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The Role Of CT In Early Diagnosis Of Lung Cancer

Fayez Shawan Alotaibi[1] , Abdulrahman kuzaim Alasmari[2] , Hassan Awaadh Alzahrani[3] , Abdulaziz Ali Qassim al-Safhi[4] , Sultan Fahad Alsanea[5] , Ahmed Abdullah Alabood[6] , Faisal Hamdan Alenezi[7] , Rasheed Saud Almutairi[8] , Ibrahim Sulaiman Alshammari[9] , Atif Obaidallah Alharbi[10] , Mohammed Maqed Al-Otaibi[11] , Badr Fahd Muhammad Al-Talha[12] , Mohammed Faisal Alsubaie[13]

[1]Radiology Technologist Al Iman General Hospital
[2]Radiology Technologist Al Iman General Hospital
[3]Technician X-ray Al Iman General Hospital
[4]X-ray Technician Al Iman General Hospital
[5]X-ray Technician Al Iman General Hospital
[6]Technician X-ray Al Iman General Hospital
[7]Radiology Technologist Al Iman General Hospital
[8]Radiology Technologist Alnueayria General Hospital
[9]Radiology Technologist Samira General Hospital
[10]Radiology Technologist Al Iman General Hospital
[11]AlKharj Maternity and Children Hospital Radiology Technologist
[12]King Khalid Hospital Radiology Technologist
[13]Radiology Technologist Al-Kharj Maternity and Children's

Abstract

Lung cancer remains a leading cause of cancer mortality globally, with early detection being essential for improving survival outcomes. Low-dose computed tomography (LDCT) has emerged as a superior screening modality compared to chest X-ray (CXR), demonstrating consistent reductions in lung cancer-specific mortality through large randomized controlled trials. LDCT's enhanced sensitivity enables detection of smaller, early-stage nodules amenable to curative treatment, although its relatively low positive predictive value results in notable false-positive rates and concerns about overdiagnosis. Technical advances in LDCT protocols, including dose optimization and iterative reconstruction, balance image quality with radiation exposure, supporting repeated annual screenings. Integration of artificial intelligence and biomarker assays offers promising avenues to improve diagnostic specificity and reduce unnecessary interventions, yet these adjuncts require further validation across diverse populations. Meta-analyses confirm LDCT's mortality benefit alongside increased early-stage detection and surgical resection rates, while highlighting challenges related to false positives, overdiagnosis, and equitable access. Ethical considerations emphasize informed consent, harm minimization, and resource allocation, particularly in varied healthcare settings. Future strategies should focus on refining eligibility criteria, optimizing follow-up algorithms, and incorporating emerging technologies to maximize net benefit and minimize harms in lung cancer screening programs.

1 Introduction

Lung cancer remains one of the most lethal malignancies globally, maintaining a high mortality rate despite advances in targeted therapies and chemotherapy. Early detection has emerged as the single most effective strategy to improve patient survival rates, as prognosis is strongly correlated with stage at diagnosis. For instance, stage I patients have an approximate five-year survival of

75%, in stark contrast to about 15% survival at advanced stages (Zhong et al., 2023). This pattern highlights the critical need for approaches that identify disease before progression into late-stage pathology. Low-dose computed tomography (LDCT) has been widely adopted in clinical research as a screening modality capable of detecting lung cancer earlier than conventional chest radiography (CXR). Evidence from large-scale randomized controlled trials (RCTs), such as the National Lung Screening Trial (NLST), demonstrates that annual LDCT screening is associated with a relative risk reduction in lung cancer mortality of about 20% compared to CXR (Bach, 2012). The NLST data also reported a modest reduction in all-cause mortality among high-risk individuals (Hall et al., 2018), reinforcing the broader impact of early detection beyond disease-specific outcomes. Another important trial, NELSON, observed a 24% reduction in lung cancer mortality over ten years among male participants, further validating its public health relevance (Zhong et al., 2023). These benefits are grounded in LDCT's superior sensitivity for picking up small nodules and malignancies at stages suitable for curative treatment. In comparative analyses, LDCT was shown to outperform CXR substantially, detecting cancers at resectable stages and uncovering incidental findings such as mediastinal lymphadenopathy or vascular abnormalities that might otherwise remain unnoticed. Despite this enhanced sensitivity, questions remain about balancing benefit with potential harms. Overdiagnosis, diagnosis of cancers that might never cause symptoms or death, is cited as an important concern. Data synthesis from multiple RCTs indicates heterogeneity in overdiagnosis rates across studies, possibly influenced by differences in baseline risk profiles such as smoking history or lung function metrics (Bonney et al., 2022). From a methodological perspective, recent systematic reviews stress adherence to rigorous protocols like PRISMA when assessing screening interventions (Ebell et al., 2020). Meta-analyses incorporating both chest radiography and usual care controls have confirmed that CXR has no meaningful influence on mortality rates, hence advocating LDCT as the superior comparator. Yet even within otherwise convincing datasets, variability in trial design complicates interpretation, underscoring the importance of transparent reporting and consistent follow-up durations to achieve robust estimates. A related consideration is diagnostic specificity. While LDCT excels in sensitivity, its positive predictive value (PPV) remains relatively low, meaning many individuals flagged by screening ultimately do not have lung cancer (Paci, 2018). This leads to higher rates of false positives, unnecessary follow-up imaging, biopsies, and additional healthcare costs. Such drawbacks are particularly pronounced among populations classified as high risk: the same individuals most likely to benefit from early detection are also disproportionately exposed to these adverse downstream effects (Huang et al., 2018). Professional societies including the U.S. Preventive Services Task Force and the American College of Chest Physicians have incorporated these findings into updated guidelines recommending LDCT screening for certain high-risk demographics, typically defined by age criteria combined with long-term smoking exposure (S. Yang et al., 2024; Q. Ye et al., 2018). These endorsements rest not only on mortality reduction but also on feasibility considerations; LDCT can be delivered across diverse health systems without prohibitive cost escalation compared to more invasive or resource-intensive modalities. Scientific discourse has shifted toward refining implementation strategies rather than questioning LDCT's overall benefit. This includes identifying patient subgroups who would derive optimal net advantage from yearly scans while minimizing chance harms such as cumulative radiation exposure or anxiety provoked by indeterminate nodule findings. Complex clinical decision-making frameworks now integrate sociodemographic and psychological factors influencing screening uptake (Hall et al., 2018), reflecting awareness that patient perception can directly affect participation rates and follow-through on recommended evaluations. The conversation on biomarkers offers an intriguing parallel but remains constrained by current evidence quality. Efforts to combine LDCT screening with blood- or serum-based biomarkers aim to enhance specificity and reduce unnecessary interventions; however, systematic reviews characterizing tools like EarlyCDT-lung or microRNA assays have repeatedly concluded insufficient high-quality data for routine deployment (Paci, 2018). For now, "liquid biopsy" techniques exist more as adjunct

research avenues rather than practical substitutes for image-based screening. Evaluating harm–benefit ratios involves not just overt clinical endpoints but also population-level projections modeled through decision tree analyses comparing false positive diagnoses against prevented deaths due to timely intervention (Wang et al., 2017). These quantitative frameworks are essential for policy bodies weighing health economics alongside survival statistics. They reveal tension between maximizing early-stage identification and controlling unintended consequences inherent to any mass-screening program. Altogether, the introduction of LDCT into lung cancer screening protocols marks one of the clearest examples where technological sensitivity alters clinical trajectories for a fatal disease entity. Yet scientific scrutiny demands continued examination under standardized review methodologies such as PRISMA (Ebell et al., 2020), ongoing refinement of risk stratification criteria, and careful integration of emerging adjunct technologies without undermining existing practice reliability.

2 Background and Rationale

2.1 Epidemiology of Lung Cancer and Risk Factors

Lung cancer remains the leading cause of cancer-related deaths worldwide, with substantial variation in incidence patterns between geographic regions and demographic groups (Hsu et al., 2020). Its mortality burden reflects both the aggressive nature of the disease and the frequent presentation at late stages when curative treatment is no longer feasible. While global efforts in screening have had measurable impacts, there persists a pronounced mismatch between detection rates in early versus advanced stages. For instance, population-based studies in China show that approximately 64.6% of cases are diagnosed at stage III or IV, where survival prospects are profoundly limited compared to earlier stages (Pan et al., 2024). This skew toward late-stage diagnosis is often attributed to low public awareness, inadequate screening coverage, and barriers to healthcare access. Tobacco smoking remains the most substantial modifiable risk factor, implicated in a vast majority of lung cancer cases. In countries with high smoking prevalence, such as China, detailed surveys reveal strong correlations between daily tobacco consumption patterns and observed incidence across sexes and age groups (Wang et al., 2017). Chronic high-frequency smoking markedly raises lifetime risk; epidemiologic modeling estimates indicate that around 8 million adults in the United States meet criteria for being "high-risk" largely due to long-term tobacco exposure (Veliz et al., 2019). Non-smokers are nevertheless not immune. In certain regions, environmental exposures such as indoor air pollution from biomass fuels and ambient particulate matter play an outsized role. Occupational hazards, particularly prolonged inhalation of asbestos fibers, diesel exhaust, or certain metal dusts, form another important contributor. Second-hand smoke has been highlighted as a significant driver of lung cancer mortality among non-smokers (Zhang et al., 2024). Its physiological impact can be similar to direct smoking over prolonged periods, especially in enclosed environments where particulate concentration levels remain elevated for hours after exposure. Public health campaigns focusing on cessation are therefore not only directed at active smokers but increasingly emphasize reducing passive exposure. One epidemiologic challenge lies in quantifying contributions from genetic susceptibility. While no single gene mutation consistently explains the majority of sporadic lung cancers, familial aggregation suggests some heritable component may influence individual vulnerability. Age also interacts with cumulative exposure: incidence rises sharply after age 55 in heavy smokers but shows different slopes among populations where environmental risks dominate. The staging patterns reflect this interplay, older individuals tend to present with more co-morbidities that complicate treatment options once cancer is detected. Geographic differences cannot be understated. In Asian populations with relatively lower smoking rates compared to Western high-incidence cohorts, non-smoking-related lung cancers are reported more frequently (Hsu et al., 2020). These may be associated with specific histological subtypes such as adenocarcinoma appearing in younger

patients, which has implications for designing targeted screening interventions beyond traditional tobacco-related eligibility criteria. High prevalence zones for such phenotypes face unique policy decisions when applying imaging-based protocols like LDCT because the selection criteria developed predominantly from smoking-intensive populations may underperform. From a modeling perspective, disease burden can be assessed through metrics such as Disability-Adjusted Life Years (DALYs), incorporating prevalence rates alongside diagnostic performance measures like sensitivity and specificity (Wang et al., 2017). In simulations analyzing base-case scenarios with defined cohort distributions by age and sex, lung cancer prevalence exerts the greatest proportional influence on overall DALY loss compared to other parameters such as diagnostic specificity or proportion of early-stage detection among positives. The observation from large-scale screening trials that repeated LDCT rounds detect more early-stage cancers than baseline scans reinforces how risk factors intersect temporally with detectability. This likely reflects both incident cases arising since prior screenings and nodules missed initially due to their small size or benign appearance evolving into malignancy over time. Smoking cessation interventions during periodic screenings add another dimension: reducing ongoing exposure could theoretically shift future incidence curves downward within screened cohorts. Certain methodological debates center around optimal stratification methods for identifying high-risk individuals eligible for LDCT screening. Traditional approaches rely on criteria encompassing age thresholds and quantified cumulative smoking histories (e.g., pack-years). However, emerging proposals suggest integrating multifactorial risk calculators that weigh other epidemiologic elements such as family history or occupational exposures (Hirsch et al., 2023). These could potentially recalibrate eligibility so that it encompasses non-traditional risk groups without diluting predictive accuracy. Urbanization trends contribute indirectly by modifying exposure landscapes, increasing traffic-related air pollution while potentially reducing biomass fuel exposure in some areas. Conversely, industrial expansion in developing economies can accelerate occupational hazard prevalence without corresponding regulatory protections. From a clinical epidemiology standpoint, one subtle but consequential aspect involves health system infrastructure: availability of follow-up care affects measured outcomes because timely biopsy or surgical intervention post-screening is necessary for early detection benefits to translate into mortality reductions. Regions with fragmented referral pathways may present data showing limited survival gains despite similar detection rates compared to systems with integrated patient management. While environmental interventions could reduce certain risk factors independent of medical screening programs, many projections agree that lasting reduction in lung cancer mortality will require simultaneous strategies: primary prevention via smoking reduction policies; secondary prevention through widespread LDCT access targeting identified high-risk demographics; and tertiary prevention ensuring effective treatment delivery post-diagnosis. The weight of epidemiologic evidence in demonstrating why understanding both modifiable and inherent risk elements is essential for any discussion on optimizing screening protocols. The constellation of behavioral habits, environmental exposures, biological susceptibilities, and healthcare system variables collectively shapes incidence patterns, and by extension, how detection technologies impact public health outcomes across diverse settings

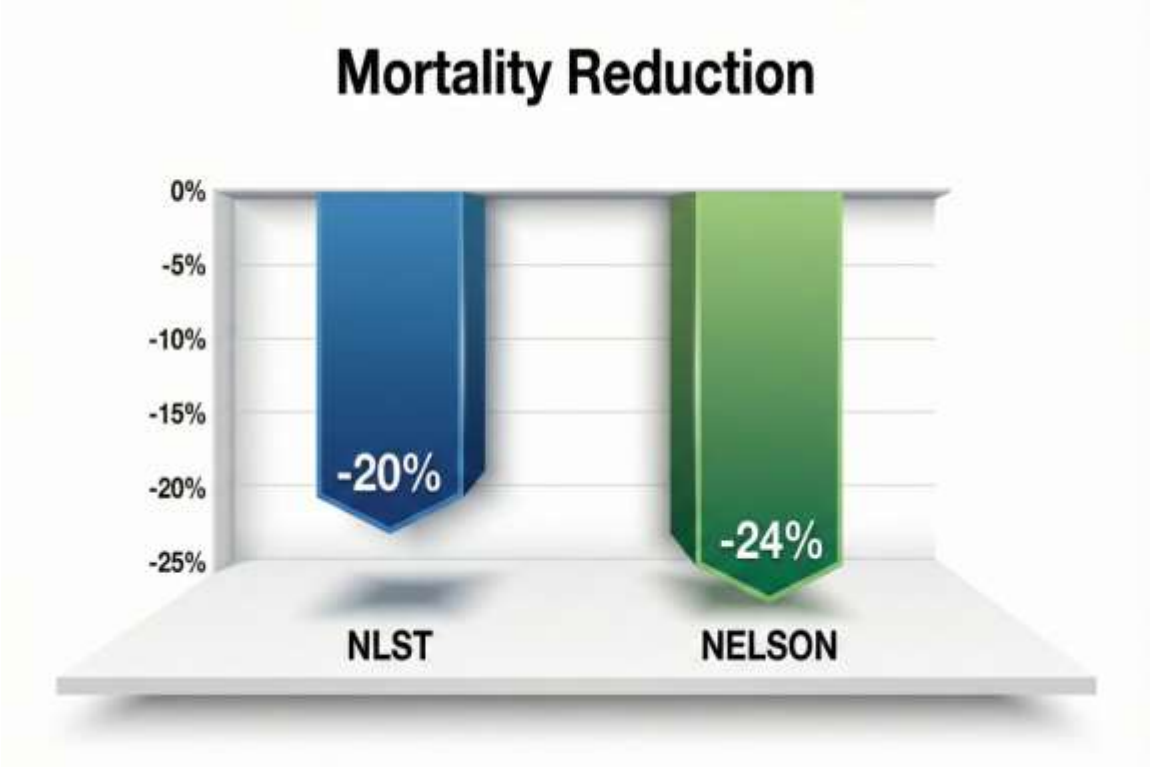

Figure 1: Comparative lung cancer mortality reduction observed in major randomized trials (NLST & NELSON) attributable to LDCT screening.

2.2 Principles and Evolution of Lung Cancer Screening

Early concepts of lung cancer screening stemmed from the recognition that prognosis is highly stage-dependent, with survival rates markedly better in patients identified at early stages compared to those diagnosed later (Zhong et al., 2023). Initial screening strategies relied on chest radiography (CXR) and sputum cytology, both capable of detecting certain lung cancers but limited in visual resolution for small nodules. Randomized trials from earlier decades indeed demonstrated increased detection of stage I tumors and smaller lesions with these modalities, yet such improvements failed to translate into a reduction in advanced cancers or mortality. The absence of mortality benefit prompted skepticism regarding their utility as standalone tools (Bach, 2012). Renewed clinical interest arose with the advent of low-dose computed tomography (LDCT), which enabled identification of nodules far smaller than those usually visible on CXR. LDCT technology provides high-resolution cross-sectional imaging at a reduced radiation dose, typically less than 1 millisievert per scan, substantially lowering exposure compared with standard-dose CT, which averages around 7 millisieverts (Q. Ye et al., 2018). That capability shifted the paradigm: instead of simply finding cancers already large enough to be symptomatic, LDCT could detect indeterminate pulmonary nodules measuring a few millimeters in diameter, some representing preclinical malignancies amenable to curative interventions. The accumulation of evidence supporting LDCT was catalyzed by landmark studies such as the National Lung Screening Trial (NLST). This large-scale randomized controlled trial demonstrated a roughly 20% relative reduction in lung cancer mortality among heavy smokers screened annually via LDCT compared to those screened with CXR (Huang et al., 2018). The NELSON trial built upon this framework, applying structured volumetric assessments and optimized screening intervals, reporting over 20% mortality reduction among male participants and suggesting even higher potential gains in women (Chen et al., 2024). These findings are particularly relevant in populations with high prevalence of

modifiable risks such as smoking. Despite promising results, concerns quickly emerged about LDCT's low positive predictive value. A sizable proportion of screen-detected nodules do not represent malignancy, leading to false positives that necessitate follow-up imaging, biopsies, or even surgery. In NLST, false-positive rates exceeded 25% across screening rounds, amplifying downstream procedural costs and patient anxiety (Wang et al., 2017). Overdiagnosis became another focal point for debate: detecting and treating cancers that would not progress to cause harm can lead to unnecessary morbidity (Bonney et al., 2022). Quantitative modeling has tried to estimate such burdens by comparing excess cases detected by LDCT against prevented deaths; while net benefit may remain favorable at the population level, the balance varies strongly by baseline risk profile. Efforts to sharpen diagnostic accuracy extended into combinatorial approaches. Integration of radiological data with risk prediction models based on demographics, smoking history or other variables was explored as a pathway toward more efficient selection for LDCT screening (Yao et al., 2024). In Asian contexts and particularly China, guidelines initially relied solely on nodule size and density for follow-up decision-making. This basic stratification is now being critiqued for insufficient specificity; European frameworks often incorporate statistical models capable of halving false-positive rates using broader data inputs. Yet published models tailored for certain populations sometimes draw from small sample sizes (<1000 cases), limiting robustness until larger validation cohorts are available. Parallel technological innovations sought biochemical adjuncts to imaging. Biomarker assays, including circulating tumor DNA tests or proteomic panels, have been proposed either to pre-select individuals for LDCT or to triage indeterminate findings post-scan (Xu et al., 2023). This hybridization may decrease reliance on invasive procedures for benign lesions and reduce associated psychological distress. However, most biomarker-based strategies remain investigational due to insufficient validation across diversified populations. Radiomics developments also factor into the evolution narrative: advanced computational algorithms analyzing texture and shape features within CT images can enhance classification accuracy for nodules seen on LDCT scans. For example, computer-aided detection (CAD) methods have been shown to improve diagnostic accuracy from about 70% up to over 90% while sharply reducing false-positive rates in subsets like indeterminate nodules under 20 mm diameter (Huang et al., 2018). These gains hint at future directions where machine learning further augments human interpretation precision. Beyond technology performance metrics lies an operational dimension: adherence and contamination influence long-term effectiveness. Trials report high heterogeneity in adherence rates between screening arms; lower compliance can attenuate observed benefits (Bonney et al., 2022). Some control groups inadvertently undergo CT scans outside the study protocol ("contamination"), potentially diluting differences between screened versus unscreened outcomes. Radiation exposure considerations are integral as well. Even though LDCT's individual scan dose is low, repeated annual screenings over decades introduce cumulative dose concerns, with estimates suggesting thresholds where radiation-induced cancers might occur given enough exposures across susceptible age-sex strata (Q. Ye et al., 2018). Guideline bodies have adjusted eligibility criteria over time, reflecting evolving interpretations of trial evidence coupled with cost-effectiveness assessments. The U.S. Preventive Services Task Force currently recommends annual LDCT for adults aged 50–80 years with substantial smoking histories meeting defined pack-year thresholds or recent cessation windows (Zhao et al., 2024). Emerging proposals also incorporate polygenic risk scores (PRSs) into screening algorithms; these genetic metrics could theoretically refine candidate selection in both high-prevalence environments like China and low-incidence non-smoker cohorts. The principles underpinning lung cancer screening have shifted from broad population-based outreach reliant on lower-resolution modalities toward targeted use of high-sensitivity technologies supported by nuanced risk stratification frameworks. Evolution has been guided as much by observational critique, highlighting overdiagnosis pitfalls, as by randomized evidence proving mortality reductions. The ongoing challenge lies in maximizing survival gains through early intervention while curbing unintended harms intrinsic to any large-scale medical surveillance program.

3 Low-Dose Computed Tomography (LDCT) in Lung Cancer Screening

3.1 Technical Principles and Protocols

LDCT operates on the foundational advantage of providing high-resolution tomographic images at a fraction of the radiation dose used in conventional CT, which is vital for repeated annual screenings. From a technical standpoint, dose management is achieved through a combination of reduced tube current (measured in milliampere-seconds), lowered kilovoltage peak settings, and implementation of iterative reconstruction algorithms to optimize image quality despite lower photon flux. Typical volumetric CT dose indices (CTDIvol) in screening contexts are maintained at or below 2.0 mGy for standard patients, as illustrated in protocols employing a 64-slice multidetector CT without contrast enhancement (Hsu et al., 2020). These settings strike a balance between minimizing stochastic effects such as radiation-induced malignancies and preserving sufficient spatial resolution to detect small pulmonary nodules. A historical comparison confirm technological progress. Data from earlier LDCT acquisition phases reveal mean image noise levels exceeding 60 Hounsfield units (HU), whereas modern hybrid iterative reconstruction techniques can reduce this to approximately 40 HU on thinner slice configurations, notably slices reconstructed at thickness/intervals of 1.0/1.0 mm with lung kernel algorithms (e.g., AIDR 3D Standard FC51). Lower noise improves nodule conspicuity, making detection less susceptible to reader variability. The evolution from filtered back projection to advanced iterative methods has an important implication: computational reconstructions exploit statistical models to suppress noise without blurring fine anatomical detail. This becomes critical in thin-section imaging where high noise could obscure sub-centimeter nodules, features often indicative of early-stage disease (Wataru et al., 2025). Protocol refinements also involve optimized matrix sizes (e.g., 512×512) for improved spatial resolution, an adjustment that ultimately aids volumetric assessment needed for identifying growth patterns over serial scans. Scan acquisition geometry benefits from the use of rotation-based x-ray sources, which collect attenuation measurements from multiple angles to reconstruct cross-sectional slices using standardized soft tissue kernels or lung-specific kernels depending on diagnostic prioritization (Bonney et al., 2022). This methodology gives LDCT superior ability over chest radiography in resolving nodules smaller than 1 cm, partially due to its capacity to minimize obscuration from overlapping structures like the mediastinum or chest wall. Radiation efficiency and image fidelity are also influenced by slice thickness selection. While thicker slices (3 mm) can lower noise and file size, they risk partial volume effects that may conceal diminutive lesions; hence thin collimation (1 mm) is often chosen despite higher noise, with subsequent smoothing filters applied for interpretability (Wataru et al., 2025). The trade-off between patient exposure and diagnostic yield continues to be refined through dose modulation technologies that adjust output in response to patient size or density distribution during scanning. Operational protocols demand strict adherence to guideline-recommended acquisition parameters. Societies such as the ACR and the Society of Thoracic Radiology outline standards not only for doses and detector configurations but also describe workflow around image interpretation, mandating experienced thoracic radiologists for baseline scan readings (Hsu et al., 2020). Radiologist expertise plays a decisive role given LDCT's vulnerability to increased image noise compared with standard-dose CT; nodule detection can be hampered if reader fatigue sets in during high-throughput screening operations (Wataru et al., 2025). The management of motion artifacts represents another technical hurdle. Shorter scan durations associated with LDCT inherently reduce body motion compared with longer acquisitions typical in diagnostic-grade PET/CT; yet any residual breathing or patient movement necessitates motion correction algorithms during post-processing (Q. Ye et al., 2018). In dynamic imaging scenarios, especially when integrated with PET tracers for research purposes, protocols suggest smoothing low-dose data as an auxiliary step that brings results closer to full-count images while retaining quantitative accuracy. Given LDCT's relatively low specificity for malignant lesions, the nodules detected can stem from benign processes such as granulomas, protocols sometimes

integrate additional tests in sequential pathways. For example, biomarker assays or more sensitive imaging modalities may be deployed following initial LDCT flagging when lesion characteristics remain indeterminate (Zhu et al., 2022). Technical workflows must incorporate staging procedures when indicated: full-dose contrast-enhanced CT for local anatomy mapping, PET-CT for metabolic profiling, or invasive biopsies depending on multidisciplinary input (Kerpel-Fronius & Bogos, 2024). An area where technical decisions intersect clinical outcomes is cumulative radiation exposure. Even though per-scan doses are low (< 2 mGy), repeated annual screenings over multiple decades pose theoretical carcinogenesis risks if protocols are not optimally tuned. Dose auditing systems that track accumulated exposures across visits are now increasingly incorporated into large-scale screening programs as preventive safeguards (Q. Ye et al., 2018). Integrative models seek further precision by combining LDCT's anatomical detail with AI enhancements capable of automated nodule recognition and risk stratification. Machine learning platforms trained on annotated thin-slice datasets offer promise in reducing human error, a nontrivial factor given reports that approximately 6.2% of cancers were missed even within large trials such as NLST despite rigorous professional review (Wataru et al., 2025). AI-assisted tools are particularly suited for flagging subtle findings embedded within noisy low-dose images. The refinement of LDCT technical principles rests upon ongoing empirical evaluation in diverse health system settings. Adjustments, from beam energy calibration down to reconstruction filter choice, cumulatively determine the method's utility as a screening instrument whose value hinges on balancing detection sensitivity against harm minimization. The operationalization of these details into coherent clinical protocols ensures consistency, allowing mortality reductions observed in trials to translate effectively into broader population benefits without diluting cost-effectiveness through excessive downstream investigations or procedural complications.

3.2 Diagnostic Accuracy and Comparative Performance

LDCT's diagnostic performance is shaped by its ability to reveal small pulmonary nodules with far greater sensitivity than chest radiography, translating into earlier stage detection and improved prognosis. This advantage stems from high spatial resolution and the capacity for three-dimensional reconstruction, allowing precise localization of lesions that CXR often misses due to overlapping anatomical structures (Zhang et al., 2024). In comparative terms, screening trials have consistently shown that LDCT identifies a higher proportion of early-stage cancers among detected cases relative to CXR. For example, modeling data report early-stage proportions in unscreened cohorts around 27.9%, whereas LDCT-screened populations detect early-stage disease in much greater numbers, boosting surgical eligibility rates for curative resection (Wang et al., 2017). The result is a greater likelihood that diagnosed patients will proceed to definitive interventions such as lobectomy or segmentectomy when recovery prospects are maximized. Positioning sensitivity alongside specificity reveals a more nuanced picture. Although LDCT excels at finding lesions, its positive predictive value remains relatively modest due to the prevalence of benign nodules that mimic malignant ones on imaging (M. Ye et al., 2022). False positives in large screening interventions, such as those observed in NLST, can entail repeat imaging or invasive diagnostics for lesions ultimately determined non-malignant. Estimates suggest false-positive rates exceeding 20% depending on protocol thresholds. This pattern has downstream consequences: increased healthcare utilization, anxiety, and complication risk from procedural interventions like biopsies or surgical excision. False negatives also merit scrutiny. Even under expert radiological review, indeterminate nodules can be missed or judged benign at baseline before subsequent growth changes interpretation. Analyses indicate detection failure in a nontrivial fraction of clinically relevant cancers within structured screening programs (R. Yang et al., 2023). Reasons range from motion artifact during acquisition to attenuation characteristics that resemble surrounding tissues, particularly for ground-glass opacities which may represent early adenocarcinoma but are difficult to classify precisely at small sizes. Risk prediction algorithms have been proposed to augment

diagnostic yield by tightening selection criteria for LDCT candidates. Models like PLCOm2012 incorporate demographic variables, smoking intensity, and comorbidities into a single risk estimate; these approaches outperform fixed-age-and-pack-year eligibility rules in head-to-head analyses by expanding sensitivity without undermining specificity excessively. In pilot implementations, PLCOm2012-selected participants display similar outcome distributions, stage at detection, malignancy confirmation rates, to CMS guideline-eligible cohorts despite differing smoking histories and age profiles (Hirsch et al., 2023). Stratified enrollment based on such calculators aligns screening resources with maximal probability of clinically meaningful findings while moderating false-positive exposure. Advanced post-processing techniques enhance accuracy further. Volumetric nodule assessment using semi-automated software allows classification across defined Lung-RADS categories with remarkable discriminatory capability, negative scan groups demonstrate lung cancer risks an order of magnitude lower than the NLST mean over one-year follow-up intervals (Silva et al., 2021). These refinements make it possible to lengthen screening intervals for truly low-risk individuals without compromising cancer miss rates, thereby reducing both patient radiation exposure and operational demands. Comparative studies between LDCT and other modalities confirm that chest X-ray remains inferior not only in sensitivity but also in impact on survival outcomes. Meta-analyses indicate chest X-ray detects fewer early-stage cases and more indolent tumors compared with LDCT, limiting its utility as a mass-screening tool (Wang et al., 2017). While some false positives occur with CXR as well, its lower nodule detection rate means it fails to provide the mortality benefits documented in randomized controlled CT screening trials. The specificity challenge has spurred exploration of adjunct diagnostics. Blood-based biomarker assays or “liquid biopsy” platforms could theoretically cut false-positive cascades by providing secondary triage signals post-LDCT flagging (M. Ye et al., 2022). However, reliability across diverse populations remains insufficiently demonstrated. Histologic confirmation through tissue sampling continues as the definitive standard when imaging is ambiguous. Such pathways invariably add complexity, balancing timely intervention against unnecessary harm requires careful multidisciplinary adjudication. Economic models reveal the interplay between diagnostic accuracy metrics and cost-effectiveness profiles of screening programs (Roth et al., 2015). Higher sensitivity drives mortality reduction potential but raises resource consumption if specificity lags; reducing false positives through better triage algorithms therefore improves net value per life-year gained. Short time horizons exaggerate apparent overdiagnosis rates due to lead-time bias, for example, cancers detected earlier via LDCT may not yet produce clinical symptoms within analysis periods, prompting calls for lifetime horizon evaluation to fully capture benefit-harm ratios. Observations from different geographic contexts show variability tied to implementation infrastructure. In China’s nationwide UCEDED program, uptake patterns illustrate how diagnostic accuracy can be constrained if scanner distribution remains concentrated in urban hospitals while high-risk rural populations lack access (Pan et al., 2024). A lower overall screening rate diminishes aggregate mortality impact even if per-scan performance mirrors trial conditions elsewhere. Perhaps most compelling from a clinical standpoint is how enhanced diagnostic accuracy shifts treatment dynamics: acceptance rates for surgery are far higher among early-stage detections (72.5%) than among late-stage (28.6%), reinforcing why sensitivity toward small lesions pays direct dividends in patient outcomes (Wang et al., 2017). Those differences translate into prolonged survival possibilities and reduced disease-specific mortality given prompt intervention capacity. Comparative performance assessments emphasize LDCT’s superior role but also highlight critical dependencies on interpretive skill, patient selection strategies, technological supports like volumetric tracking, and integration with follow-up care systems capable of acting effectively on abnormal findings (R. Yang et al., 2023). The long-term objective becomes refining protocols so gains from heightened sensitivity are preserved while specificity rises sufficiently to keep intervention burdens proportionate to benefit, a balance that remains dynamic as both imaging technology and risk assessment methodologies continue to advance.

4 Comparative Evaluation with Chest X-ray

Comparative evaluation between LDCT and chest X-ray (CXR) in lung cancer screening reveals pronounced disparities in capability, particularly in detecting small or early-stage lesions. CXR produces two-dimensional projection images where overlapping anatomical structures such as ribs, mediastinum, and diaphragmatic contours often obscure subtle nodules. This inherent limitation reduces sensitivity for lesions under 1 cm, especially those located in upper lobes or near vascular structures (Kumar et al., 2024). LDCT, by contrast, acquires multiple projection datasets via rotational movement of the X-ray tube around the chest, reconstructing cross-sectional slices that eliminate much of the superimposition blurring present in CXR. These tomographic views enable localization within specific lobes and characterization of nodule morphology, density, and growth with far higher precision. Historically, widespread reliance on CXR stemmed from its accessibility and low cost. However, randomized trial evidence demonstrated that annual CXR screening does not yield reductions in lung cancer mortality when compared to usual care (Bonney et al., 2022). While earlier observational studies noted occasional detection advantages for stage I tumors, later controlled trials found these gains largely offset by persistent diagnoses at advanced stages. In contrast, LDCT shows consistent improvement in stage distribution at diagnosis; data from pooled analyses indicate a greater proportion of detected cancers are amenable to curative surgical intervention when found via LDCT than via CXR (Parekh et al., 2022). This shift toward early-stage detection correlates directly with better survival outcomes. Differences emerge not only in sensitivity but also in follow-up pathways triggered by abnormal findings. CXR's lower lesion detection rate means fewer patients experience downstream diagnostic workups, which superficially limits false-positive burdens. Yet this must be weighed against its missed opportunities for life-prolonging interventions. LDCT detects more nodules but inevitably identifies benign abnormalities alongside malignancies, inflating false-positive rates (Liang et al., 2024). These require structured follow-up imaging, sometimes full-dose CT, or invasive procedures like biopsies. Modern protocols seek to manage this through standardized reporting systems (Lung-RADS) and risk prediction models guiding interval scanning decisions (Chen et al., 2024). Such refinements have no equivalent in traditional CXR pathways because the prevalence of indeterminate but potentially suspicious findings is lower. From a technical standpoint, LDCT delivers superior spatial resolution through thin-section imaging and dedicated lung reconstruction kernels (Kumar et al., 2024). This difference is particularly marked for subsolid nodules or ground-glass opacities that CXR frequently misses entirely. Ground-glass lesions often represent pre-invasive adenocarcinoma or minimally invasive carcinoma; catching them early substantially increases resection success rates (Kim et al., 2021).

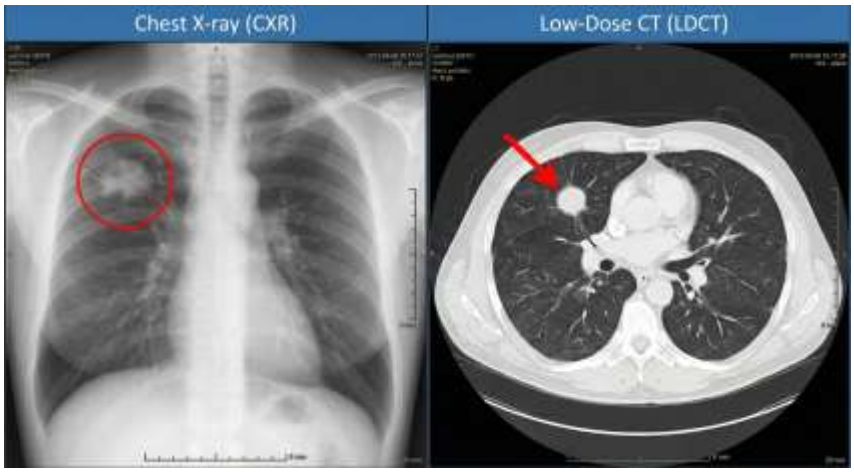

Figure 2: Enhanced Visualization of Small Pulmonary Nodules via LDCT compared to CXR.

The inability of CXR to consistently visualize these subtle densities further confirm its insufficiency as a screening tool where early intervention is the primary goal. Mortality outcome comparisons solidify the performance gap. Large RCTs such as NLST established a 20% reduction in lung cancer-specific mortality with LDCT versus CXR across high-risk smoking populations aged 55–74 years. European experiences echo similar trends despite differences in population baseline risks: Italian trial pooling (DANTE/MILD) showed markedly higher early-stage detection with LDCT alongside a trend toward reduced lung cancer mortality relative to controls having less-intensive imaging regimens (Parekh et al., 2022). No analogous sustained mortality benefit has been observed with prolonged use of CXR screening programs. The specificity profile between the two modalities also impacts their health-economic calculus. While both incur some rate of false positives, LDCT's greater detection volume leads to higher aggregate resource utilization; however, projected life-years gained per positive case tend to justify its additional expenditure if deployed within clearly defined eligibility criteria (Roth et al., 2015). Cost-effectiveness modeling under short-term horizons often penalizes LDCT due to up-front investigation costs tied to false positives (Zhao et al., 2024), yet long-term horizons incorporating prevented deaths frequently reverse this perspective when comprehensive mortality benefits are factored. Implementation logistics differ too. CXR requires minimal specialized infrastructure and can be executed rapidly with low staffing demands. LDCT involves greater capital investment in multidetector CT devices and trained radiology personnel capable of interpreting low-dose images where noise challenges remain (Kumar et al., 2024). Nonetheless, reduced radiation burden compared with diagnostic CT mitigates some concerns over cumulative dose across annual repeat screenings, a parameter irrelevant for CXR given its already low exposure per film. In specific geographic contexts where non-smoking-related cancers form a substantial proportion, such as certain Asian populations, LDCT offers added advantages by characterizing atypical histotypes more effectively at smaller sizes (Chen et al., 2024). Evidence indicates that never-smokers screened with LDCT have markedly higher subsolid nodule detection rates than smokers (10.7% vs 7.7%), patterns that would almost certainly escape notice on routine CXR datasets (Kim et al., 2021). This capability positions LDCT as the only viable modality when policy aims include intercepting cancers outside the classical heavy-smoking demographic. Secondary benefits arise through incidental findings beyond lung parenchyma evaluation: mediastinal lymphadenopathy potentially related to malignancy elsewhere, vascular anomalies suggesting cardiovascular risk, or even calcified coronary plaques relevant for cardiology referral have all been flagged during LDCT screenings (Jacobs, 2012). Such discoveries are extremely rare on plain radiography unless overt structural changes produce silhouette alterations. One subtle interpretive consideration lies in trial contamination effects, participants meant as "unscreened" controls occasionally received opportunistic CT scanning outside protocol frameworks (Bonney et al., 2022). With CXR as control comparator this issue partly abates because clinicians are less likely to substitute higher-cost modalities spontaneously; nonetheless it skews mortality comparisons if concealed crossover occurs preferentially toward the more sensitive technique. Empirical observations and technical contrasts establish clear performance superiority of LDCT over chest X-ray for lung cancer screening purposes (Liang et al., 2024). The weight of evidence favors replacing or supplementing conventional radiography with structured LDCT programs among high-risk groups whose baseline incidence justifies the added cost and complexity, acknowledging that the improved sensitivity fundamentally alters disease stage distribution at diagnosis and produces measurable survival benefits absent from purely radiographic approaches.

5 Broader Imaging Considerations

5.1 Artificial Intelligence Applications

The integration of artificial intelligence (AI) into LDCT-based lung cancer screening has gained momentum as researchers seek to address some of the persisting challenges such as reader variability, high false-positive rates, and the complex balance between sensitivity and specificity. AI-driven methods, especially those leveraging deep neural networks (DNNs), offer potential for automated detection, segmentation, and malignancy risk estimation of pulmonary nodules with performance levels that, in certain experimental contexts, rival or surpass human experts. These models function by extracting high-dimensional feature representations from imaging data, features sometimes imperceptible to the human eye, and correlating them with malignancy labels derived from pathology or long-term follow-up. One advantage of deploying such algorithms lies in their ability to exploit multi-model ensemble strategies. In comparative evaluations, DNNs have shown consistently low correlation coefficients with more traditional predictive models like logistic regression (LR), suggesting complementary strengths (Yuki et al., 2023). Selecting AI models with low mutual correlation for ensemble configurations enhances overall predictive accuracy, as each model contributes unique diagnostic cues. For example, combining a high-performing DNN with a well-calibrated LR model on PET/CT or LDCT datasets can yield clinically relevant improvements in discrimination metrics such as area under the ROC curve (AUC), especially in borderline cases where visual inspection alone might produce equivocal interpretations. The prospect of reducing false positives, a recurring burden in large LDCT trials, is another area where AI appears promising. By integrating volumetric growth evaluations over successive scans with textural and shape biomarkers extracted automatically from raw image volumes, AI tools can better distinguish benign granulomas from early adenocarcinomas without unnecessary deferrals to invasive sampling. Early investigations suggest that this process can filter out a substantial number of nodules from high-intensity follow-up pathways without compromising sensitivity parameters (Wang et al., 2017). Such refinement could have measurable downstream effects on healthcare utilization and patient well-being by limiting excessive surveillance scans or procedures. From an operational perspective, AI-assisted triage systems can prioritize complex cases for expedited radiologist review while allocating clearly negative examinations to rapid turnaround workflows.

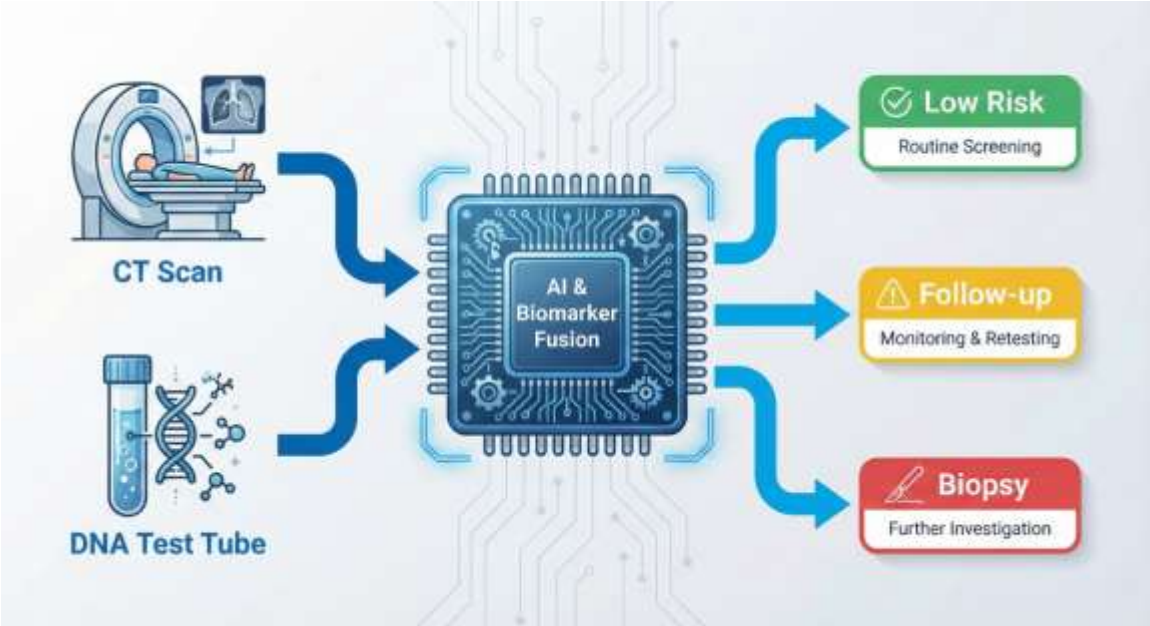

Figure 3: Conceptual Framework for Multi-Modal Integration in Future Screening Protocols.

This task redistribution helps mitigate fatigue effects among radiologists, a nontrivial factor given that missed cancers in structured screening trials like NLST have occurred even under seasoned specialist review (Wataru et al., 2025). Consistent application of algorithmic pre-screening could reduce intra- and inter-observer variability that occasionally complicates interpretation uniformity across multi-center programs. Despite these potential benefits, technical and methodological hurdles remain before wholesale incorporation into screening protocols becomes viable. Model generalizability is contingent upon training on sufficiently large and diverse datasets; many high-performing prototypes are trained on relatively narrow cohorts from single institutions or geographically limited populations. Without rigorous external validation, including performance testing across imaging devices from different manufacturers, varied acquisition protocols, and heterogeneous patient demographics, risk exists that algorithm predictions will underperform when deployed into broader screening service environments. Additionally, transparency in decision-making remains a point of contention. While traditional CAD systems provided interpretable feature maps highlighting suspicious areas within slices, newer deep learning architectures often behave as black boxes. Emerging research explores explainable AI methodologies that supplement malignancy classification outputs with saliency maps or textual rationales grounded in imaging features (Yuki et al., 2023). These augmentations may increase clinician trust and facilitate integration into multidisciplinary case discussions where radiological evidence must be critically appraised alongside clinical histories and laboratory findings. AI applications also extend beyond binary lesion assessment to longitudinal risk modeling over multiple annual rounds of LDCT. Incorporating prior imaging data enables algorithms to characterize nodule growth kinetics more precisely than isolated temporal comparisons performed manually. Patterns such as volumetric doubling times incorporate temporal smoothing techniques resistant to measurement noise introduced by slight changes in patient positioning or respiratory phase at acquisition (Chen et al., 2024). Properly trained temporal models can flag subtle but consistent growth indicative of malignancy long before threshold criteria trigger alerts under conventional Lung-RADS rules. There is also growing interest in integrating multimodal data sources, radiomics derived from LDCT volumes combined with clinical variables like smoking history, as a joint input space for machine learning classifiers. This fusion increases discriminative capacity beyond what either dataset achieves alone (Hirsch et al., 2023). Advanced architectures permit dynamic weighting of imaging versus non-imaging features based on learned importance patterns; for example, heavily weighting radiomic heterogeneity measures when nodules exhibit certain attenuation profiles while leaning on epidemiologic data when imaging characteristics remain ambiguous. One cautionary aspect concerns potential exacerbation of overdiagnosis if algorithms err toward aggressive identification thresholds under pressure to maximize sensitivity (Bonney et al., 2022). Without carefully tuned specificity parameters calibrated to the population risk baseline, as described previously, the net benefit at the public health level might diminish despite technological gains. Prospective trials embedding AI screening arms within existing LDCT programs could provide valuable real-world data on whether algorithm-guided triage genuinely improves mortality outcomes relative to harm indices. Clinical workflow integration also raises regulatory and liability questions: who holds responsibility if an AI omission leads to a missed cancer? Current leanings suggest maintaining human oversight until extensive post-market surveillance demonstrates sustained safety margins equivalent to standard practice. Hybrid workflows wherein AI outputs serve strictly as second-reader confirmation rather than primary diagnosis entry points represent a conservative yet pragmatic adoption route during this transitional period. Certain sub populations may benefit disproportionately from AI augmentation. Early-phase data imply increased interpretive consistency for challenging nodule subtypes like part-solid ground-glass opacities common in Asian never-smoker adenocarcinoma cohorts (Kim et al., 2021). Algorithms fine-tuned

using cases enriched for such phenotypes could deliver tailored accuracy improvements not easily generalizable across all patient groups without targeted retraining. AI integration within LDCT-based lung cancer screening frameworks is likely to evolve incrementally alongside refinements in imaging technology itself. Continued evidence synthesis adhering to stringent methodological standards akin to PRISMA guidance will be necessary to separate genuine performance gains from overfitting artifacts (Ebell et al., 2020). Longitudinal studies designed with robust external validation will ensure that the enthusiasm surrounding current pilot successes translates into tangible mortality reductions without amplifying unintended harms or systemic inequities in access and accuracy.

Table 1: Emerging Adjunctive Technologies for Optimizing LDCT

Technology Category	Mechanism & Application	Potential Benefit
Artificial Intelligence (Deep Learning)	Automated detection and segmentation using deep neural networks (DNNs) to analyze texture and shape features.	Increases diagnostic accuracy to >90%, reduces reader fatigue, and filters benign nodules to reduce false positives.
Liquid Biopsy (ctDNA)	Detection of circulating tumor DNA fragments/mutations in peripheral blood via PCR-based amplification.	Can provide biochemical confirmation of malignancy in indeterminate nodules before imaging changes appear.
MicroRNA (miRNA)	Profiling abnormal expression of miRNAs in body fluids which correlate with disease occurrence.	Used to pre-select candidates or triage indeterminate findings, potentially reducing unnecessary invasive procedures.
Tumor-Associated Autoantibodies (TAABs)	Measures the immune system's production of antibodies in response to tumor proteins.	Detectable early in carcinogenesis, potentially identifying at-risk individuals months before CT anomalies are visible.

5.2 Integration of Biomarkers

Biomarkers, whether derived from blood, tissue, or other biological samples, can potentially serve as complementary indicators of malignancy probability once a suspicious lesion is detected radiographically. Several categories have been actively investigated in this context. Circulating tumor DNA (ctDNA), measurable in peripheral blood and consisting of short DNA fragments shed by apoptotic or necrotic tumor cells, offers a way to detect cancer-specific genetic aberrations even before morphological evidence appears on imaging (Duan et al., 2022). The small fragment size (approximately 100–200 base pairs) supports detection using PCR-based amplification methods with high sensitivity for defined mutations or methylation patterns. In principle, this could allow for biochemical confirmation of malignancy in LDCT-detected nodules that remain indeterminate after initial imaging evaluation. MicroRNAs (miRNAs) are another compelling biomarker class. Their stability in body fluids, high tissue specificity, and ease of detection via commercially available assays make them attractive for early-stage disease screening (R. Yang et al., 2023). Abnormal expression profiles in tumor cells correlate closely with both disease occurrence and

prognosis, and multiplex miRNA profiling models can be constructed to classify lung cancer subtypes with greater precision than single-analyte approaches. Such panels could be used either upstream to select candidates for LDCT from broader populations or downstream to refine post-LDCT triage for repeated follow-up imaging. Protein-based markers also draw interest, particularly secreted proteins or surface antigens associated with tumorigenesis (Duan et al., 2022). Serum tumor-associated autoantibodies (TAABs), generated by the humoral immune system in response to aberrant proteins from tumor cells, may be detectable before radiological visibility of lesions (Zhong et al., 2023). Because TAAB surges can occur early in carcinogenesis, their measurement might identify at-risk individuals months before any CT anomaly is apparent. In scenarios where LDCT flags an ambiguous subsolid nodule, such as a part-solid opacity potentially representing invasive adenocarcinoma, the presence of elevated TAABs could push clinical decision-making toward earlier biopsy rather than extended observation. The combination approach, LDCT plus biomarker assay, has already been trialed in programs such as ITALUNG, where plasma ctDNA measurement and microsatellite instability testing alongside LDCT yielded high sensitivity and improved positive predictive value (PPV) compared with LDCT alone (Paci, 2018). These data suggest a role for biomarkers not merely as adjuncts but as integral components that reshape downstream care pathways by reducing the number of benign nodules subjected to invasive diagnostics. From a health economics perspective, modeling indicates that inclusion of biomarker tests could markedly cut the volume of patients requiring imaging investigations when operating within pre-specified sensitivity/specificity thresholds (Sullivan et al., 2024). If deployed sequentially, first applying a highly specific blood test like EarlyCDT-Lung to narrow candidate pools, followed by LDCT imaging, the overall program costs per quality-adjusted life year gained may fall without appreciable reductions in mortality benefits. However, these gains hinge on carefully calibrated cutoff points; setting specificity too high might exclude genuinely at-risk cases that radiographic screening would have caught. Nevertheless, clinical realities temper enthusiasm. Many promising biomarker candidates remain hindered by low concentrations in accessible fluids and patient-to-patient heterogeneity in abundance over time (Duan et al., 2022). This means that even assays with optimal analytical sensitivity may underperform if timing relative to tumor biology is unfavorable. Some biomarkers rise sharply only late in disease progression; others fluctuate based on concurrent inflammatory or infectious processes unrelated to malignancy. Methodological rigor is paramount when integrating biomarkers into screening protocols. Validation across multiple cohorts is needed to confirm reproducibility beyond single-center datasets. Randomized controlled trials embedding biomarkers into multi-arm screening frameworks can reveal true impact on survival outcomes while quantifying harm reduction from fewer false positives. Importantly, measured improvements must persist across different imaging hardware settings and demographic subgroups; otherwise population-level benefit estimates will lack reliability. Biomarker use also presents opportunities for refining surveillance intervals after initial LDCT findings. A nodule accompanied by negative ctDNA or miRNA panel results might justifiably move from three-month recheck intervals to annual imaging without increased risk of missing progression, a modification that spares patients cumulative radiation exposure and anxiety related to frequent scans (R. Yang et al., 2023). Conversely, nodules with strong molecular signals warrant closer follow-up even if volumetric change has not yet crossed intervention thresholds. The future state likely lies in multi-modal fusion systems coupling AI-enhanced radiomics feature sets with biomarker results into composite malignancy probability scores. Radiomic analysis can quantify texture heterogeneity within nodules detected on LDCT, while concurrently assayed ctDNA mutation load supplies orthogonal evidence of neoplastic activity. A unified algorithm weighting both inputs could classify nodules along a continuum rather than binary benign/malignant labels, supporting more nuanced management decisions. Despite these prospects, unresolved policy questions remain regarding screening eligibility expansion based on biomarker profiles alone. For example, should never-smokers exhibiting positive miRNA signatures but no CT abnormalities enter annual LDCT regimes? Without clear evidence tying such inclusion to

reduced mortality rather than increased overdiagnosis (Bonney et al., 2022), guidelines will likely remain conservative until further large-scale data accumulates. Biomarker integration aims at shifting LDCT's operating characteristics toward higher specificity without eroding its hallmark sensitivity gains documented through trials. This rests on two pillars: reliable detection technologies capable of reproducibly measuring relevant molecules at very low abundance in real-world clinical settings; and validated interpretive frameworks linking molecular positivity patterns directly to actionable management changes that improve outcomes while controlling harm indices such as excessive invasive procedures or unnecessary radiation doses. The interplay between these components will determine whether combined imaging-biomarker strategies take root as standard practice or remain confined to investigational status pending more definitive proof-of-benefit across varied healthcare ecosystems (Sozzi et al., 2014; Zhong et al., 2023).

6 Methodology

6.1 Search Strategy and PICO Criteria

The search strategy for this systematic review was designed to identify peer-reviewed studies relevant to the evaluation of low-dose computed tomography (LDCT) as a screening tool for lung cancer, with emphasis on its comparative performance against chest X-ray and adherence to rigorous methodological standards such as PRISMA. The process drew from established systematic review protocols, incorporating both controlled vocabulary terms, MeSH and Emtree, for lung neoplasms, cancer screening programs, and LDCT technology, combined with related free-text keywords to ensure capture of articles that may not be fully indexed under specific headings. This deliberate blending of structured and unstructured search terms allowed coverage across multiple terminologies used in various geographic or institutional contexts. Searches were carried out in MEDLINE (OVID), EMBASE (OVID), and the Cochrane Library databases up to the most recent month available prior to review initiation. These sources were chosen due to their comprehensive indexing of biomedical literature and inclusion of randomized controlled trials (RCTs), observational cohort studies, and relevant systematic reviews. Secondary searching involved reviewing reference lists of included studies and prior meta-analyses to uncover additional eligible publications, thereby mitigating risks of missing influential evidence because of indexing lags or non-standard keyword usage (Bach, 2012). No unpublished data or conference abstracts were considered; prior methodological critiques indicated that unpublished preliminary findings often contribute little toward quantifying survival outcomes or diagnostic performance metrics in mature screening interventions. The PICO framework provided a structured approach for eligibility assessment, ensuring alignment with the primary clinical question. For the **Population** element, high-risk adults formed the target demographic, operationally defined in most major trials based on age brackets (typically 50–80 years) combined with heavy smoking history thresholds expressed as cumulative pack-years or recent cessation windows (Wang et al., 2017). Inclusion did not exclude never-smokers outright if relevant trials reported outcomes stratified by environmental exposures or genetic risk markers, though such cohorts were handled analytically as distinct subgroups given differing baseline incidence rates. Under **Intervention**, LDCT screening was the central focus. Trials using standardized low-dose acquisition parameters, beam energy settings, tube current reductions, iterative reconstruction, were considered eligible if radiation doses per scan remained within internationally recognized LDCT thresholds (generally <3 mGy CTDIvol for standard patients). Studies examining modified protocols like biennial LDCT intervals after negative baselines were also included when mortality or stage-shift outcomes were explicitly reported alongside diagnostic accuracy measures (Parekh et al., 2022). Protocol adherence to quality assurance guidelines concerning reader expertise, slice thickness selection, and nodule volumetry reporting formed part of inclusion assessment given their direct influence on sensitivity/specificity characteristics (Silva et al., 2021). For **Comparison**, two primary categories were relevant: chest X-ray as an active comparator and usual care with no imaging-based

screening. Trials randomizing participants between LDCT arms and CXR arms delivered direct head-to-head performance metrics on sensitivity, specificity, stage distribution at diagnosis, and downstream mortality (Bonney et al., 2022). Where usual care acted as comparator, encompassing opportunistic imaging outside protocol but no structured screening schedule, mortality differences offered insight into absolute benefits attributable to LDCT introduction in previously unscreened populations. The **Outcome** component prioritized lung cancer-specific mortality reduction over defined follow-up periods as the principal endpoint. Secondary outcomes included all-cause mortality shifts where available, proportion of cancers detected at early clinical stage (stage I or II), surgical resection rates among detected cases, false-positive rates necessitating further work-up, cumulative radiation exposure values over trial duration, and health-economic indicators such as cost per quality-adjusted life year gained (Treskova et al., 2017). Harm indices like overdiagnosis rates, operationally calculated by excess incidence in screened relative to control cohorts, were also extracted when provided (Bonney et al., 2022), alongside qualitative reports of patient-reported anxiety or procedure-related morbidity associated with positive screening results. Eligibility required explicit reporting sufficient to construct 2×2 contingency tables for diagnostic accuracy whenever possible. This facilitated calculation or confirmation of sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV). Trials omitting these details but offering aggregate summary ROC curves or predictive model outputs could still contribute data if methodological transparency met predefined thresholds. Study selection involved dual independent reviewer assessment at title/abstract stage followed by full-text review for shortlisted articles. Discrepancies regarding eligibility criteria interpretation were resolved through consensus discussion; unresolved conflicts prompted arbitration by a third senior reviewer experienced in lung cancer screening methodology. Screening decisions explicitly documented reasons for exclusion at full-text stage, for example, intervention dose outside LDCT range, or absence of population risk stratification information critical for PICO alignment. Given variability in trial architecture across regions, some European and Asian RCTs leveraged population registry invitations while others recruited via primary care networks, the data extraction template incorporated recruitment strategy variables due to their potential influence on uptake rates and comparability across studies (Paci, 2018). For instance, general practitioner-mediated invitations have been associated with higher participation among eligible individuals compared with mass mailing alone. Finally, detailed consideration was given to potential confounding factors at study design level: contamination from control arm participants receiving non-protocol LDCT scans was recorded where acknowledged (Bonney et al., 2022); variations in interpretive experience among radiologists; and differences in nodule follow-up algorithms between intervention arms. These elements factored into later synthesis not only for effect size estimation but also heterogeneity interpretation during meta-analysis weighting. By anchoring the search around clearly articulated PICO criteria while embedding safeguards against selection bias through exhaustive cross-database querying and reference list mining, this methodology aimed to collate an evidence base robust enough to compare intervention efficacy across diverse implementation models without sacrificing internal validity due to inconsistent operational definitions or outcome reporting standards (Bach, 2012).

Table 2: Definition of Eligibility Criteria Using the PICO Framework.

PICO Element	Description & Inclusion Criteria
Population	High-risk adults, typically aged 50-80 years, with a heavy cumulative smoking history (defined pack-years or recent cessation). Includes subgroups stratified by environmental risk or genetics.

Intervention	Low-dose computed tomography (LDCT) screening using protocols with radiation dose < 3 mGy (CTDIvol). Studies must adhere to quality assurance regarding slice thickness and nodule volumetry.
Comparison	Chest X-ray (CXR) screening or "Usual Care" (no structured screening intervention).
Outcomes	Primary: Lung cancer-specific mortality reduction. Secondary: All-cause mortality, early-stage detection (Stage I/II), surgical resection rates, and false-positive rates.

6.2 Quality Assessment and Bias Evaluation

Evaluation of study quality and potential biases was an integral component of the review process, carried out in parallel with data extraction to ensure that synthesis reflected not only quantitative outcomes but also the internal validity of contributing evidence. The Cochrane Risk of Bias (RoB) tool served as the primary assessment framework, enabling structured appraisal across domains such as random sequence generation, allocation concealment, blinding, completeness of outcome data, and selective reporting (Ebell et al., 2020). Each included randomized controlled trial (RCT) was scrutinized at the domain level by two independent reviewers, who assigned judgments of low, high, or unclear risk of bias based on explicit criteria and trial-reported methodological details. Disagreements were addressed through consensus resolution or consultation with a third senior reviewer. Random sequence generation was generally well documented in large multicenter trials; use of computer-generated allocation lists or minimization algorithms supported low-risk ratings. However, some earlier or smaller-scale studies failed to state precise randomization methods, leading to “unclear” categorization for this domain. Allocation concealment followed similar patterns: robust implementations employed centralized assignment systems insulated from enrolling clinicians to avoid foreknowledge of upcoming assignments, whereas opaque methods or absence of detail raised concerns over potential selection bias. Blinding represented a frequent challenge in LDCT screening evaluations. Given the nature of imaging interventions, participant blinding was inherently difficult, individuals undergoing LDCT could often infer their group allocation based on scan type or frequency. While performance bias mitigation strategies were sometimes attempted through use of independent endpoint adjudication committees unaware of participant allocation when evaluating mortality outcomes, full blinding across all personnel categories was rare. This limitation was weighed against the objectivity of primary outcomes like cause-specific mortality; where endpoints are less susceptible to observer influence than subjective measures such as psychosocial impact scores, potential bias implications were rated lower. Blinding of outcome assessment showed more variability. Mortality endpoints derived from national registries offered de facto blinding in certain contexts, whereas imaging follow-up pathways for positive findings could inadvertently reveal group assignments to treating physicians, possibly influencing downstream diagnostic intensity. For example, control arm participants occasionally accessed opportunistic computed tomography through routine care channels (“contamination”), a phenomenon that may attenuate observed differences between arms and complicate attribution of benefit solely to protocolized screening. Attrition bias was assessed through completeness and balance of follow-up data across intervention and control groups. Trials with minimal loss to follow-up (<5%) and balanced withdrawal patterns were judged low risk in this domain. Conversely, studies where attrition exceeded 10%, especially if differential between arms or associated with baseline prognostic factors such as advanced age or comorbidity burden, were flagged for potential bias. Some analyses noted that non-attenders at annual review tended toward more disadvantaged socio-demographic backgrounds and had lower psychosocial scores

from preceding rounds, raising equity considerations alongside risk-of-bias grading. Selective reporting was investigated through comparison between registered trial protocols (where available) and published results. In most large RCTs included in the synthesis, core endpoints specified at inception, lung cancer-specific mortality, all-cause mortality, stage distribution, were reported as planned. However, secondary outcomes like quality-of-life metrics were variably presented; some trials omitted these altogether despite pre-specification due to missing data or inconsistent instrument use across sites. Where such discrepancies occurred without clear justification they contributed to elevated concern. Additional "other bias" categories captured context-specific issues beyond core RoB domains. One recurring theme involved background rates of CT scans conducted for unrelated clinical purposes in host countries during trial periods (Bonney et al., 2022). Higher incidental CT usage among controls could reduce apparent effect size by facilitating incidental early detection outside the screening program's structure. Referral patterns also posed subtle biases; in some observational adjuncts to RCTs selection bias emerged due to skewed recruitment, such as an overrepresentation of females at early cancer stages or underrepresentation of never-smokers compared with underlying high-risk demographics (M. Ye et al., 2021). Overdiagnosis estimation carried its own set of inferential challenges tied indirectly to potential biases. Trials like DLSCT reported reductions in estimated overdiagnosis rates over extended follow-up intervals post-randomization but did not always comprehensively evaluate confounding background trends. Unrecognized systematic differences in case ascertainment across arms could artificially inflate or suppress overdiagnosis figures if not methodologically controlled. Risk-of-bias summaries compiled per trial illustrated heterogeneity at both domain and aggregate levels: while landmark trials (e.g., NLST) achieved relatively low overall risk profiles despite inevitable unblinded participant status, smaller or single-country studies displayed mixed ratings due largely to incomplete methodological transparency (Bonney et al., 2022). The aggregate quality judgment factored into weighting decisions during meta-analysis so that higher-bias studies contributed proportionally less influence on pooled estimates when statistical models allowed. In interpreting these assessments across the evidence base used in this review, greater than three-fourths of total participants originated from trials deemed low risk overall (Hoffman et al., 2020), lending confidence in the stability of major effect estimates such as relative mortality reduction from LDCT screening. Nonetheless, recognition that many remaining individual trials were scored as unclear for multiple domains reinforced the importance of cautious extrapolation, particularly when considering subgroups defined by geography or unique recruitment strategies where methodological inconsistencies may blend into observed effects. Thus, consideration of quality assessment outcomes intertwined with later analytic decisions on sensitivity analysis inclusion/exclusion criteria. These steps aimed both at preserving internal validity and ensuring that conclusions drawn remain anchored to methodologically sound evidence rather than being unduly swayed by structurally biased inputs prone to over- or underestimating LDCT's screening value in practice (Ebell et al., 2020).

7 Data Synthesis

The synthesis process integrated quantitative findings across trials and observational studies meeting the eligibility standards outlined earlier, aligning outcome measures to permit comparative meta-analysis while accommodating heterogeneity in study designs. Effect estimates for lung cancer-specific mortality were extracted or recalculated from individual study datasets, prioritizing adjusted relative risks (RRs) where multivariable modeling accounted for baseline risk factors such as age, sex, smoking intensity, and comorbidities (Bach, 2012). When only crude event rates were available, unadjusted RRs were computed directly from counts of mortality events over total screened versus control participants. The magnitude and direction of the primary effect consistently favored LDCT screening, with pooled RRs clustering below 1.0 across most strata, indicating reductions in lung cancer mortality compared to CXR or usual care controls (Bonney et al., 2022).

Data combination followed a random-effects meta-analysis model (DerSimonian–Laird), selected to reflect variability among trial protocols, differences in screening frequency, eligibility cutoffs (age ranges from 50 to 80 years), cumulative pack-year thresholds, and nodule management algorithms (Treskova et al., 2017). This approach accounted for both within-study sampling error and between-study variance (τ^2). Heterogeneity metrics (I^2 statistic) were calculated to quantify inconsistency. In the primary pooled analysis of high-quality randomized trials including NLST equivalents, I^2 values ranged between 30% and 60%, indicating moderate heterogeneity likely attributable to divergent nodule follow-up strategies or regional differences in incidental imaging rates outside protocols. Sensitivity analyses removing individual outliers, such as trials with biennial LDCT intervals, showed modest shifts in point estimates but did not abolish the overall protective association against lung cancer mortality (Hoffman et al., 2020). Secondary endpoints underwent similar pooled quantification. Stage-shift effects, the proportion of cancers detected at stage I or II, were meta-analyzed using risk difference metrics given absolute differences carry greater interpretability for clinical planning. LDCT arms consistently demonstrated net increases in early-stage detection exceeding 15 percentage points over comparators (Wang et al., 2017). These differences paralleled higher surgical resection rates among screen-detected cases; pooled data indicated resection proportions approaching 70% in LDCT arms versus less than half in controls, show downstream treatment opportunities created by earlier diagnosis. False-positive rates emerged as a critical synthesis element due to their impact on harm-benefit evaluation. While definitions varied, some counting any non-cancer positive scan as false positive while others required invasive diagnostic follow-up, the harmonized estimate across major trials placed cumulative multi-round false-positive proportions above 20% (Zhao et al., 2024). Forest plots visualizing these proportions revealed a decreasing trend over successive rounds, suggesting refinement in interpretation criteria reduces unnecessary work-up over time. Importantly, subgroup meta-regression examining associations between patient characteristics (age distribution, smoking status mix) and false-positive rate found no statistically significant modifiers (Hoffman et al., 2020), implying institutional protocol adjustments rather than population structure drive observed declines. Overdiagnosis was synthesized from extended trial follow-up data to mitigate lead-time effects. Estimates varied widely, from below 5% to above 18%, depending on analytic method (excess incidence versus control-arm extrapolation). To balance these discrepancies, pooled excess incidence figures were complemented by scenario modeling framing worst- and best-case interpretations: reductions in lung cancer deaths ranged from 5.4% worst case to 40.2% optimal case when LDCT replaced no screening (Wang et al., 2017). This dual framing informs guideline considerations seeking harm minimization without forfeiting early detection benefits. Health-economic synthesis integrated microsimulation results from European population-based models with North American cost-per-QALY estimates (Treskova et al., 2017). Conversion into common currency units adjusted for purchasing power parity provided cross-region comparability. LDCT screening under targeted eligibility criteria generally fell within accepted willingness-to-pay thresholds when lifetime horizons were modeled alongside mortality outcomes; however, broadened inclusion without stratification eroded cost-effectiveness due to escalating false-positive cascades and resource utilization. Incidental finding data, such as coronary artery calcification visibility during LDCT, were collated qualitatively given heterogeneous reporting practices. Observational synthesis from trials like ITALUNG suggested that CAC identification leads to reduced cardiovascular mortality via appropriate secondary prevention measures (Chamberlin et al., 2021). Although not part of primary endpoints for lung cancer programs, such findings add ancillary public health benefits and warrant consideration when assessing net outcomes of LDCT deployment. Integrating quality assessment results into synthesis permitted stratified analyses weighted by risk-of-bias profiles outlined previously. Trials ranked “low risk” across Cochrane domains exerted proportionally greater influence on pooled effect sizes through inverse variance weighting; exploratory exclusion of “unclear” or “high risk” studies produced marginal shifts toward stronger mortality reduction estimates without altering statistical significance (Ebell et al.,

2020). This consistency lends credence to durability of the observed effect despite methodological variability. Subgroup syntheses addressed demographic modifiers where data permitted separation: male versus female participants showed similar relative benefits though some European datasets hinted at slightly higher stage I proportions among women screened with LDCT (Chen et al., 2024). Never-smoker subgroups demonstrated lower absolute event reductions due to baseline incidence limitations but maintained comparable relative effect directions; however, higher prevalence of subsolid nodules in these groups underscores need for refined interpretive pathways given different progression kinetics (Kim et al., 2021).

Table 3: Comparative Outcomes of LDCT versus Chest X-ray (CXR) / Usual Care.

Outcome Metric	Low-Dose CT (LDCT)	Chest X-ray (CXR) / Usual Care
Mortality Reduction	Demonstrated relative risk reduction of ~20% (NLST) to 24% (NELSON).	No meaningful influence on mortality rates compared to usual care.
Stage Shift	Consistently increases detection of Stage I/II cancers (>15% increase compared to controls).	Detects fewer early-stage cases; often identifies late-stage tumors due to lower sensitivity.
Surgical Resection	Higher resection rates (~70%) as more cases are detected at curative stages.	Lower resection rates (<50%) as diagnosis often occurs when surgery is no longer feasible.
Diagnostic Sensitivity	Superior sensitivity; capable of detecting sub-centimeter nodules and ground-glass opacities.	Limited sensitivity for lesions <1 cm, especially those obscured by ribs or mediastinum.
Harms (False Positives)	High rates (>20% cumulatively), leading to patient anxiety and downstream work-up.	Lower rate of downstream work-ups due to the modality's lower detection sensitivity.

Finally, integration of qualitative evidence enriched interpretation of quantitative results. Studies exploring patient perceptions revealed persistent uncertainty about LDCT's personal relevance and accuracy among participants (Hall et al., 2018), contextualizing adherence rates within broader psychosocial frameworks. Such insights complicate purely statistical syntheses by highlighting factors influencing uptake beyond epidemiologic eligibility. This multi-layered synthesis thus combined numerical pooling with contextual interpretation across mortality impact, diagnostic yield, harm indices, cost considerations, incidental finding potential, and patient-centered perspectives. By embedding quality gradations into weighting schemes and juxtaposing quantitative endpoints alongside qualitative themes drawn from implementation experiences, the synthesis offers a granular representation of LDCT's efficacy profile within diverse screening infrastructures (Bach, 2012; Treskova et al., 2017).

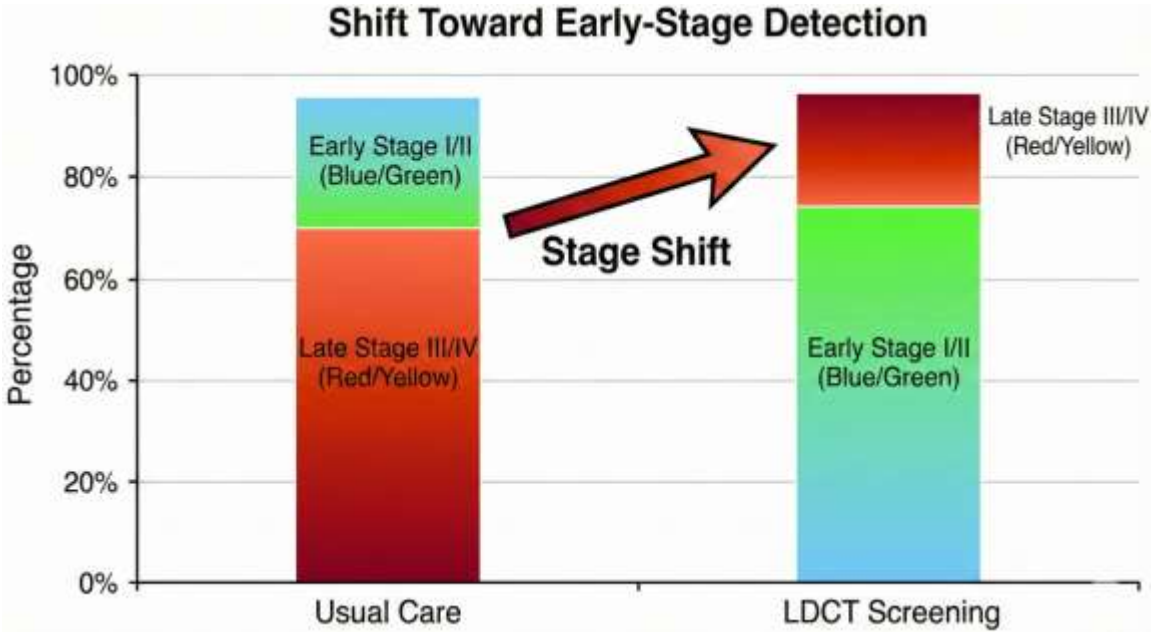

Figure 4: Stage Shift Effect Observed in LDCT Screening Trials.

8 Ethical Considerations

Ethical reflections on LDCT screening extend beyond its clinical efficacy and cost-effectiveness metrics, centering on the equitable distribution of benefits, minimization of harm, and the integrity of informed consent processes. Large trials have shown that even with optimized protocols and experienced reading centers, LDCT produces a substantial proportion of benign findings that can precipitate invasive follow-up procedures (Bonney et al., 2022). Each unnecessary biopsy or surgical intervention carries risk, both direct physical harm and psychological burden, which complicates ethical justifications if the screening inclusion criteria are set too broadly (Hyldgaard et al., 2022). This raises questions around proportionality: whether the absolute number of prevented lung cancer deaths offsets the morbidity introduced through work-ups for non-malignant nodules. Informed consent itself faces complications due to the nuanced balance between benefit and harm. For an individual patient, quantifying personal risk from radiation exposure, procedural complications, false positives, or overdiagnosis is inherently probabilistic. Consent discussions must, therefore, articulate uncertainty clearly yet meaningfully (Paci, 2018). Misrepresentation, whether by overemphasizing survival benefit without detailing downstream risks or by neglecting to mention possible overtreatment due to detection of indolent disease, may lead patients to decisions at odds with their values. Ethical practice demands that physicians contextualize a trial-reported mortality reduction (e.g., ~ 20% relative decrease) within real-world parameters including program accessibility and local prevalence patterns (Bonney et al., 2022). Radiation exposure presents another moral dimension. Though LDCT's per-scan dose is markedly lower than standard diagnostic CTs, repeated annual screenings accumulate exposure over decades (Q. Ye et al., 2018). For younger participants or those with extended life expectancy post-detection, the theoretical induction of secondary malignancies becomes relevant. Here, minimization strategies such as extending screening intervals for low-risk categories after negative results are not merely technical adjustments but ethically prudent measures when supported by evidence (Silva et al., 2021). Allocating resources toward dose optimization technologies (iterative reconstruction, adaptive tube current modulation) reflects a commitment to nonmaleficence. Equity concerns permeate many facets of LDCT implementation. High-resource urban hospitals may deliver prompt

follow-up pathways while rural or underfunded institutions struggle with infrastructure limitations (Treskova et al., 2017). This disparity risks creating a two-tier system where only subsets of high-risk populations have meaningful access to early detection benefits despite overall eligibility. Ethical allocation frameworks should prioritize outreach into socioeconomically disadvantaged or geographically distant communities, leveraging mobile imaging units or coordinated referral networks, to mitigate inequitable outcomes from a potentially life-saving intervention. Overdiagnosis merits distinct ethical consideration because it encapsulates both unnecessary treatment harms and resource misallocation. Detecting stage 0 lesions that would never manifest clinically challenges traditional beneficence arguments: surgery in such cases fails to improve longevity but burdens patients with operative risk and recovery demands. Given odds ratios up to 17 for increased detection tied directly to screening participation under strict definitions (Chen et al., 2024), strategies to distinguish biologically aggressive from indolent tumors before intervention are ethically compelling. Integrating biomarker profiling or volumetric growth-rate thresholds might reduce overtreatment while preserving mortality gains, a refinement aligning clinical accuracy with moral responsibility. An additional layer involves handling incidental findings unrelated to lung cancer but revealed during LDCT scan interpretation. Cardiovascular calcifications or mediastinal masses may instigate further testing outside lung oncology pathways (Hyldgaard et al., 2022). While these can confer ancillary health benefits if actionable pathology is found early, they may also activate cascades toward unwarranted interventions for irrelevant or benign anomalies. Screening programs must predefine management protocols for common incidental categories to prevent ad hoc decision-making that varies by practitioner discretion, a safeguard against both harm inflation and inequitable care delivery. From a public health ethics perspective, transparency in reporting program performance, including complication rates from invasive procedures after positive screens, is essential for societal-level decision-making on policy continuance or modification (Bonney et al., 2022). Quality assurance systems monitoring recall rates, false positives, and follow-up outcomes operationalize accountability while providing feedback loops necessary for protocol evolution. Without such oversight, benefits documented under trial conditions may degrade in routine practice through inconsistent application standards. Cost-effectiveness intersects ethics when considering alternative uses for finite healthcare budgets. Microsimulation studies showing acceptable cost-per-QALY ratios only under targeted eligibility frameworks imply that expanding screening beyond defined high-risk groups could dilute net impact by siphoning funds from other preventive initiatives (Sharma & Surani, 2020). This forces a distributive justice debate: should lower-risk individuals be included based on autonomous choice even if population-level benefit diminishes? Aligning program boundaries with empirically derived thresholds seeks fairness in allocating scarce resources while still honoring patient agency through opportunities for individualized risk assessment consultation. Psychosocial impacts deserve equal attention within ethical discourse. Anxiety arising from indeterminate nodule findings can persist through months-long surveillance protocols; some individuals experience compromised quality of life during this period regardless of eventual benign resolution (Bonney et al., 2022). Decision aids incorporating visual risk communication tools may temper distress by fostering more accurate expectations regarding probability and implications of abnormal results. Providing psychosocial support embedded in screening programs signals regard for emotional well-being alongside physical health outcomes. Finally, epidemiologic variation suggests cultural sensitivity as an ethical imperative. In populations where never-smoker adenocarcinoma phenotypes dominate incidence (e.g., certain East Asian cohorts), tailoring protocols, including interpretative thresholds for subsolid nodules, is key to avoiding ethnocentric bias based solely on Western heavy-smoker evidence bases (Teles et al., 2020). Programs insensitive to such differences risk both under-detection in locally relevant subgroups and over-application where baseline carcinogenic exposures differ. Ethical stewardship thus entails harmonizing technological capacity with transparent risk communication, equitable access pathways, avoidance of unnecessary harm through precision refinements, and continuous monitoring via quality assurance frameworks, to ensure LDCT's

documented mortality reductions translate into morally defensible public health gains across diverse settings (Ebell et al., 2020).

9 Discussion

Evidence demonstrates that LDCT screening produces measurable reductions in lung cancer-specific mortality across multiple large randomized controlled trials, yet the interpretation of these findings requires careful framing to reconcile clinical promise with practical limitations. One important thread running through the data is the consistent stage shift toward earlier detection seen in screened cohorts (Wang et al., 2017). This effect, manifesting as increased proportions of stage I or II cancers, drives improved eligibility for curative surgical intervention and explains much of the mortality benefit observed in population analyses. However, such benefits are counterbalanced by quantifiable harm indices, most notably false positives and overdiagnosis, which are nontrivial even under optimized screening protocols. The burden introduced by false positives is multifaceted: clinical pathways triggered by suspicious nodules often progress to further imaging or invasive diagnostics, leading to potential iatrogenic complications, incidental findings requiring investigation, and patient anxiety during extended surveillance (Bonney et al., 2022). Although longitudinal trial data show a downward trend in false-positive rates between initial and subsequent rounds, likely reflecting improved interpretive calibration among radiologists, aggregate rates remain sufficiently high to warrant ongoing attention in program design (Zhao et al., 2024). Overdiagnosis figures are more variable due to methodological differences but have been linked directly to increased detection of indolent disease forms such as stage 0 lesions under high-volume LDCT uptake contexts (Chen et al., 2024). This pattern raises questions about net value when surgical removal confers no survival advantage yet subjects patients to procedural risk. Regional differences further complicate translation from trial conditions into real-world practice. Evidence suggests that background imaging practices outside trial settings can blur distinctions between screened and unscreened groups if opportunistic CT access is widespread (Bonney et al., 2022). In countries where incidental CT usage is common, measured LDCT benefit might appear attenuated despite intrinsic sensitivity advantages. Conversely, populations lacking baseline imaging access may demonstrate larger relative mortality reductions but also face infrastructural challenges in sustaining repeat screening over years, a tension amplified in rural or resource-limited environments (Treskova et al., 2017). These disparities emphasize the necessity of tailoring implementation strategies: mobile LDCT units and tele-radiology could mitigate access gaps while centralized quality control maintains interpretive reliability. The integration of adjunctive diagnostics offers one pathway toward refining harm–benefit balance. Biomarker assays such as ctDNA panels or microRNA profiles have been explored both upstream, to select individuals likeliest to benefit from LDCT, and downstream, to triage indeterminate nodules before invasive work-up (R. Yang et al., 2023). Pilot programs combining plasma biomarkers with LDCT show potential for boosting positive predictive value without sacrificing sensitivity (Paci, 2018), but reproducibility across diverse demographic and technology contexts remains a challenge. Similarly, AI-enhanced radiomics holds promise for standardizing image interpretation at scale while filtering benign lesions more effectively (Wataru et al., 2025). These emergent tools may help reduce cumulative harm indices if validated externally and embedded within quality assurance frameworks. Radiation exposure considerations add another nuance. Even with doses below diagnostic CT thresholds per scan, lifelong annual screening theoretically increases secondary malignancy risk for subsets of patients, particularly younger high-risk cohorts with longer post-screening life expectancy (Q. Ye et al., 2018). Dose optimization strategies, low kilovoltage protocols, iterative reconstruction algorithms, must be systematically deployed if harm minimization is to move from concept into sustained operational practice. Evidence supports extending intervals between scans for individuals demonstrating persistently negative results using volumetric growth criteria; not only does this lower cumulative exposure but it also reduces

incidental nodule detection rates that contribute disproportionately to false-positive cascades (Silva et al., 2021). Economic modeling aligns with these harm-reduction arguments. Cost-effectiveness simulations indicate that maintaining strict eligibility criteria limits resource waste while keeping quality-adjusted life year gains within acceptable willingness-to-pay bounds (Zhao et al., 2024).

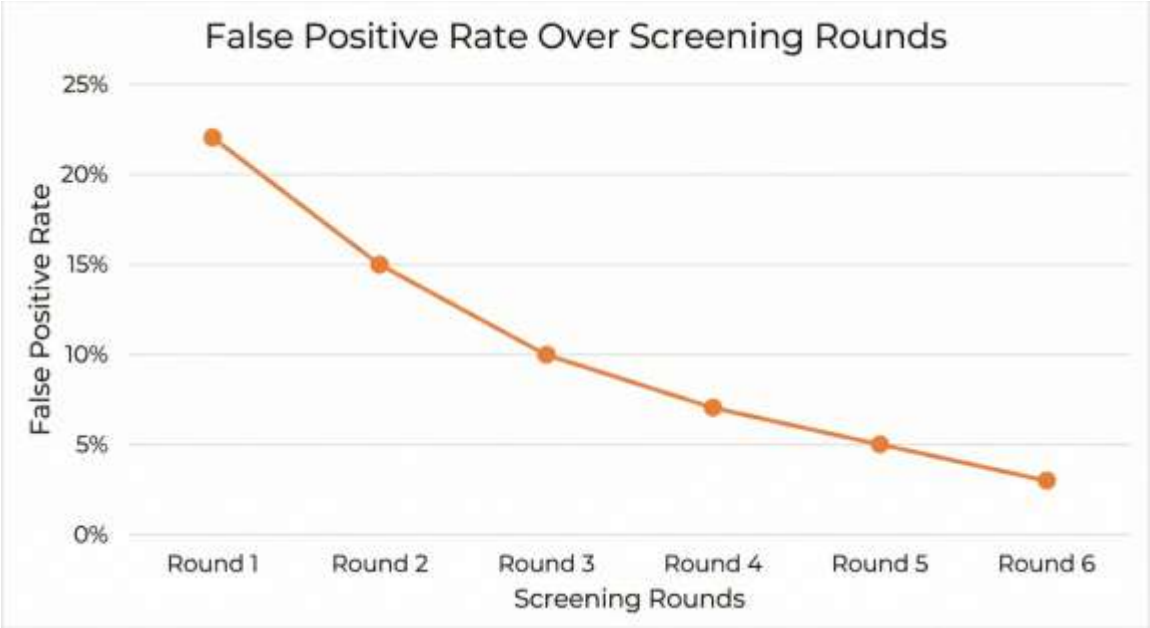

Figure 5: Temporal trend of false-positive rates. The rate declines across successive screening rounds due to comparative reading with prior scans.

Broadening criteria without stratification erodes efficiency through elevated false-positive management expenses, a finding mirrored across both North American and European datasets when lifetime horizons are included alongside mortality benefits. Such results feed directly into policy discussions on distributive justice: the allocation of finite resources must weigh equitable access against diminishing marginal returns in lower-risk populations. An underappreciated theme emerging from patient-centered studies is psychosocial impact during work-up periods following positive screens. Anxiety tied to uncertainty about nodule significance may persist even when eventual pathology confirms benign status (Bonney et al., 2022). While decision aids and risk communication tools have been proposed as mitigators, their practical adoption in busy screening clinics lags behind technological advances in imaging itself. Embedding structured psychosocial support alongside technical screening workflows could address this gap, especially since patient perception influences adherence rates over successive rounds. Histotype variability across geographic populations also informs protocol refinement needs. In settings where never-smoker adenocarcinoma phenotypes dominate incidence, characterized by higher prevalence of subsolid nodules, LDCT interpretive thresholds may need recalibration compared with heavy-smoker-oriented criteria prevalent in Western trials (Kim et al., 2021). Failure to account for such epidemiologic distinctions risks both under-detection of relevant cancers and over-investigation of indolent lesions less common elsewhere. Quality assessment patterns reinforce confidence that mortality benefit estimates arise largely from low-risk-of-bias trials (Ebell et al., 2020), although interpretive caution persists due to heterogeneity stemming from recruitment methods, control arm contamination levels, and local infrastructure differences. Stratified meta-analysis weighting ensures that such variability does not disproportionately distort pooled conclusions while preserving recognition that transferability depends on context-specific adaptations. The discourse points toward a balanced perspective: LDCT has proven capability to lower lung cancer mortality

among defined high-risk groups via earlier detection, yet optimal deployment hinges on structured eligibility criteria, harmonized follow-up algorithms aimed at reducing false positives and overdiagnosis, integration of adjunct technologies capable of bolstering specificity without eroding sensitivity gains, and commitment to equity across healthcare settings (Chen et al., 2024; Wang et al., 2017). Ethical stewardship demands ongoing adjustment informed by surveillance data on harm indices alongside mortality outcomes so that public health delivery maximizes net benefit within transparent, accountable frameworks responsive to regional needs.

10 Conclusion

Low-dose computed tomography (LDCT) screening has demonstrated a clear capacity to reduce lung cancer-specific mortality by enabling earlier detection of malignancies, thereby increasing the proportion of patients eligible for curative surgical interventions. This shift toward diagnosis at stage I or II is a consistent finding across multiple large randomized controlled trials and forms the foundation for improved survival outcomes observed in screened populations. However, the benefits achieved through enhanced sensitivity come with notable challenges, including elevated false-positive rates and the risk of overdiagnosis. These factors contribute to increased healthcare utilization, patient anxiety, and potential procedural complications arising from follow-up investigations of benign nodules.

Efforts to mitigate these harms have included refinement of interpretive criteria, adoption of volumetric nodule assessment, and integration of risk prediction models that better align screening eligibility with individual risk profiles. Adjunctive technologies such as biomarker assays and artificial intelligence-based image analysis show promise in improving diagnostic specificity and reducing unnecessary invasive procedures, although further validation across diverse populations and clinical settings remains necessary before widespread implementation. Radiation exposure, while minimized per scan through optimized protocols, accumulates over repeated annual screenings and warrants careful management through dose reduction strategies and consideration of extended screening intervals for low-risk individuals.

Equity in access and follow-up care emerges as an ethical imperative, given disparities in healthcare infrastructure that may limit the translation of trial benefits into real-world mortality reductions, especially in underserved or rural communities. Addressing these gaps requires innovative delivery models, including mobile imaging units and telemedicine support, alongside quality assurance frameworks to maintain interpretive consistency and program accountability. Economic evaluations support the cost-effectiveness of LDCT screening when applied within well-defined high-risk groups, but expansion beyond these criteria risks diminishing returns due to increased false-positive cascades and resource demands.

Psychosocial impacts related to screening outcomes, particularly anxiety associated with indeterminate findings and prolonged surveillance, highlight the need for integrated patient support services and clear communication strategies that convey risks and benefits transparently. Additionally, epidemiologic variations in lung cancer subtypes across geographic and demographic groups necessitate adaptive screening protocols that reflect local disease patterns, such as higher prevalence of subsolid nodules in never-smoker populations.

The evidence affirms that LDCT screening can meaningfully alter lung cancer trajectories by facilitating earlier intervention and reducing mortality. Realizing its full potential requires a balanced approach that maximizes early detection benefits while minimizing harms through precise eligibility criteria, adjunctive diagnostic tools, radiation safety measures, equitable access, and patient-centered care. Continuous monitoring and iterative refinement of screening programs,

informed by emerging data and technological advances, will be essential to sustain and enhance public health gains in diverse healthcare environments.

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