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Article

A Cost-Effectiveness Analysis of Lung Cancer Screening With Low-Dose Computed Tomography and a Diagnostic Biomarker

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Abstract

Background: The Lung Computed Tomography Screening Reporting and Data System (Lung-RADS) reduces the false-positive rate of lung cancer screening but introduces prolonged periods of uncertainty for indeterminate findings. We assess the cost-effectiveness of a screening program that assesses indeterminate findings earlier via a hypothetical diagnostic biomarker introduced in place of Lung-RADS 3 and 4A guidelines. **Methods:** We evaluated the performance of the US Preventive Services Task Force (USPSTF) recommendations on lung cancer screening with and without a hypothetical noninvasive diagnostic biomarker using a validated microsimulation model. The diagnostic biomarker assesses the malignancy of indeterminate nodules, replacing Lung-RADS 3 and 4A guidelines, and is characterized by a varying sensitivity profile that depends on nodules' size, specificity, and cost. We tested the robustness of our findings through univariate sensitivity analyses. **Results:** A lung cancer screening program per the USPSTF guidelines that incorporates a diagnostic biomarker with at least medium sensitivity profile and 90% specificity, that costs $250 or less, is cost-effective with an incremental cost-effectiveness ratio lower than $100 000 per quality-adjusted life year, and improves lung cancer-specific mortality reduction while requiring fewer screening exams than the USPSTF guidelines with Lung-RADS. A screening program with a biomarker costing $750 or more is not cost-effective. The health benefits accrued and costs associated with the screening program are sensitive to the disutility of indeterminate findings and specificity of the biomarker, respectively. **Conclusions:** Lung cancer screening that incorporates a diagnostic biomarker, in place of Lung-RADS 3 and 4A guidelines, could improve the cost-effectiveness of the screening program and warrants further investigation.

Lung cancer remains the leading cause of cancer-related deaths with an estimated 131 880 new deaths in 2021 in the United States alone (1). In 2021, the US Preventive Services Task Force (USPSTF) revised their 2013 recommendation on lung cancer screening, by lowering the screening start age from 55 to 50 years and the minimum smoking exposure criterion from 30 pack-years to 20 pack-years, while maintaining the annual screening frequency, stopping age at 80 years (inclusive) and years since smoking cessation to 15 years (2-5). Nevertheless, the cost-effectiveness of lung cancer screening is at risk because of the high false-positive rates associated with screening and potential subsequent harms from diagnostic procedures (6).

The National Lung Screening Trial (NLST) showed that among all positive screening findings, 96% were false-positives (7). To standardize reporting and management of screening findings, the American College of Radiology developed the Lung Computed Tomography Screening Reporting and Data System (Lung-RADS) introducing serial low-dose computed tomography (LDCT) exams in 3 or 6 months from the time of detection to assess the malignancy of small screen-detected pulmonary nodules of unknown clinical significance (ie, indeterminate findings) (8). A retrospective assessment of the impact of Lung-RADS on NLST estimated that 11.7% and 3.5% of the screening findings at baseline and subsequent screening exams, respectively, were indeterminate findings (ie, Lung-RADS category 3 and 4A findings) (9). The same study estimated the false-positive rate at baseline screen with Lung-RADS was 12.8% and 5.3% at any subsequent screening exam. Despite reducing the false-positive rate associated with the screening program, the prolonged period of uncertainty attributed to the delay in diagnostic testing of Lung-RADS 3 and 4A findings, combined with

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the high prevalence of such findings, impacts the cost-effectiveness of lung cancer screening (6).

Diagnostic biomarkers are actively being pursued under the premise that a biomarker that characterizes suspicious nodules has the potential to improve the effectiveness and cost-effectiveness of lung cancer screening by 1) reducing the number of cases undergoing unnecessary invasive procedures, 2) shortening the uncertainty period following indeterminate findings, and 3) reducing the number of diagnostic screening exams. Blood-based biomarkers are minimally invasive and contain several circulating proteins that may be indicative of lung cancer (10-30). Proposed markers report a wide range of sensitivity and generally high specificity and could detect cancer as early as 29 months prior to lung cancer diagnosis (31). Examples of blood-based biomarkers currently available or being actively evaluated as standalone diagnostic biomarkers for pulmonary nodules include the EarlyCDT-Lung (OncImmune) (32), the Nodify XL2 (Biodesix) (33), and a 4-protein biomarker panel (34). Although promising, none of these candidate biomarkers for early detection of lung cancer are regularly used in clinical practice, despite studies reporting benefits from using a biomarker before the LDCT exam to assess eligibility (35-37).

In this study, we assessed the impact of a hypothetical, noninvasive diagnostic biomarker introduced in place of Lung-RADS 3 and 4A guidelines on the effectiveness and cost-effectiveness of lung cancer screening. Using a microsimulation model, we evaluated the long-term benefits and harms of lung cancer screening with and without a hypothetical diagnostic biomarker guiding the management of indeterminate findings on the US population. We varied the sensitivity and specificity of the biomarker using a range that includes the reported sensitivity and specificity levels of existing biomarkers and identified the corresponding cost of the biomarker for which the screening program would be cost-effective.

Methods

Lung Cancer Natural History and Screening Microsimulation Model

We simulated a virtual cohort of 1 million male and female individuals born in 1950 and 1960 thereby targeting the current lung cancer screening eligible US population based on age. We followed individuals from age 50 years until death using the Lung Cancer Outcomes Simulator (LCOS); a well-validated microsimulation model developed within the Cancer Intervention and Surveillance Modeling Network (CISNET) consortium (38).

At the core of LCOS lies a natural history model that simulates disease progression in the absence of any intervention (39). The natural history model assumes exponential growth for the primary tumor and growth of metastasis that is proportional to the primary tumor's growth and models sex-specific natural histories of 4 different subtypes of lung cancer (adenocarcinoma, squamous cell carcinoma, large cell, and small cell). Through LCOS, we superimposed screening and diagnostic follow-up interventions onto the natural history model and aggregated individual-level results to obtain population-level outcomes (6,38). All input parameters associated with LDCT were calibrated to data from NLST and validated in the Prostate, Lung, Colorectal, Ovarian screening trial (38).

We obtained smoking histories representative of the US population from the CISNET's smoking history generator: a microsimulation model that provides individual-level smoking histories consisting of ages at smoking initiation and cessation, smoking intensity, and age at death from competing causes (40,41). Individual smoking histories were transformed into annual lung cancer risk using a validated lung carcinogenesis model; (42) the annual lung cancer risk estimates were then used as inputs to the LCOS model. The LCOS along with the smoking history generator model were used in comparative analyses performed by the CISNET Lung Working Group to inform the 2013 and 2021 USPSTF recommendations on lung cancer screening (3,4).

Follow-up of Indeterminate Findings in the Absence and Presence of a Diagnostic Biomarker

For the purposes of this study, we compared the cost-effectiveness of the 2013 USPSTF lung cancer screening strategy (2), with and without a hypothetical diagnostic biomarker used to assess malignancy of indeterminate findings and guide the follow-up management, in place of existing Lung-RADS 3 and 4A guidelines (see Figure 1). In the absence of a diagnostic biomarker, each individual detected with an indeterminate finding followed Lung-RADS guidelines (8). The LCOS explicitly models Lung-RADS for managing screening findings (6). Specifically, on detection of a pulmonary nodule, the simulated individual exited the general screen-eligible population and entered the Lung-RADS protocol. Per Lung-RADS, depending on the size of the nodule at the time of detection, the patient returned in 3- or 6-month time to undergo a serial LDCT to assess malignancy of indeterminate findings based on the growth of the nodule.

In the presence of a diagnostic biomarker, individuals with indeterminate findings (ie, Lung-RADS categories 3 and 4A) underwent testing with the diagnostic biomarker 1 month from the time of detection. If the biomarker was positive, additional diagnostic positron emission tomography–computed tomography (PET/CT) and/or tissue sampling was required to confirm diagnosis; otherwise, the screening finding was considered a false-positive, and the individuals returned to the general screening population as long as they met the screening eligibility criteria. The earlier assessment of nodules' malignancy with the diagnostic biomarker as compared with Lung-RADS (1 month vs 3 or 6 months) may generate additional health benefits by 1) diagnosing the true cancer cases earlier and 2) reducing the prolonged anxiety associated with indeterminate findings. We applied false-positive rates associated with LDCT from a published calibration study of LCOS to NLST data because the diagnostic biomarker was assumed to replace Lung-RADS, and LCOS does not explicitly model the growth of benign nodules (Supplementary Table 1, available online) (9,38). In both scenarios, nodules classified as Lung-RADS categories 4B and 4X findings were assessed with PET/CT and/or biopsy with no delay from follow-up.

Sensitivity and Specificity of the Hypothetical Biomarker

The sensitivity of the biomarker was assumed to be a nondecreasing function of nodule diameter, represented as a logistic function (see Figure 2; Supplementary Table 2, available online). Three different sensitivity profiles were modeled representing high, medium, and low sensitivity. For example, for a 6-mm nodule, the biomarker had a 90%, 60%, and 30% sensitivity per the high, medium, and low sensitivity profile, respectively. The sensitivity of the diagnostic biomarker as a function of nodule diameter represents the likelihood that larger size nodules are

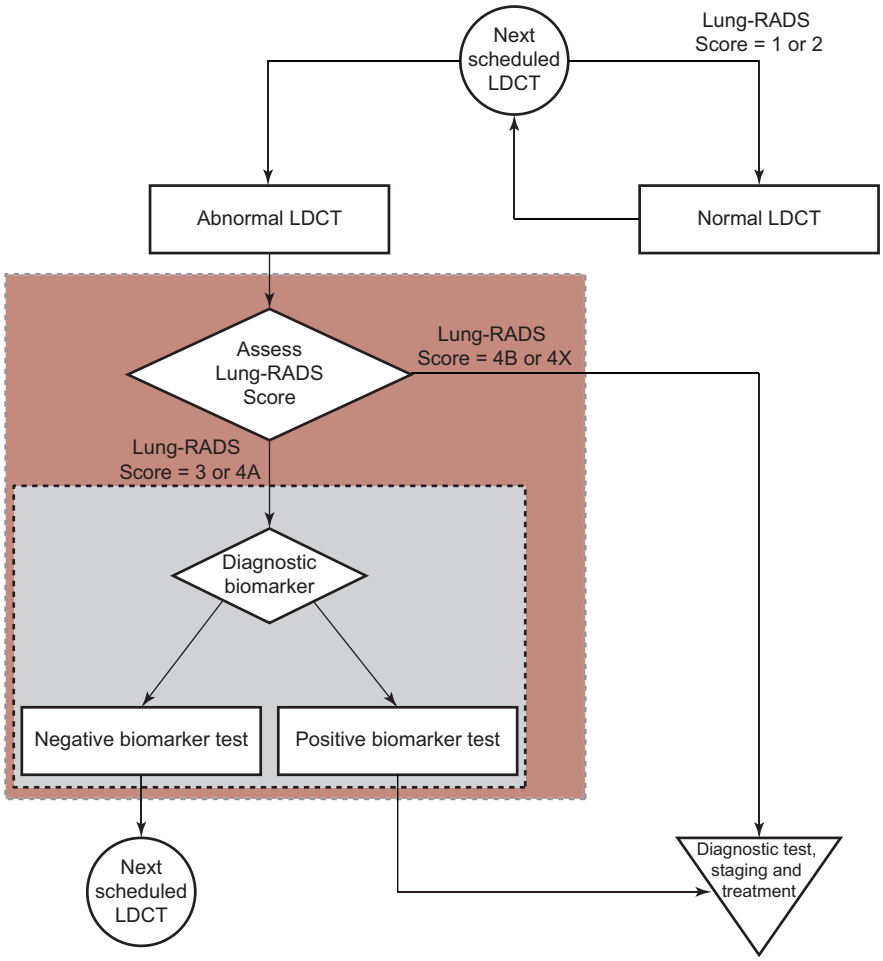

Figure 1. Schematic representation of the screening decision process when LDCT screening is supplemented by a diagnostic biomarker test to guide the management of indeterminate findings. In the absence of the diagnostic biomarker, every nodule with a Lung-RADS score of 3 or 4A directly enters Lung-RADS follow-up management. LDCT = low-dose computed tomography; Lung-RADS = Lung Computed Tomography Screening Reporting and Data System.

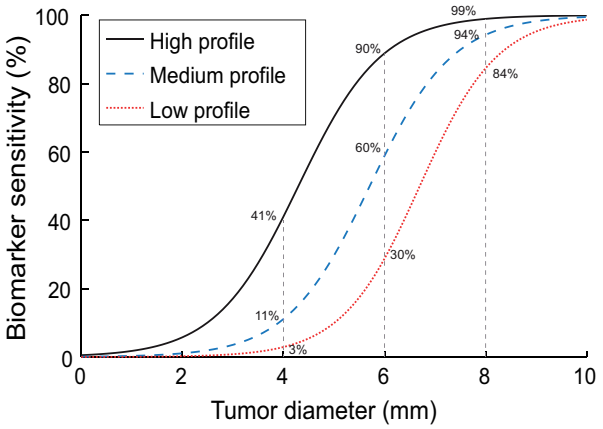

Figure 2. Sensitivity profiles of the diagnostic biomarker as a function of tumor size.

more likely associated with the higher expression levels of the biomarker and thus are more likely to be malignant.

The specificity of the diagnostic biomarker, in contrast, was assumed to be independent of the nodule's size. We considered 4 different levels of specificity: 1) 95% denoted as "almost perfect," 2) 90% denoted as "high," 3) 75% denoted as "medium," and 4) 50% denoted as "low" specificity. Finally, we considered the 2 extreme scenarios of "zero" and "perfect" sensitivity and specificity thus providing the lower and upper bounds of the health benefits associated with the biomarker (Supplementary Table 3, available online).

It is important to recognize that the terminology *sensitivity* and *specificity* is applied in different contexts throughout the manuscript, namely, to characterize the LDCT screen exam, the biomarker, and the overall screening program. The sensitivity and specificity of LDCT were not affected by the sensitivity and specificity of the biomarker. However, the sensitivity and specificity of the overall screening program were impacted by the biomarker's sensitivity and specificity. In the presence of the diagnostic biomarker, a false-positive finding was defined as an abnormal LDCT with a subsequent positive biomarker result in a cancer-free individual, whereas in the absence of the biomarker, a false-positive result was defined as an abnormal LDCT with a positive serial LDCT per Lung-RADS for a cancer-free individual.

Health Utilities and Costs

To adjust the remaining lifetime of individuals for quality of life, we used published utility scores for the various health

states, age, and interventions considered in our study (Supplementary Table 4, available online) (6,43-47).

We assumed that the diagnostic biomarker occurred 1 month after the abnormal screening exam and it was noninvasive, thus, the harmful effects on quality of life for individuals undergoing the biomarker were negligible. The disutility (a metric that quantifies the harmful effects associated with an intervention or a health state) associated with indeterminate findings was 0.04 (48). That is, if an individual with a true-negative LDCT gained 1 quality-adjusted life-year (QALY) until the next screening exam, an individual with an indeterminate finding for the same time frame would accrue 0.96 QALY because of the harmful effects associated with indeterminate findings (eg, anxiety and psychological distress). The disutility of indeterminate findings was applied from the time of detection up to the first negative subsequent exam (either a LDCT exam or a biomarker) or lung cancer diagnosis or death, whichever occurred first.

We obtained cost estimates associated with screening and diagnostic interventions using the Medicare reimbursement rates (Supplementary Table 5, available online). We included cost estimates associated with downstream treatment interventions based on related literature (49,50). All costs were in 2018 US dollars.

Outcome Measures

Primary outcome measures included the incremental cost-effectiveness ratio (ICER), QALYs, and costs relative to the 2013 USPSTF strategy with Lung-RADS. We discounted all outcomes using an annual discount rate of 3% (Supplementary Table 6, available online). Screening programs were considered economically viable if their corresponding ICER was below the commonly used willingness-to-pay thresholds of $100 000 per QALY saved (51) . Secondary outcome measures included lung cancer-specific mortality reduction, number of follow-up screening exams, number of diagnostic biomarker exams, and number of false-positive findings.

Base-Case Analysis and Sensitivity Analysis

For our base-case analysis, we evaluated the health benefits and harms associated with a lung cancer screening program that incorporated diagnostic biomarkers of different sensitivity levels and costs and specificity fixed at 90% on the 1960 US birth cohort. We compared the ICERs of the USPSTF guidelines with the diagnostic biomarkers of varied accuracy and costs against the USPSTF guidelines with Lung-RADS using the single payer or insurer perspective.

We tested the sensitivity of our results to key input parameters through a series of univariate sensitivity analyses in which we varied the specificity and cost associated with the diagnostic biomarker and the disutility associated with indeterminate findings. Furthermore, beyond the 1960 birth cohort, we assessed the cost-effectiveness of the US population born in 1950, because this was the cohort used by the USPSTF for their 2013 recommendations (3).

Results

Base-Case Analysis

Relative to Lung-RADS, the incremental QALY per person associated with a screening program that incorporates a diagnostic biomarker with 90% specificity and cost of $500 increased from -0.002 to 0.0015 as the sensitivity of the biomarker increased from 0% to 100% (Figure 3). Health benefits increased in part because the time period to assess indeterminate findings was shortened (1 month with the biomarker vs 3 or 6 months with Lung-RADS), providing earlier diagnosis of false-positives and lung cancer cases. Concurrently, the costs of the screening program increased from $12 to $103 per person as the sensitivity of the biomarker increased from 0% to 100%, relative to Lung-RADS, because of the added biomarker cost and earlier initiation of cancer treatment. A lung cancer screening program that incorporates a diagnostic biomarker with 90% specificity was cost-effective using a willingness-to-pay threshold of $100 000 per QALY, if the biomarker cost $250 or less and had at least a medium sensitivity profile (Table 1 and Figure 3). For a diagnostic biomarker costing $500, the lung cancer screening was cost-effective if the biomarker had high sensitivity profile. If the biomarker's cost was $750 or more, the screening program was not cost-effective. As the specificity of the biomarker reduced, the sensitivity of the biomarker must increase, and its cost must decrease for the screening program to be cost-effective (Supplementary Figures 1-3, available online).

The reduction in lung cancer–specific mortality produced by the USPSTF strategy with Lung-RADS (6.72%) was comparable to the mortality reduction achieved by a screening program that incorporates a diagnostic biomarker with a low sensitivity profile (6.70%) (Figure 4, A). When the biomarker's sensitivity profile improved to medium or high, the mortality reduction increased to 6.98% or 7.31%, respectively (Figure 4, A). Existing guidelines averted 3258 lung cancer deaths per 1 million individuals, as compared with 3248, 3385, and 3545 lung cancer deaths averted when Lung-RADS was replaced by a diagnostic biomarker with low, medium, and high sensitivity profile, respectively (Figure 4, B).

As the sensitivity of the diagnostic biomarker decreased from "perfect" to "zero," the total number of annual LDCT screening exams per 1 million people increased by approximately 3000 tests (from 2 075 000 to 2 078 000) as a result of delayed diagnoses and additional screening exams resulting from false-negative biomarker results (Figure 4, C). Similarly, the number of biomarker tests per 1 million individuals increased as the sensitivity of the test decreased (Supplementary Figure 4, available online).

The number of false-positive findings reduced as the specificity of the biomarker increased (Figure 4, D). A screening program with Lung-RADS yielded 78 000 false-positives per 1 million individuals; with a diagnostic biomarker, the screening program yielded more false-positives if the specificity of the biomarker was 50% or less but fewer false-positives when the specificity of the biomarker was 75% or higher. Introducing a diagnostic biomarker to supplement Lung-RADS could increase overdiagnosis (Figure 4, E).

Sensitivity Analysis

The specificity associated with the biomarker affects the cost of the screening program; as the specificity of the biomarker increased from 0% to 100%, the cost per person decreased from $197 to $94 (Figure 5, A).

The health benefits accrued from screening were sensitive to the value of the disutility associated with indeterminate findings (Figure 5, B). When we doubled the negative effects of indeterminate findings, a screening program was cost-effective if it

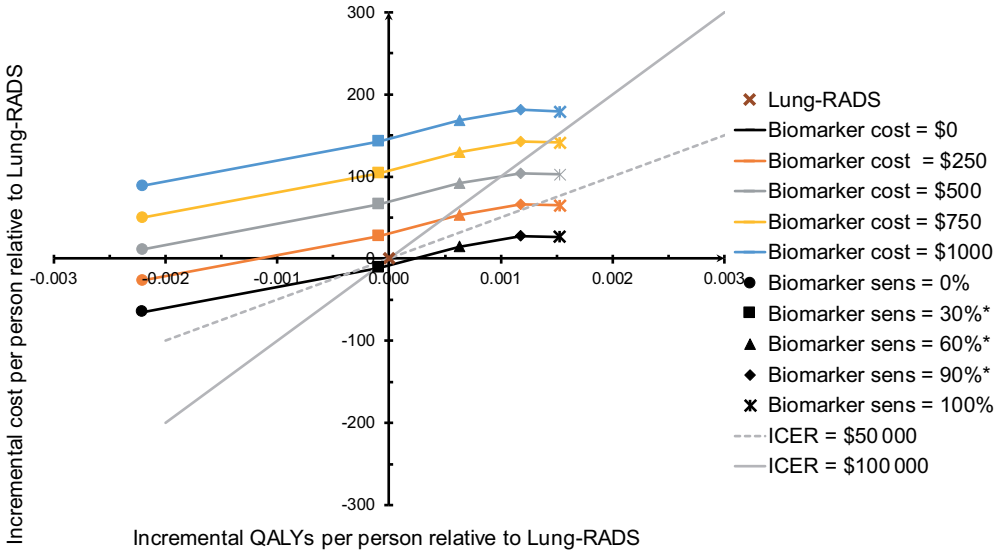

Figure 3. Cost-effectiveness plane of the 2013 USPSTF recommendations on lung cancer screening that incorporates a diagnostic biomarker with varying sensitivity and cost and specificity of 90% when applied to 1960 birth cohort, relative to the current USPSTF recommendations on lung cancer screening with Lung-RADS follow-up management (at the origin). [a]The sensitivity profile of the biomarker is assumed to be a nondecreasing function of nodule diameter, represented as a logistic function (Figure 2; Supplementary Table 2, available online). Zero and perfect sensitivity profiles provide the unrealistic lower and upper bounds of performance and are assumed to be independent of the nodule's diameter. ICER = incremental cost-effectiveness ratio; Lung-RADS = Lung Computed Tomography Screening Reporting and Data System; QALYs = quality-adjusted life-years; USPSTF = US Preventive Services Task Force.

Table 1. Incremental cost-effectiveness ratios of a lung cancer screening program per the 2013 USPSTF strategy that incorporates a diagnostic biomarker to assess Lung-RADS 3 and 4A nodules applied on the US 1960 birth cohort, relative to the 2013 USPSTF lung cancer screening recommendations using Lung-RADS

	Specificity					
Cost of the biomarker and 6-mm sensitivity[a]	0%	50%	75%	90%	95%	100%
Cost of the biomarker = $250						
0% sensitivity	Dominated	Dominated	$5295	$12 176	$14 484	$16 781
30% sensitivity	Dominated	Dominated	Dominated	Dominated	Dominated	Dominated
60% sensitivity	$231 320	$149 531	$108 499	$84 378	$76 303	$68 256
90% sensitivity	$134 316	$90 650	$68 737	$55 855	$51 544	$47 243
100% sensitivity	$103 071	$69 330	$52 401	$42 449	$39 118	$35 794
Cost of the biomarker = $500						
0% sensitivity	Dominated	Dominated	Dominated	Dominated	Dominated	Dominated
30% sensitivity	Dominated	Dominated	Dominated	Dominated	Dominated	Dominated
60% sensitivity	$292 322	$210 533	$169 501	$145 381	$137 305	$129 258
90% sensitivity	$166 853	$123 186	$101 273	$88 391	$84 080	$79 779
100% sensitivity	$128 196	$94 455	$77 526	$67 574	$64 243	$60 920
Cost of the biomarker = $750						
0% sensitivity	Dominated	Dominated	Dominated	Dominated	Dominated	Dominated
30% sensitivity	Dominated	Dominated	Dominated	Dominated	Dominated	Dominated
60% sensitivity	$353 324	$271 535	$230 503	$206 383	$198 307	$190 260
90% sensitivity	$199 389	$155 723	$133 809	$120 928	$116 617	$112 316
100% sensitivity	$153 321	$119 580	$102 651	$92 699	$89 368	$86 045
Cost of the biomarker = $1000						
0% sensitivity	Dominated	Dominated	Dominated	Dominated	Dominated	Dominated
30% sensitivity	Dominated	Dominated	Dominated	Dominated	Dominated	Dominated
60% sensitivity	$414 326	$332 537	$291 505	$267 385	$259 310	$251 262
90% sensitivity	$231 925	$188 259	$166 346	$153 464	$149 153	$144 852
100% sensitivity	$178 446	$144 705	$127 777	$117 824	$114 493	$111 170

[a]6-mm sensitivity corresponds to the sensitivity of the diagnostic biomarker for a 6-mm pulmonary nodule. Lung-RADS = Lung Computed Tomography Screening Reporting and Data System; USPSTF = US Preventive Services Task Force.

incorporated a diagnostic biomarker with high sensitivity profile and 90% specificity, costing $500, with an ICER of $76 921 per QALY. If the disutility of indeterminate findings was small (0.01 incurred up to the first normal test result or lung cancer diagnosis), the ICER of the screening program increased to $99 521.

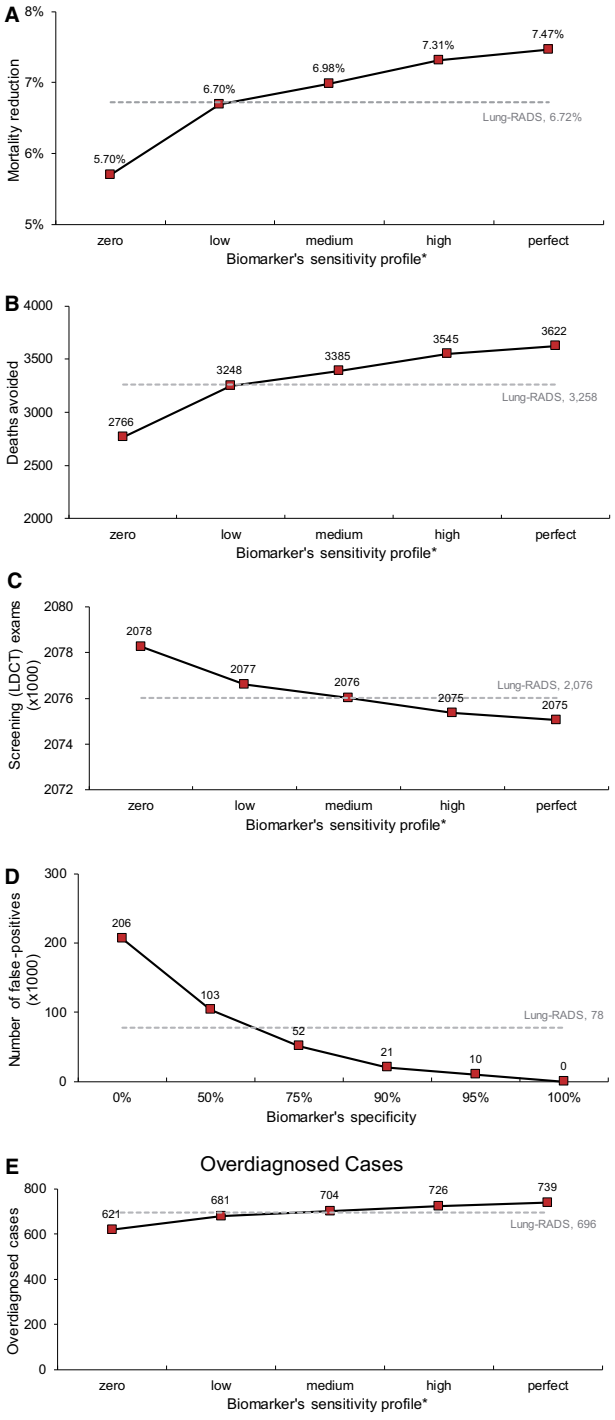

Figure 4. Screening outcomes associated with a screening program using a diagnostic biomarker to evaluate Lung-RADS 3 and 4A nodules per 1 million individuals randomly selected from the general population born in 1960. **A)** Mortality reduction, **(B)** number of lung cancer deaths avoided, **(C)** number of screening exams using LDCT, **(D)** number of false-positive findings, and **(E)** number of overdiagnosed cases are shown. The sensitivity profile of the biomarker is assumed to be a nondecreasing function of nodule diameter, represented as a logistic function (Figure 2; Supplementary Table 2, available online). LDCT = low-dose computed tomography; Lung-RADS = Lung Computed Tomography Screening Reporting and Data System.

When we analyzed the impact of the diagnostic biomarker on the 1950 birth cohort, we observed similar patterns as those obtained from our analysis of the 1960 birth cohort, despite some differences on the absolute effects due to discrepancies in the smoking prevalence of the two cohorts (Supplementary Figures 5-7 and Supplementary Table 7, available online).

Discussion

We assessed the effectiveness and cost-effectiveness of lung cancer screening per the USPSTF recommendation when a diagnostic biomarker, with varying cost, sensitivity, and specificity levels, is introduced to guide the management of indeterminate findings in place of Lung-RADS 3 and 4A guidelines. We showed that lung cancer screening programs incorporating such a hypothetical diagnostic biomarker with medium sensitivity profile or better would be cost-effective if the biomarker cost was $250 or less, using a willingness-to-pay threshold of $100 000 per QALY. We demonstrated that as the cost of the biomarker increases, its sensitivity must improve for the screening program to be cost-effective. When the cost of the biomarker was $750 or more, the screening program was not cost-effective. Note that existing biomarkers, when tested retrospectively on lung cancer patients, report sensitivity and specificity over 75% yet are not in clinical use (20,21). If their accuracy is proven prospectively on asymptomatic individuals, our findings suggest that employing such diagnostic biomarkers to guide the management of indeterminate screening findings in place of Lung-RADS could improve the cost-effectiveness of the screening program, dependent on costs. In addition, a screening program that incorporates a diagnostic biomarker to guide the management of indeterminate findings could yield higher lung cancer–specific mortality reduction, as compared with Lung-RADS guidelines, if the biomarker has at least a medium sensitivity profile. Of course, prospective studies are required to assess the accuracy of diagnostic biomarkers and verify the findings of retrospective studies prior to incorporating diagnostic biomarkers into screening programs.

In a retrospective study, Pinsky et al. (9) demonstrated that managing screen-detected pulmonary nodules per Lung-RADS would reduce the false-positive rate of NLST. We demonstrated that replacing Lung-RADS with a diagnostic biomarker could further reduce the false-positive rate associated with lung cancer screening well below the Lung-RADS rates, depending on the specificity of the biomarker. As compared with Lung-RADS, a diagnostic biomarker with specificity of 75% and 90% was estimated to decrease the number of false-positive findings by 34% and 73%, respectively. Furthermore, the diagnostic biomarker shortens the time an individual with an indeterminate finding incurs anxiety and psychological distress if completed within 1 month from the time of screen detection. Alternatively, per Lung-RADS individuals need to wait at least 3 months before having a definitive diagnosis. It is important to note that the cost-effectiveness of the screening program was sensitive to the disutility associated with indeterminate findings as well as to the cost of the diagnostic biomarker. The disutility associated with indeterminate findings has been shown to affect the cost-effectiveness of the 2013 USPSTF guidelines with Lung-RADS and necessitates careful quantification (6).

Our approach had limitations. First, we assumed that individuals adhere to the screening program perfectly. Although in practice the uptake of lung cancer screening has been low, estimated between 4.4% and 14.4% (52,53), we evaluated the screening program under perfect adherence to capture the full extent of benefits and harms associated with lung cancer screening.

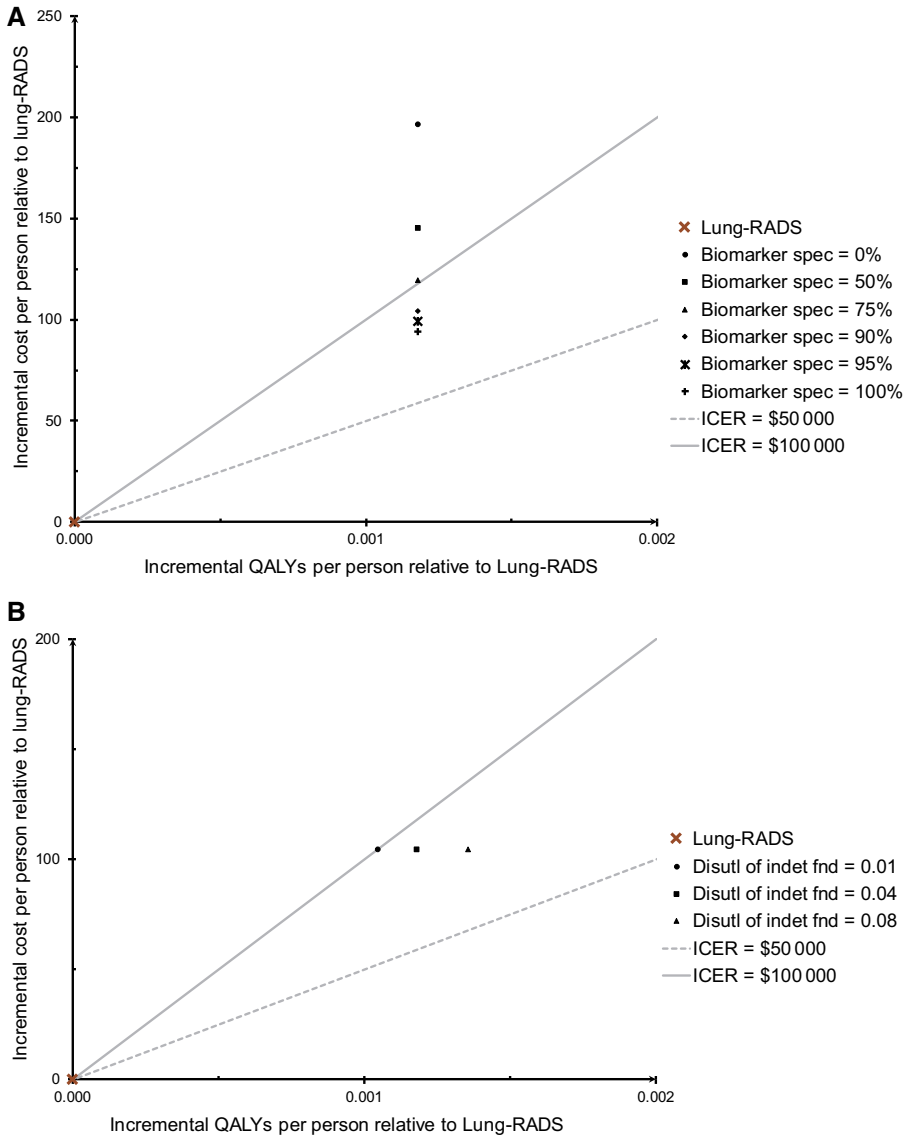

Figure 5. Sensitivity analysis varying the **(A)** specificity of the diagnostic biomarker while keeping the sensitivity profile of the biomarker fixed at high and cost at $500 and **(B)** disutility associated with indeterminate findings for the 1960 birth cohort. Note that the origin represents the scenario where routine screening with LDCT follows the 2013 USPSTF guidelines on lung cancer screening with Lung-RADS. Disutl of Indet Fnd = disutility of indeterminate findings; ICER = incremental cost-effectiveness ratio; LDCT = low-dose computed tomography; Lung-RADS = Lung Computed Tomography Screening Reporting and Data System; QALYs = quality-adjusted life years; Spec = specificity; USPSTF = US Preventive Services Task Force.

Second, our analysis was limited to solely solid tumors because the natural history model does not model subsolid nodules. Third, we underestimated the health benefits and costs associated with lung cancer screening because we did not consider incidental findings in our analysis. Finally, for the purposes of this study, we considered a hypothetical noninvasive diagnostic biomarker that was not histology specific and which had hypothetical sensitivity and specificity levels. When evaluating a specific biomarker, the test's sensitivity and specificity would need to be assessed and validated extensively in independent populations to verify the performance of the biomarker and its generalizability. We attempt to provide evidence on how to best use diagnostic biomarkers and what level of accuracy is required to positively affect the cost-effectiveness of lung cancer screening rather than assess the impact of a specific diagnostic biomarker.

In summary, we showed that informing Lung-RADS with a diagnostic biomarker could improve the cost-effectiveness of lung cancer screening and yield higher lung cancer mortality reduction. We have identified the minimum levels for the sensitivity and specificity of the biomarker necessary such that the overall screening program would be cost-effective at a given cost of the biomarker. Incorporating diagnostic biomarkers into lung cancer screening warrants further investigation.

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Author contributions: SKP provided administrative support and acted as the overall guarantor. The authors made the following contributions: Conceptualization and study design: IT, SAE, SKP; Data acquisition: IT, SAE, MB; Data analysis: IT; Data interpretation: IT, MB, SAE, AL, SKP; Writing, original draft: IT; Writing, review & editing: IT, MB, SAE, AL, SKP.

Data Availability

The data underlying this article are available in the article and in its online supplementary material.

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