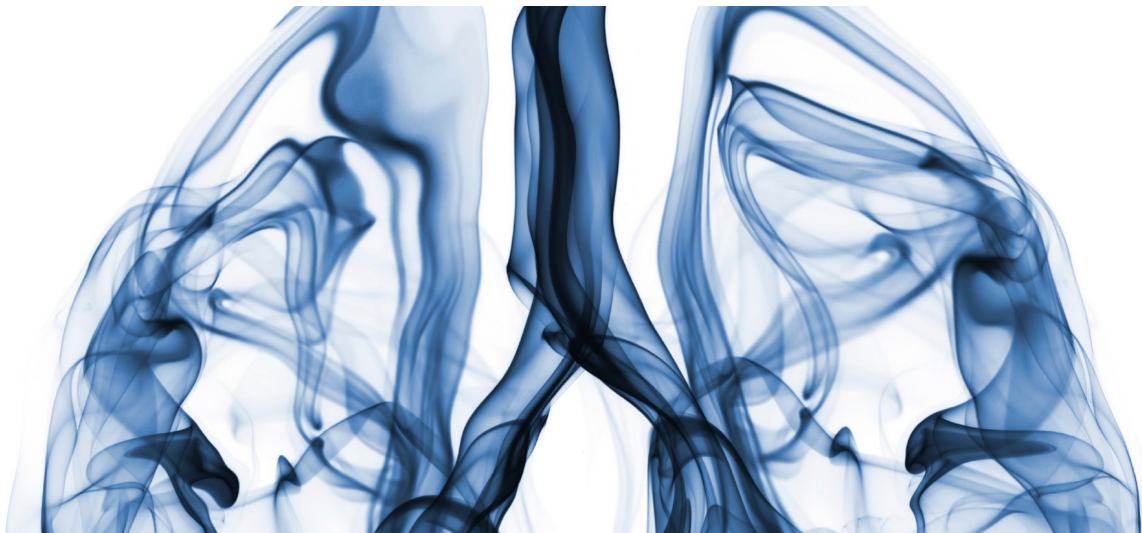


The Challenges of Reducing Lung Cancer Mortality with Screening

By Michael Orsi, M.D., Board Certified Radiologist · Updated for 2026 by Intrinsic Imaging



Lung cancer remains the leading cause of cancer death in the United States. Two large randomized trials, NLST and NELSON, have shown that low-dose CT (LDCT) screening reduces lung cancer mortality, and U.S. eligibility was broadened in 2021. Yet the challenges that shaped the first edition of this issue remain: false positives, overdiagnosis, radiation, and the biases that can make screening look more effective than it is. Artificial intelligence for nodule detection and characterization adds new opportunity, and new questions that only well-designed trials can answer.

Lung Cancer

Lung cancer causes more cancer deaths in the United States than any other cancer, in both men and women. The American Cancer Society estimates 229,410 new cases and 124,990 deaths from lung cancer in 2026, about one in five of all U.S. cancer deaths.¹

Screening Methodologies

Interest in early detection has always been strong, because patients diagnosed at an early stage have far better outcomes than those with advanced disease. Lung cancer is aggressive, and by the time patients present with symptoms, the prognosis is usually poor.

Screening methods include chest radiography and CT, with or without computer-assisted detection or diagnosis (CAD). Computer-assisted detection points out possible findings for the radiologist to evaluate; computer-assisted diagnosis analyzes lesion features to estimate the level of suspicion. Both may offer the most benefit to less experienced readers and may help standardize performance. Today, deep-learning tools for nodule detection, volumetry and malignancy risk are commercially

available, but evidence that they improve patient outcomes in screening, rather than reader performance alone, is still being established.

Biases in Lung Cancer Screening

Screening studies are vulnerable to biases that can make survival appear improved. **Lead-time bias** makes survival look longer simply because disease is detected earlier, not because treatment is more effective. **Length-time bias** arises because screening preferentially finds slower-growing, less aggressive cancers. **Overdiagnosis** occurs when cancers are found and treated that would never have caused death. These biases are why survival is not an adequate endpoint, and why lung cancer mortality in randomized trials is the standard of proof.

Clinical Trials

Randomized trials of chest radiography and sputum cytology in the 1980s found more early-stage, resectable cancers but no significant reduction in lung cancer mortality. Interest then shifted to LDCT, which delivers more radiation than a chest radiograph but far less than a conventional CT. Early studies found that LDCT detects early-stage cancers but produces many false

positives, leading to repeat imaging, biopsies and surgery for benign nodules.

In 2011, the National Lung Screening Trial (NLST) randomized more than 53,000 high-risk participants to three annual screens with LDCT or chest radiography and reported a 20% relative reduction in lung cancer mortality with LDCT.² It was the first major trial to show a mortality benefit. In 2020, the European NELSON trial confirmed the result using volume-based CT screening: among 13,195 men followed for 10 years, lung cancer mortality was 24% lower with screening (rate ratio 0.76), with a trend toward greater benefit in women.³ NELSON also showed that volumetric nodule management can substantially reduce false positives.

The U.S. Preventive Services Task Force first recommended LDCT screening in 2013. In 2021 it broadened eligibility to adults aged 50 to 80 with a 20 pack-year smoking history who currently smoke or quit within the past 15 years.⁴ The American Cancer Society now recommends annual LDCT for eligible adults regardless of when they quit.¹

Path Forward

Effective screening raises new questions: cost-effectiveness, optimal intervals and protocols, and the harms of radiation, overdiagnosis and invasive procedures. A reanalysis of NLST data estimated that about 18% of screen-detected cancers were indolent.⁵ Uptake of screening in eligible adults remains low, and the role of AI in reading, triage and risk prediction must be proven in prospective studies with clinically meaningful endpoints.

Guidance for Sponsors

Designing a lung screening or nodule AI study

- **Choose endpoints that resist bias.** Survival alone is distorted by lead-time and length-time bias; use mortality, stage shift or validated diagnostic endpoints.
- **Standardize LDCT acquisition.** Specify dose, slice thickness and reconstruction kernel, which directly affect nodule detection and volumetry.
- **Use volumetric measurement.** Volume and volume-doubling time reduce false positives compared with diameter alone.³
- **Establish ground truth carefully.** Confirm cancers with pathology and benign nodules with stability on follow-up.
- **Measure harms as well as benefits.** Report false-positive rates, downstream procedures and potential overdiagnosis.⁵
- **Test AI as it will be used.** Multi-reader studies should reflect real reading workflows and the eligible screening population.

Summary

Low-dose CT screening reduces lung cancer mortality, as two large randomized trials have now shown. The remaining challenges are to screen the right people, reduce false positives and overdiagnosis, and prove the value of computer assistance. Each depends on carefully constructed clinical trials with standardized imaging and independent, unbiased assessment.

About the Author

Dr. Michael Orsi, a board-certified, fellowship-trained radiologist, wrote the original edition of this issue at Intrinsic Imaging. He completed a fellowship in cross-sectional imaging, covering thoracic and abdominal imaging, at Johns Hopkins Hospital in Baltimore, and his residency in diagnostic radiology at the University of Texas Health Science Center at San Antonio, where he served as chief resident. He is board-certified in diagnostic radiology and specializes in imaging of the thorax, abdomen and pelvis. He has published original research on minimally invasive techniques such as radiofrequency ablation of the liver and on advanced MRI techniques for the liver.

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Headquartered in Bolton, Massachusetts, Intrinsic Imaging is an imaging CRO and core lab supporting Phase I–IV drug trials, medical device studies and AI/CAD validation studies. The company has completed three FDA Bioresearch Monitoring Program inspections, each with zero Form FDA 483 observations, and holds five BSI certifications: ISO 9001, ISO 13485, ISO 22301, ISO/IEC 27001 and ISO/IEC 27018. Its network of more than 1,000 board-certified, fellowship-trained physicians has supported trials at more than 4,000 sites in 64 countries.



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