related to the cancer risk.

The success of every LCS program is directly related to the assessment of the risk group, which can be complemented with prediction models. Prediction models can improve clinical interventions and the development of care for the population, as well as being ancillary tools for optimizing resources.

After the publication of the study conducted by Bach et al.,[99] research into risk prediction models for LC intensified.[100] Such probabilistic models, which were based on traditional variables, biomarkers, LDCT, and data exploration techniques, currently have good sensitivity and specificity. The most commonly used traditional variables are smoking intensity, occupational exposure to asbestos, the presence of emphysema, COPD, or pneumonia, and a family history of LC.[101]

The 2012 Prostatic, Lung, Colorectal and Ovarian Cancer Screening Model (PLCOm2012) was developed in smokers in the control arm of the PLCO study.[102] In comparison with the USPSTF criteria, the PLCOm2012 criteria include more personal factors (e.g., history of malignancy), a more detailed smoking history, family history, and the personal history of COPD.

The Lung Cancer Risk Assessment Tool risk model and Lung Cancer Death Risk Assessment Tool risk model were developed and validated in the control and chest X-ray arms of the PLCO study, respectively.[103,104]

Other LC risk models include the Kovalchik model, the Bach model, the Liverpool Lung Project model (and its simplified version), the Knoke model, the Hunt Lung Cancer model, and three two-stage clonal expansion models that predict the incidence of and death from LC.[105,106] Such models have included a variety of additional risk factors,[105,106] such as smoking intensity (cigarettes per day); occupational exposure to asbestos; emphysema, COPD, and pneumonia; and family history of LC.

The results are estimated by applying each risk model to previous cohorts, which serves as external validation. However, there is currently no consensus regarding the cutoff point that should be applied to LCS prediction models. In other words, the percentage of risk on which the recommendation for LCS should be based has not been defined.

In a systematic review of three different risk prediction models (a modified version of the PLCOm2012, the Lung Cancer Death Risk Assessment Tool model, and the Kovalchik model), estimation of outcomes in four different cohorts showed greater prevention of mortality in comparison with the risk factor-based criteria used by the NLST or USPSTF (2013 recommendations).[107]

Three of those studies demonstrated that screening efficiency (determined by the NNS) was better when

Chart 2. Incidental findings on low-dose CT.

Intrathoracic abnormalities
Cardiovascular
• They are common and cause more deaths than does LC. LDCT without ECG synchronization has a high false-negative rate.
• CAC: The identification of calcifications can help predict and reduce morbidity and mortality from cardiovascular diseases.
◦ Standardization in the description and consensus regarding its diagnostic criteria and clinical significance are necessary.
◦ The Society of Cardiovascular Computed Tomography and the Society of Thoracic Radiology confirm the combined use of LDCT in LCS and the CAC score as predictors of the risk of cardiovascular deaths in asymptomatic patients.
◦ CAC scores by LDCT are applied through visual analysis.[b]
• Aortic aneurysm: Aortic dimensions increase with age and should be described in asymptomatic individuals.
◦ At 70 years of age, the ascending and descending segments measure up to 3.5 cm and 2.7 cm, respectively.
◦ Dilation becomes classified as an aneurysm when it is 50% greater than the normal diameter.
◦ There is no recommendation to investigate aneurysms, unless there is a family history or associated genetic defect.
◦ There are recommendations for annual or biennial monitoring of aneurysms, depending on their size, type, and location.
◦ Aneurysm surgery (in the ascending or descending segment) is recommended if the diameter is ≥ 5.5 cm.[c]
COPD
• Individuals screened for LC are four times more likely to present changes suggestive of COPD (thickening of the bronchial walls, air trapping, hyperinflation, and emphysema) on LDCT.[a]
• Patients with COPD have a two to three times higher risk of developing LC.
• One third of individuals screened for LC have COPD, and its early detection can reduce morbidity and mortality.
Extrathoracic abnormalities[c]
Neck
• The *American College of Radiology* does not recommend further investigation for thyroid lesions ≤ 1.5 cm in patients > 35 years of age and without suspicious findings (invasion of adjacent structures or abnormal lymph nodes) and recommends ultrasonography for lesions > 1.5 cm or with findings suspicious for neoplasia.
Abdomen
• Liver: Changes are common, and most do not require additional investigation, especially lesions < 1.5 cm and findings suggestive of benignity (well-defined, homogeneous margins, and < 20 HU)
• Pancreas: Cystic lesions should be monitored by imaging.
• Gallbladder: Stones, calcifications, mural thickenings, distension, and polyps ≤ 6 mm do not require follow-up.
◦ Ultrasonography is useful for evaluating polyps measuring 7-9 mm and indicating cholecystectomy for lesions ≥ 10 mm
• Spleen: Homogeneous lesions, with ≤ 20 HU and thin walls, do not require further investigation.
• Kidneys: Small, homogeneous lesions with a density of −10 to 20 HU or > 70 HU do not require further investigation.
◦ MRI is recommended for lesions with a density of 21-69 HU, heterogeneous lesions or lesions with a density ≤ 10 HU with multiple calcifications or a calcification > 4 cm.
• Adrenal lesions < 1 cm, measuring 1-4 cm with < 10 HU, or that are stable for more than 1 year do not require additional testing; in other situations, it is recommended that other imaging methods (CT, MRI, or PET) be used.

LDCT: low-dose CT; CAC: coronary artery calcifications; LC: lung cancer; LCS: lung cancer screening; and ECG: electrocardiogram. [a]Based on Gierada et al.[94]. [b]Based on Kauczor et al.[92]. [c]Based on Mazzone et al.[90].

screening employed risk prediction models than when risk factor-based screening was used, whereas one study showed mixed results.[108]

A recent study of LCS in Brazil demonstrated that the yield of LDCT screening is lower in low-risk individuals than in high-risk individuals, the rates of positivity and LC detection being significantly lower in the former.[109] Therefore, screening low-risk patients could increase the number of LDCT examinations because of the lower diagnostic yield, resulting in increased costs compared with screening only the high-risk population. However, incorporating the PLCOm2012 with a 6-year LC risk ≥ 0.0151 as the eligibility criterion appears to increase the efficacy of LCS.[109] In that same study, the false-positive rate for the PLCOm2012 criteria was lower than was that for the NLST criteria, indicating a possible improvement in screening efficiency, even in a country with a high incidence of granulomatous diseases like Brazil.[109]

In general, the LC risk models are highly accurate, indicating that their use is viable for identifying high-risk populations. However, the model development process and the reports generated from the models are still not ideal, because they present a high risk of bias,

which limits their credibility and predictive accuracy, thus hindering their promotion and development.

MINIMUM REQUIREMENTS FOR LDCT

- Slice thickness ≤ 2.5 mm, preferably ≤ 1.0 mm
- Gantry rotation time of ≤ 500 ms
- Chest scanning time < 10 s
- Tube voltage of 100-120 kVp (for standard-sized patients)
- Tube current (mAs) preferably automatically modulated by the CT device
- Volumetric dose index of 3 mGy—effective radiation dose ≤ 1 mSv (for standard-sized patients)—the maximum radiation dose established for screening

Fundamental technical parameters for LCS using LDCT have been recommended by major international societies, especially the American College of Radiology (ACR) and the Society of Thoracic Radiology.[110]

The LDCT images should be acquired in scanners with at least 16 detector rows, with the helical technique and without intravenous administration of iodinated contrast. Obviously, the scan must cover the entire lungs, and it is extremely important that the patient performs a deep inspiration and adequate breath-hold, in order to guarantee the quality of the images, avoiding artifacts that could hinder the analysis of the examination.[110]

The slice thickness should be ≤ 2.5 mm, preferably ≤ 1.0 mm, and the gantry rotation time should be ≤ 500 ms. A chest scanning time of < 10 s is recommended.

For standard-sized patients (height, 170 cm; weight, 70 kg), the tube voltage should be set to 100-120 kVp, and the tube current (mAs), although it can be fixed, should preferably be modulated automatically by the CT scanner, which takes into account the physical characteristics of the patient, the tube voltage, and the table pitch (typically 0.7-1.5).

The maximum radiation dose established for LCS using LDCT corresponds to a volumetric dose index of 3 mGy—effective radiation dose ≤1 mSv—for a standard-sized patient, with appropriate dose reductions and increases for smaller and larger patients, respectively,[111] always following the premise that tomography should be performed with the lowest possible dose of radiation that guarantees a good quality diagnostic examination.

Suggested protocols for performing LDCT on a variety of devices from major manufacturers are available on the website maintained by the American Association of Physicists in Medicine.[74,75]

It is noteworthy that, in the wake of constant and important technological advances in the area, the most modern CT scanners currently available have features such as iterative reconstruction and deep learning, making it possible to obtain images of better quality (with less noise), even with greatly reduced radiation doses.

The radiation dose employed in LDCT is equivalent to approximately one-fifth of that of a "standard-dose" chest CT, and one-quarter of the average background radiation to which a person is exposed over the course of a year in the United States. The risk of radiation-induced malignancies in patients undergoing LCS with LDCT is considered low; greater attention should be paid to other risks such as false-positive results, overdiagnosis, and IFs without clinical relevance, which can prompt unnecessary additional interventions and generate anxiety in patients.[112]

After the examination has been performed, at least two image volumes should be reconstructed: one with a "standard" filter for evaluating soft tissues (including, for example, mediastinal structures); and another with a "lung" filter, which provides greater "spatial" (i.e., anatomical) resolution for evaluating the lung parenchyma, as well as for measuring and analyzing the contours of any nodules detected. Maximum intensity projections and multiplanar (coronal and sagittal) reconstructions are recommended for the detection and characterization of nodules, respectively.[113]

NODULE POSITIVITY CRITERIA: TWO-DIMENSIONAL MEASUREMENT VS. VOLUMETRY

- Potential gains when using volumetric measurement:
  - Greater reproducibility of measurements
  - Three-dimensional assessment of nodules
  - Increased sensitivity for assessing nodule growth
- Potential challenges when using volumetric measurement:
  - Difficulties in segmenting nodules adjacent to other lung structures
  - Difficulty in the assessment of subsolid nodules
  - Differences between measurements determined by different software
  - Variations according to CT reconstruction protocol
  - Issues related to equity in the availability of software throughout Brazil

Although several aspects, such as attenuation, shape, and location, should be considered when evaluating pulmonary nodules; size and growth are assumed to be the most important variables in estimating the probability of malignancy.[114] Regarding those two parameters, there are variations in nodule management algorithms in the screening protocols proposed to date, which differ in terms of positivity criteria and growth indicators. Therefore, the choice between linear measurements and volumetry is a sensitive point. For example, the NLST (conducted in the United States), as well as the BRELT1 and BRELT2 (both conducted in Brazil), used linear measurements in the assessment of solid nodules, whereas the NELSON trial primarily used volumetry, as have other European screening algorithms.[9,10,15,16,18]

The management protocol first suggested by the ACR—Lung-RADS, version 1.1—used linear measurements (specifically, calculating the mean nodule diameter to the first decimal place); however, volumetric notation was included as a possibility (ACR Lung-RADS 2019), a feature that was maintained in the latest version (ACR Lung-RADS 2022).[115,116]

The NELSON trial defined nodule growth as a 25% increase in the volume of a solid nodule or the solid component of a subsolid nodule, with subsequent stratification based on the volume doubling time (VDT), whereas the Lung-RADS defined it as an increase of 1.5 mm in the mean diameter or of 2 mm^3 in volume.[16,115-117]

The potential gains achieved by using volumetry rather than linear measurements include greater reproducibility of measurements, three-dimensional assessment of nodules, and increased sensitivity for assessing nodule growth, allowing, for example, the calculation of VDT, which would be a better parameter for determining their behavior.[118]

The use of linear measurements to measure solid nodules is associated with significant intraobserver and interobserver variability. In a study conducted by Revel et al.,[119] changes in size < 1.7 mm had only a 5% chance of representing a real change in the size of the nodules, an aspect that could have an impact not only on the categorization of nodules and the positivity rate but also on the definition of their growth.

In a study evaluating the categorization of solid nodules within the Lung-RADS criteria, interobserver agreement on the dimensions of nodules was found to be better when automated volumetric assessment was used than when automated or manual diameter measurement was used, and automated volumetric assessment was found to result in some nodules being reclassified to lower categories.[120]

Lung nodule volume is determined through semi-automated or automated analysis with specific software based on segmentation. It should be borne in mind that calculating the volume of nodules directly from their diameters leads to a significant overestimation of that volume. Heuvelmans et al.[121] showed that calculating the volume of nodules directly from their diameters (thus assuming sphericity) overestimated that volume, in comparison with semi-automated volume analysis, by approximately 47.2% when the mean diameter was used and by 85.1% when the maximum diameter was used.

Although there are advantages to the use of volumetry, it poses many challenges in clinical practice, including the following[118]: difficulties in segmenting nodules that are adjacent to other lung structures (e.g., pleural and vascular interfaces); difficulty in the evaluation of subsolid nodules; differences between measurements determined by the various types of software and the versions thereof; variations according to the CT reconstruction protocol (slice thickness, overlapping images, and different reconstruction algorithms); and, as one can imagine, issues related to equity in the availability of software throughout Brazil. Regarding variations in the measurements of nodule volume when different software is used, Zhao et al.,[122] for example, compared the performance of software from three different manufacturers, finding variations of up to 50% when comparing the measurements acquired.

Given the potential and challenges of volumetry, it would be acceptable for screening programs based on nodule diameter measurements to consider including a volume equivalent in their management algorithms.[91]

RISKS ASSOCIATED WITH LCS

- Radiation exposure—relatively low risk with LDCT
- Patient anxiety, unnecessary examinations/interventions, and poorer quality of life, due to the following:
  - False-positive results
  - Overdiagnosis
  - Irrelevant IFs
  - Incorrect decisions

Note: In relation to education and appropriate guidance on LCS, these risks can be minimized through the work of the multidisciplinary team and shared practice.

Prospective participants in an LCS program should be informed, through various means of communication but especially through a detailed explanation from their physician, about the benefits and potential risks of their participation.

Participation should be well documented, and written informed consent should be obtained before any procedure is performed. The authorization granted should extend to planned visits to carry out LDCT at regular intervals, as well as to the use of data, including the description of health status, test results, and reports of adverse effects, in subsequent studies.[123]

The following are the main risks related to LCS with LDCT:

Radiation exposure—Irradiation associated with one LDCT scan ranges from 0.65 mSv to 2.36 mSv, and the cumulative exposure over 25 years of annual screening would be 20.8-32.5 mSv. For example, the mean irradiation during a PET/CT scan is 4 mSv. To date, there have been no studies estimating the overall risk of cancer in general or of fatal cancer induced by irradiation in annual screening up to 80 years of age.[74,75]

False-positive results—Any result that leads to additional investigation and which does not result in a diagnosis of cancer is considered a false-positive. The false-positive rate depends on a series of confounding factors, such as the nodule size considered positive, the use of VDT, and the characteristics of the nodule to be considered in each study. In cohort studies, the reported proportion of false positives ranges from 9.6% to 49.3% at baseline (prevalent round), and that rate decreases with each additional round of screening

(incident rounds), with a variation of 5.0-28.6%.[74,75] The false-positive rate in the baseline examination has been shown to be lower when a structured CT reading instrument with the Lung-RADS method is used than when the NSLT reading method is used (12.8% vs. 26.0%).[124]

The worst harm caused by a false-positive result is that it creates a need for diagnostic clarification, with or without invasive procedures.[74,75]

In a study involving 3,280 patients selected for LCS, 342 (10%) had category 4 findings according to the Lung-RADS reading. Of those, 100 (approximately 30%) were found to have LC, the vast majority diagnosed at an early stage, when the disease is potentially curable. That represents a 3% yield, and only 15 patients (0.45%) underwent some type of surgical procedure in which the result did not confirm cancer, with practically no morbidity and zero mortality.[125]

- Overdiagnosis—Overdiagnosis can be defined as the detection of cancer that would not have become clinically significant during the lifetime of the patient. The overdiagnosis rate ranges from 0% to 67%.[74,75] In a meta-analysis, it was observed that there is a significant increase in overdiagnosis during the follow-up period.[126]
- Psychological risk—Although participating in LDCT screening has not been found to worsen quality of life or anxiety over 2 years of follow-up, a significant increase in distress and anguish has been observed, especially in cases with indeterminate results.[127,128] The understanding that an early-stage cancer could be discovered during screening has served to overcome fears of undergoing an unnecessary procedure.[74,75,127,128]
- IFs—The rate of IFs varies greatly, depending on the definition of what is considered an IF and on the mean age of the study participants.[74,75,129] Although the detection of some IFs can cause distress, it can improve the diagnosis and early management of potentially serious diseases.

The risks of LCS are relatively low and can be reduced with a quality diagnostic assessment, practices based on valid algorithms, and the involvement of a multidisciplinary team.

MINIMUM STRUCTURE AND THE ROLE OF A MULTIDISCIPLINARY TEAM

- Screening centers
  - Multidisciplinary team for recruiting, as well as for the acquisition and interpretation of radiological images, with the ability to carry out the differential diagnosis in cases with positive results and appropriate treatment in cases of cancer
- Minimal structure
  - Access to a smoking cessation program
  - Radiology clinic with LDCT (low voltage, 16 channels)
  - Specialized team and standardized (Lung-RADS) description in reports
  - Access to PET/CT for diagnosis and preoperative staging
  - Interventional radiology and bronchoscopy to perform biopsies
  - Surgical center with the capability to perform thoracotomy and video-assisted surgery
  - Structure for patient navigation

An LCS program is established on a population basis and therefore requires an articulated organizational structure to reconcile two important aspects:

- It should be offered in the form of a large cohort with universal distribution, and there should therefore be centers that are close to the places of residence of the participants.
- There should be local or regional screening centers with multidisciplinary teams for recruiting, as well as for the acquisition and interpretation of radiological images, with the ability to carry out the differential diagnosis in cases with positive results and to provide appropriate treatment in cases of cancer.[123]

It is known that the cost-effectiveness of LCS increases when it is applied in conjunction with a smoking cessation program, and a program structured for that purpose should therefore be part of the minimum structure.[130,131]

Local and regional centers must be certified, authorized, and accredited by a national organization. The minimum structure for an LCS center should include a radiology clinic with a 16-channel CT scanner (although it is possible with a 4-channel CT scanner, as was used in the NSLT), whenever possible with a computerized program for volumetric reading of the lesion, the ability to describe the results in a standardized way using the Lung-RADS system, and a quality control sector. The centers should have access to PET/CT for diagnostic follow-up of suspicious nodules and preoperative staging.

Another crucial point is the capacity to perform biopsy, which can be guided by CT, or another minimally invasive surgical procedure, preferably with preoperative markup in the case of lesions that are invisible or nonpalpable. Although an interventional pulmonology clinic with endobronchial bronchoscopy is desirable, the economic conditions of each center must be taken into account so as not to make the program unfeasible. The surgical center should be structured to allow thoracotomy and video-assisted thoracoscopic surgery to be performed.

Finally, the LCS center should have a professional structure to help patients navigate the program, guiding them through invasive investigation and periodic examinations of the lesions identified or referring them to the smoking cessation program.

The administrative structure of each center should have the capacity to record all data and results in order to store and report all information to the national screening center. Of equal importance is sector planning to promote continued training for the entire team.[132,133]

Interaction between the primary care clinician and the thoracic surgeon, pulmonologist, or both, as well as between them and the radiologist, pathologist,

oncologist, and radiotherapist, is of fundamental importance for the success of the screening program. No less important is the participation of the nursing and social assistance sectors.

All of the professionals should be subject to regional or central administrative medical authority that is responsible for communication at different levels and a referral and counter-referral system, as well as for storing data and images to be consulted over time.[22,123] Test results should be communicated to participants in written form and orally, the impact of the result being weighed for each individual.[132] Everyone on the multidisciplinary team should have a clear understanding of their role, be familiar with the brief guidelines on smoking cessation, and know how to recommend facilities for intensive treatment.[134,135]

At LCS centers, decisions should be made jointly and should be based on the six pillars of quality health care, which are safety, effectiveness, efficiency, timeliness, equity, and patient-centeredness. Adherence to LCS is not high and could be improved through clear discussion about the advantages and potential risks of screening and not screening.[136] In addition, continuity of care must be guaranteed when a participant moves from one setting to another, and information about their goals, beliefs, and values, as well as their current clinical status, should always be reported in order to avoid misunderstandings.[134]

Ensuring the benefits of an LCS program requires an organized structure, trained staff, and appropriate equipment, concentrated at LCS centers.[123]

POST-LDCT MANAGEMENT ALGORITHM—LUNG-RADS

In 2014, the ACR developed the Lung-RADS, which was modeled on the success of its Breast Imaging Reporting and Data System.[116]

The Lung-RADS allows uniform reporting and management of abnormal findings on LDCT examinations in LCS and aims to facilitate successful implementation in radiology practice outside the scope of clinical trials.[116] The Lung-RADS is also an essential part of quality assurance and screening log reports. The latest Lung-RADS version, released by the ACR in 2022, was based on evidence collected in previous years,[116] as detailed in Tables 3 and 4.

The Lung-RADS Committee is made up of 8 of the most prominent experts in the field, who carry out studies of the existing literature and publish periodic updates. We believe that using the Lung-RADS recommendations is the way to make the most accurate decisions after LDCT in an LCS program.

COST-BENEFIT ANALYSIS OF SCREENING

- LCS with LDCT is probably cost-effective, and its cost-benefit ratio, despite involving multiple factors, also tends to be adequate.

Cost-benefit analysis is one of the most important aspects of public health policies. When evaluating screening, for benign and malignant diseases alike, it is necessary to demonstrate its advantages in relation to its costs, especially for the funding sources.[137]

In relation to LCS, it is expected that there will be a high number of LDCT examinations for each patient diagnosed and treated, which increases the overall cost of the program. Cost-effectiveness, as well as the benefit of reducing mortality and increasing early diagnosis, should be clearly demonstrated.[137-139]

It is also necessary to understand the difference between a cost-effectiveness analysis, which considers the cost of the program only for the examination and the determined outcome, and a cost-benefit analysis, which also takes into account other benefits, such as smoking cessation.[137,138]

The cost-effectiveness analysis model that comes closest to reality is the ***MI****crosimulation* ***SC****reening* ***An****alysis-Lung* (MISCAN-Lung), which uses a semi-Markov model to simulate the appearance of neoplasms at the population scale.[139] A study conducted in Canada showed that, according to the MISCAN-Lung model, LCS is cost-effective for high-risk populations and that the cost decreases as smoking history in pack-years increases, although the number of life-years gained does not increase.[139]

To analyze the cost-benefit of screening, the cost-effectiveness relationship was initially assessed in a systematic review that included 45 studies and employed a ***P****atients of interest,* ***I****ntervention to be studied,* ***C****omparison of interventions, and* ***O****utcome of interest* (PICO) type of strategy, as follows[140]: patients/population of interest—smokers (or former smokers) between 55 and 79 years of age with a smoking history > 20 pack-years; intervention—LDCT; comparison—chest X-ray or no screening; and outcome of interest—cost-effectiveness of screening with LDCT.

In that study,[140] it was clear that annual screening with LDCT is cost-effective for the desired population, and the cost-effectiveness ratio is even greater for biennial screening, although the roles of risk prediction models and smoking cessation interventions were unclear.

Another systematic review corroborated the cost-effectiveness findings and suggested that such screening programs should be implemented even in situations of limited financial resources and even if LDCT has to be performed at a lower (biennial) frequency.[141] However, that review does not necessarily reflect the reality in Brazil.

A study carried out in China, an upper-middle-income country with a high prevalence of granulomatous diseases and whose indicators are comparable to those of in Brazil, showed, using the Markov model, that screening with LDCT for patients over 60 years of age cost US$113.88 million but was cost-effective, reducing LC-related deaths by 16.1%.[142]

Chart 3. Lung CT Screening Reporting and Data System, version 2022: classification and recommendations for lung nodule management during lung cancer screening (part 1).

Category		Description	Management
0	Incomplete data (estimated population prevalence: ≈ 1%)	Localized anterior chest CT examination for comparison (see Note 1)	Comparison with previous chest CT
		Part or all of the lungs cannot be evaluated	Additional LDCT required for LCS
		Findings suggestive of an inflammatory or infectious process (see Note 2)	LDCT in 1-3 months
1	Negative (estimated population prevalence: 39%)	No pulmonary nodules OR nodule with benign characteristics • Complete, central, popcorn-shaped, concentric ring or fat-containing calcifications	LDCT screening every 12 months
2	Benign Based on image features or indolent behavior (estimated population prevalence: 45%)	Juxtapleural nodule • Mean diameter < 10 mm (524 mm^3) at baseline or new AND • Solid nodule; smooth margins; oval, lentiform, or triangular shape	
		Solid nodule • < 6 mm (< 113 mm^3) at baseline OR • New nodule < 4 mm (< 34 mm^3)	
		Subsolid nodule • < 6 mm mean total diameter (< 113 mm^3) at baseline	
		Non-solid nodule • < 30 mm (< 14,137 mm^3) at baseline, new or growing OR • ≥ 30 mm (≥ 14,137 mm^3) stable or growing slowly (see Note 3)	
		Airway nodule, subsegmental at baseline, new or stable (see Note 4)	
		Category 3 nodules that are stable or decreased in size on 6-month follow-up CT OR Category 3 or 4A nodules that disappear on follow-up OR Category 4B findings proven to be of benign etiology upon diagnostic evaluation	
		Subsolid nodule • ≥ 6 mm mean total diameter (≥ 113 mm^3) with a solid component < 6 mm (< 113 mm^3 at baseline • OR • New nodule < 6 mm mean total diameter (< 113 mm^3)	
		Non-solid nodule • ≥ 30 mm (≥ 14.137 mm^3) at baseline or new	
		Atypical lung cyst (see Note 5) • Enlarging cystic component (mean diameter) of a thick-walled cyst	
		Category 4A nodule that is stable or has decreased in size at 3 months of CT follow-up (excluding airway nodules)	

Modified from American College of Radiology Committee on Lung-RADS.[116]
Lung-RADS: Lung CT Screening Reporting and Data System; LDCT: low-dose CT; and LCS: lung cancer screening.
Notes:
1. Previous examinations: If waiting for previous examinations (either a pre-screening test or CT), Lung-RADS Category 0 is temporary until the comparison study is available and a new Lung-RADS Category is determined.
2. Suspected infectious or inflammatory disease:
a. In the case of Lung-RADS 0 with 1-3 months of follow-up, LDCT may be recommended on the basis of pulmonary findings, suggesting an undetermined infectious or inflammatory process. Such findings may include segmental or lobar consolidation, multiple (> 6) new nodules, large (> 8 mm) solid nodules appearing within a small interval, and new nodules in certain clinical settings (e.g., immunocompromise). At 1-3 months of follow-up, a new management recommendation and Lung-RADS classification should be provided based on the most suspicious nodules.
b. New solid or subsolid nodules with imaging features more concerning for malignancy than an inflammatory or infectious process, with the Lung-RADS 4B size criteria may be classified as such provided they have the appropriate clinical diagnosis/evaluation.
3. Slow-growing solid or ground-glass nodules: A ground-glass pattern nodule that demonstrates growth on multiple screening tests but does not meet the size increase threshold of > 1.5 mm for any 12-month interval may be classified as Lung-RADS 2 until the nodule meets criteria for another category, such as development of a solid component (after which the case should be managed according to the solid nodule criteria, on a per-patient basis).

Chart 4. Lung CT Screening Reporting and Data System, version 2022: classification and recommendations for lung nodule management during lung cancer screening (part 2).

Category		Description	Management
3	Probably benign Based on imaging features (estimated population prevalence: 9%)	Solid nodule • ≥ 6 to < 8 mm (≥ 113 to < 268 mm³) OR • New 4 mm to < 6 mm (34 to < 113 mm³) Subsolid nodule • ≥ 6 mm mean total diameter (≥ 113 mm³) with solid component < 6 mm (< 113 mm³ at baseline OR • New < 6 mm mean total diameter (< 113 mm³) Non-solid nodule • ≥ 30 mm (≥ 14.137 mm³) at baseline or new Atypical lung cyst (see Note 5) • Enlarging cystic component (mean diameter) of a thick-walled cyst Category 4A nodule that is stable or has decreased in size at 3 months of CT follow-up (excluding airway nodules)	New LDCT at 6 months
4A	Suspicious (estimated population prevalence: 4%)	Solid nodule • ≥ 8 to < 15 mm (≥ 268 to < 1,767 mm³) at baseline OR • Growth < 8 mm (< 268 mm³) OR • New 6 to < 8 mm (113 to < 268 mm³) Subsolid nodule • ≥ 6 mm mean total diameter (≥ 113 mm) with solid component of ≥ 6 mm to < 8 mm (≥ 113 to < 268 mm ³) at baseline OR • New or growing solid component < 4 mm (< 34 mm³) Nodule in the airways Segmental or more proximal at baseline or new (see Note 4) Atypical lung cyst (see Note 5) • Thick-walled cyst OR • Multilocular cyst (at baseline) OR • Thin- or thick-walled cyst that becomes multilocular	New LDCT at 3 months PET/CT may be considered if there is a nodule or solid component ≥ 8 mm (≥ 268 mm³)
4B	Very suspicious (estimated population prevalence: 2%)	Nodule in the airways Segmental or more proximal, and stable or growing (see Note 4) Solid nodule • ≥ 15 mm (≥ 1,767 mm ³) at baseline OR • New or growing ≥ 8 mm ³ (≥ 268 mm ³) Subsolid nodule • Solid component ≥ 8 mm (≥ 268 mm³) at baseline OR • New or growing solid component ≥ 4 mm (≥ 34 mm³) Atypical lung cyst (see Note 5) • Thick-walled cyst with increasing thickness/nodularity OR • Multilocular cyst growth (mean diameter) OR • Multilocular cyst (with increased loculation or new/increased opacity (nodular, ground glass, or consolidation) Solid or subsolid nodule that demonstrates growth on multiple screening examinations	Referral for future clinical evaluation Diagnostic chest CT, with or without contrast PET/CT may be considered if there are nodules or solid components ≥ 8 mm (≥ 268 m³); removal of tissue samples; or referral for further clinical assessment Management depends on clinical assessment, patient preference and likelihood of malignancy (see Note 6)
4X	(estimated population prevalence: < 1%)	Category 3 or 4 nodules with additional features or imaging findings that increase suspicion of lung cancer	

Continue...▶

Chart 4. Lung CT Screening Reporting and Data System, version 2022: classification and recommendations for lung nodule management during lung cancer screening (part 2). (Continued...)

Category		Description	Management
S	Significant or potentially significant (estimated population prevalence: 10%)	Modifier: May add to category 0-4 for clinically significant or potentially clinically significant non-lung cancer findings	According to the specific finding

Modified from American College of Radiology Committee on Lung-RADS.[116]
Lung-RADS: Lung CT Screening Reporting and Data System; LDCT: low-dose CT.
Notes:
4. Nodules in the airways
a. Endobronchial or endotracheal abnormalities that are segmented or more proximal are classified as Lung-RADS 4A
b. Segmental abnormalities or multiple tubular abnormalities favor an infectious process. If no underlying obstructive nodules are found, these findings can be classified as Lung-RADS 0 (probably infectious or inflammatory) or 2 (benign).
c. The presence of air in segmental or more proximal airway abnormalities generally favors secretions. If no underlying soft tissue nodule is identified, these findings can be classified as Lung-RADS 2.
d. Segmental or more proximal airway nodules that are stable or enlarging at 3 months of CT follow-up are upgraded to Lung-RADS 4B with management recommendations for future clinical evaluations (typically bronchoscopy).
5. Atypical lung cysts
a. Thin-walled cysts—unilocular cysts with a uniform thickness < 2 mm. Thin-walled cysts are considered benign and are not classified or managed by Lung-RADS.
b. Thick-walled cysts—unilocular with uniform thick wall, asymmetric wall thickening, or nodular wall thickening ≥ 2 mm (cystic component is the dominant feature); manage as an atypical pulmonary cyst.
c. Multilocular cyst—thin- or thick-walled cyst with internal separations; manage as an atypical pulmonary cyst.
d. Cavitary nodule—wall thickening is the dominant feature; manage as a solid nodule (mean total diameter).
e. Cyst with associated nodule: any cyst with a nodule (solid, subsolid, or ground glass); management is based on Lung-RADS criteria for resources of most concern.
f. Growth—> 15 mm increase in nodule size (mean diameter), wall thickness, and/or cystic component size (mean diameter) occurring within a 12-month interval.
g. Fluid-containing cysts may represent an infectious process and are not classified in Lung-RADS unless other features of concern are identified.
h. Multiple cysts may indicate an alternative diagnosis such as Langerhans cell histiocytosis or lymphangioleiomyomatosis if they are not classified on the Lung-RADS unless other worrisome features are identified.
6. Category 4B
Management is impaired based on clinical assessment (comorbidities), patient preference and risk of malignancy; radiologists are encouraged to use the McWilliams et al.[159] assessment tool when making recommendations.

To arrive at the cost-benefit ratio based on cost-effectiveness, we should consider, in addition to the cost-effectiveness ratio of LDCT in relation to LC-related mortality, the following aspects[4,137,143,144]:

1. Treating early-stage disease is potentially less costly than is treating advanced-stage disease and has better outcomes. Screening will likely increase the number of individuals diagnosed at an early stage.
2. Screening ends up changing the staging of LC that would be diagnosed late, as observed in the IELCAP study.[144]
3. There are costs associated with ancillary tests, such as biopsies.
4. The treated patient, even if still asymptomatic, tends to return to work more quickly, thus reducing the socioeconomic impact of the disease.
5. There is an increase in the number of hospitalizations due to factors associated with advanced-stage disease, such as dyspnea, thromboembolism, and intractable pain, which increases costs.
6. The screening program should be associated with the smoking history, which in itself leads to the prevention of other diseases and therefore to a cost reduction.
7. The cost of LDCT is low (approximately US$250 in the United States in 2023), and its availability has increased, even in low- and middle-income countries.
8. LDCT examinations end up diagnosing diseases other than LC, which can be treated in a timely manner. Their diagnosis and treatment increase the program costs but tend to reduce overall nonspecific mortality.

The analysis considering such factors is complex, and no predictive model can accurately estimate the costs. There are estimates for the United States, although with divergent values, depending on health insurance and other factors.[137] Nevertheless, there is agreement on the possibility of a good cost-benefit ratio for the at-risk population.[145] Although there is a lack of data on cost-effectiveness and cost-benefit in Brazil, it is possible to assume, by interpreting the results of international studies, that LCS will produce similar results in the country.

After that analysis, it can be concluded that LCS with LDCT is probably cost-effective, and its cost-benefit ratio, despite involving multiple factors, also tends to be adequate. Although data from Brazil are needed in order to validate these models, this is an open field that is of great interest, especially to patients who

would benefit from early diagnosis and treatment, with reduced mortality.

SCREENING PERSPECTIVES (NEW MARKERS)

- New markers are promising, although their efficacy is still under evaluation and their costs are high.
- The use of molecular or protein-based tumor biomarkers, bronchoscopy with autofluorescence, DNA methylation, exhaled breath, circulating free DNA, microRNA, metabolomics, and the combination of images (deep learning) with biomarkers are being studied.

In recent years, new LCS modalities have been investigated. The main unmet clinical needs are risk refinement to improve the selection of individuals undergoing screening and the characterization of indeterminate nodules found during LDCT-based screening.

In the NLST, blood, urine, and sputum samples from more than 10,000 participants were stored for later analysis.[146,147] However, there are as yet no molecular or protein-based tumor biomarkers that can be used efficiently and implemented reliably in a screening program.[92]

Autofluorescence bronchoscopy has greater sensitivity for detecting precancerous lesions of the bronchial mucosa than does conventional bronchoscopy. However, the results of most previous studies do not support its use as an LCS tool.[148]

Some studies have pointed to DNA methylation as one of the key factors in the progression of LC. Recent studies have been performed on tumor tissue; findings in blood and other samples showed lower sensitivity and specificity.[149] Another study found that, for five of the six genes evaluated (*SOX17*, *TAC1*, *HOXA7*, *CDO1*, *HOXA9*, and *ZFP42*), DNA methylation in plasma and sputum was more common in patients with LC than in control patients ($p < 0.001$).[150]

It is possible to detect volatile fragments of cells and DNA in exhaled breath condensate. Some studies have suggested that this matrix can be used in order to differentiate between benign and malignant nodules, as well as to predict the treatment response and recurrence. Studies for training in and validation of the use of a portable electronic nose for LCS have found it to have a diagnostic accuracy of 83%. These findings suggest that exhaled breath is a valid marker of LC and could be useful for triage.[151,152]

Circulating free DNA appears to be more suitable for identifying mutations in the driver gene in patients with known neoplasia than for making an early diagnosis. Initial studies have shown that it does not predict the risk of LC but does predict perioperative survival. However, a retrospective analysis of microRNAs showed their potential to increase the specificity of LDCT, with a notable (five-time) reduction in the false-positive rate.[153] In combination with LDCT findings, microRNA can help stratify the risk of LC. That risk stratification is now being tested prospectively in a screening trial involving more than 4,000 people.[154,155]

Changes in LC metabolites (metabolomics: changes in glycolysis, citric acid cycle, amino acid metabolism, and cell membrane synthesis) provide a direct functional reading of phenotypic changes associated with the development of lung tumors and can help differentiate between histological subtypes or target mutations.[156]

Combining image-based deep learning with biomarkers can be an effective means of characterizing lung nodules. Radiomics analysis is capable of identifying *EGFR* and *KRAS* mutations, as well as of predicting survival. Some studies have shown that integrating biomarkers and radiological characteristics is a good method for predicting LC. The use of integrated models has been shown to be superior to that of serum biomarkers in isolation and represents a quite promising approach for the future of early LC detection, especially if artificial intelligence is incorporated.[147]

The scientific community is also awaiting the results of the Circulating Cell-Free Genome Atlas study for the early detection of cancer. In that study, plasma samples collected during a 5-year follow-up period will be analyzed by whole genome sequencing and integrated with patient clinical information.[157,158]

All of these tools could be of great importance for the future of screening. However, the high cost of developing and implementing them could hinder their incorporation into clinical practice in population-based health care.

FINAL CONSIDERATIONS

Early detection of LC is essential for improving clinical outcomes. The approach to the vulnerable population, especially smokers, should be carried out in a multidisciplinary manner, with the help and participation of public authorities, community health agents, family members, and patient support organizations.

In this document, experts from three of the main medical societies dedicated to the treatment of chest diseases (the SBPT, SBCT, and CBR) came together to form the study group, aiming to formulate the first LCS recommendations for Brazil, and this is a first step toward discussions on the topic, which is of great importance.

In Figure 2, we present an infographic summarizing the main points of these recommendations.

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AUTHOR CONTRIBUTIONS

All of the authors participated in one or more phases of the drafting of this consensus: 1) study conception

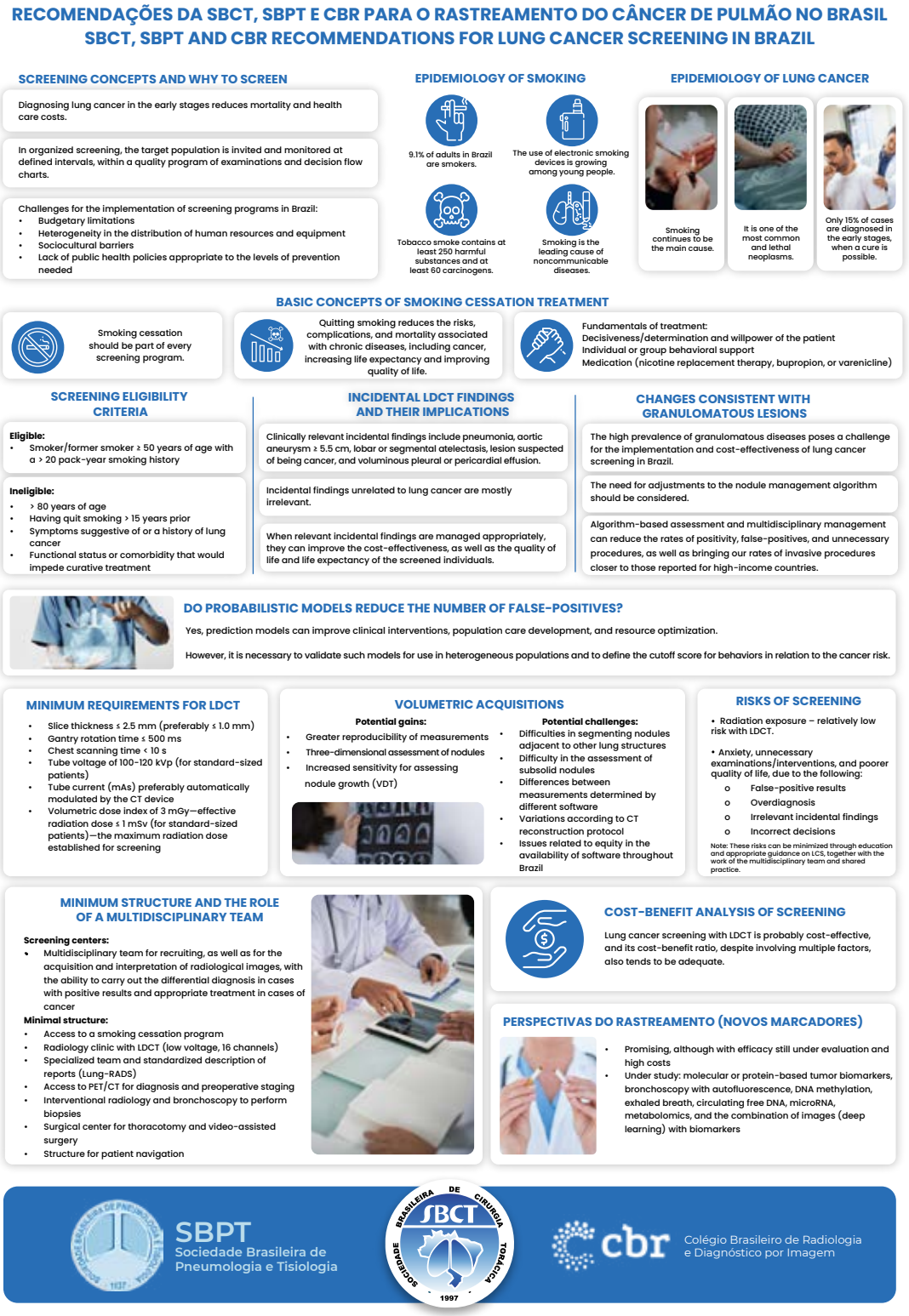

Figure 2. Summary of the main points of recommendations for lung cancer screening in Brazil. LDCT: low-dose CT; VDT: volume doubling time; and Lung-RADS: Lung CT Screening Reporting and Data System.

and planning, as well as interpretation of evidence; 2) drafting and revision of the preliminary and final versions of the manuscript; and 3) approval of the final version of the manuscript. The final version was

prepared by LFFP, RSS, DOB, and JF, after agreement by all members of the working group.

CONFLICTS OF INTEREST

None declared.

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