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A bronchial-airway gene-expression classifier to improve the diagnosis of lung cancer: Clinical outcomes and cost-effectiveness analysis

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Bronchoscopy is the safest procedure for lung cancer diagnosis when an invasive evaluation is required after imaging procedures. However, its sensitivity is relatively low, especially for small and peripheral lesions. We assessed benefits and costs of introducing a bronchial gene-expression classifier (BGC) to improve the performance of bronchoscopy and the overall diagnostic process for early detection of lung cancer. We used discrete-event simulation to compare clinical and economic outcomes of two different strategies with the standard practice in former and current smokers with indeterminate nodules: (*i*) location-based strategy—integrated the BGC to the bronchoscopy indication; (*ii*) simplified strategy—extended use of bronchoscopy plus BGC also on small and peripheral lesions. Outcomes modeled were rate of invasive procedures, quality-adjusted-life-years (QALYs), costs and incremental cost-effectiveness ratios. Compared to the standard practice, the location-based strategy (*i*) reduced absolute rate of invasive procedures by 3.3% without increasing costs at the current BGC market price. It resulted in savings when the BGC price was less than $3,000. The simplified strategy (*ii*) reduced absolute rate of invasive procedures by 10% and improved quality-adjusted life expectancy, producing an incremental cost-effectiveness ratio of $10,109 per QALY. In patients with indeterminate nodules, both BGC strategies reduced unnecessary invasive procedures at high risk of adverse events. Moreover, compared to the standard practice, the simplified use of BGC for central and peripheral lesions resulted in larger QALYs gains at acceptable cost. The location-based is cost-saving if the price of classifier declines.

Introduction

Despite declining smoking rates, lung cancer remains the leading cause of cancer-related death and was responsible for 155,870 deaths in the US in 2017.[1] Over the decades, surgical, radiotherapeutic and chemotherapeutic advances have not improved 5-year survival, mainly because the majority of cases are still diagnosed at a late stage, for which the survival rate is very low.[1] Thus, there has been increasing enthusiasm for earlier detection with low-dose computed tomography (LDCT), reducing lung cancer mortality by up to 20% among current and former smokers.[2,3]

Indeterminate pulmonary nodules, defined as noncalcified solid lesions with a risk of malignancy between 5 and 60%, are frequently identified on LDCT imaging.[4] In such cases, a careful assessment, based on surgical risk, ability to biopsy and individual preferences, is essential to decide between surveillance imaging and invasive evaluation.[5] When an invasive evaluation is required, the procedure adopted is selected based on considerations such as location and lesion size, adenopathy, safety and patients' characteristics.[6,7] Bronchoscopy is the procedure with the smallest rate of complications but also relatively low sensitivity, especially for small and peripheral lesions.[6,7] In contrast,

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Abbreviations: ^{18}F-FDG PET: 18F-fluorocholine positron emission tomography; AEGIS: Airway Epithelial Gene Expression in the Diagnosis of Lung Cancer Studies 1 and 2; BGC: bronchial-airway gene-expression classifier; ICER: incremental cost-effectiveness ratio; LDCT: low-dose computed tomography; POM: probability of malignancy; QALY: quality-adjusted life years; TTNA/B: transthoracic needle aspiration or biopsy
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What's new?

Bronchoscopy is the safest procedure for lung cancer diagnosis when an invasive evaluation is required following imaging procedures. Its sensitivity is relatively low, however. This study assesses benefits and costs of introducing a bronchial gene-expression classifier (BGC) to improve the performance of bronchoscopy and the overall process for early detection of lung cancer. When compared with standard practice, an extended use of BGC for diagnosis of central and peripheral pulmonary lesions improves quality-adjusted life expectancy, reduces unnecessary invasive procedures, and has an incremental cost-effectiveness ratio of US $10,109 per quality-adjusted life year gained, without increasing mortality.

transthoracic needle biopsy and wedge resection have a satisfying diagnostic performance but are associated with substantial complications.[6,7] Moreover, because nondiagnostic bronchoscopic examinations are common, patients often require further invasive investigations after bronchoscopy, increasing their overall risk of complicated procedures and costs.

In early 2015, 8 million Americans became eligible for annual LDCT screening through Medicare program or private insurance.[8] This is expected to increase the number of indeterminate pulmonary nodules detected and, consequently, nondiagnostic bronchoscopic examinations and complicated procedures in patients ultimately found with benign lesions.[2,9] Methods that improve the diagnostic performance of bronchoscopy have the potential to improve clinical outcomes, avoid complications and potentially lower healthcare costs. Recently, the Airway Epithelial Gene Expression in the Diagnosis of Lung Cancer (AEGIS) studies showed that combining bronchoscopy with a bronchial gene-expression classifier can significantly improve diagnostic sensitivity in current and former smokers, independent of lesion size, location, stage and presence of adenopathy.[9] The classifier uses both information on cancerous gene-expression patterns in bronchial epithelium cells, collected by brushing the proximal airways during the bronchoscopy, and demographic factors such as age, gender and pack-years smoking. The clinical utility of the classifier, as adjunct exam to the bronchoscopy, is to better identify candidates who do not require further invasive investigations among those with indeterminate nodules.[9,10]

We estimated clinical benefits and costs of using the classifier for the diagnosis of lung cancer in patients with indeterminate pulmonary nodules who are currently eligible for LDCT lung cancer screening.

Methods

Decision model

We developed a discrete-event simulation model using Arena, version 15.00 (Rockwell Automation, Milwaukee, WI), to simulate the diagnostic pathways and progression of pulmonary lesions among current or former smokers undergoing LDCT screening for suspected lung cancer. We generated a hypothetical cohort of 10,000 patients with the baseline characteristics similar to the cohorts from two multicenter prospective observational studies that enrolled patients undergoing bronchoscopy from different practice settings and geographic locations (i.e., US, Canada, Irland)—the AEGIS-1 and AEGIS-2 trials (Table 1).[9] We assumed that the patients in our model were all potentially operative candidates.

Figure 1 illustrates our model for the three diagnostic strategies: (*a*) standard diagnostic strategy, following the current guidelines[6,7]; (*b*) location-based diagnostic strategy, integrating the bronchial-airway gene-expression classifier (BGC) to the bronchoscopy indication on the current guidelines; (*c*) simplified diagnostic strategy, with an extended use of bronchoscopy plus BGC also for peripheral lesions.

Each patient was tracked throughout a time horizon of 2 years after the initial lung cancer screening, which is the surveillance period recommended by guidelines.[6] We assumed that all patients entered the model already with a suspected lesion identified on LDCT. For each individual, a specific age, clinical probability of malignancy (POM) and a cancerous or no cancerous lesion status were assigned based on the observed distribution of those variable in the AEGIS trials. We assumed all affected patients had cancers at Stage I at the entry, and lung cancer progression to be a function of time. Thus, malignancies, that were undetected at the end of the first year, progressed at Stage II within the subsequent year.

Diagnostic strategies

Patients who were at intermediate or unknown POM were screened with ^{18}F-fluorocholine positron emission tomography (^{18}F-FDG PET) imaging, while those with high POM underwent directly surgery. Patients with a low POM or mild/low ^{18}F-FDG nodule uptake received two repeat LDCT within the subsequent 2 years, according to the watchful waiting approach.[6] If a cancer progression was detected during the 2-year follow-up, these patients were surgically treated.

Patients with moderate/intense ^{18}F-FDG nodule uptake faced different diagnostic and treatment pathways according to the three alternative strategies of our model.

In the standard strategy, patients were referred to bronchoscopy, transthoracic needle aspiration or biopsy (TTNA/B) or surgery, consistent with the current recommendations.[6,7] We assumed that all patients with central or central and peripheral lesions were first investigated with bronchoscopy and those with only peripheral lesions with TTNA/B or surgery.[6,7] Because of the high rate of false negatives at the bronchoscopy, a nondiagnostic bronchoscopic result (true and false negatives) led to further invasive investigations; while a

Table 1. Model parameters and assumptions

Input parameter			
Cohort characteristics (n = 639)[1]	***n* (%)**	**Median (IQR)**	**References**
Age		63 (55–71)	Silvestri *et al.*[9]
Men	440 (69)		Silvestri *et al.*[9]
Smoking status			Silvestri *et al.*[9]
Current	315 (49)		
Former	324 (51)		
Tobacco use—pack year		43 (24–63)	Silvestri *et al.*[9]
Lesion location			Silvestri *et al.*[9]
Central	225 (35)		
Peripheral	194 (30)		
Central and peripheral	192 (30)		
Unknown	28 (5)		
Distribution of clinical probability of malignancy (POM)			Silvestri *et al.*[9]
Low	62 (10)		
Intermediate	101 (16)		
High	426 (67)		
Unknown	50 (7)		
Probability of malignancy within POM categories			Silvestri *et al.*[9]
Low	3 (5)		
Intermediate	41 (41)		
High	405 (95)		
Unknown	38 (76)		
Performance of diagnostic examinations	**Base case**	**Distribution (a,b)**	**Reference**
Bronchoscopy (BC)			Silvestri *et al.*[9]
Sensitivity stratified by POM			
Low	0.33	β (1, 2)	
Intermediate	0.41	β (17, 24)	
High	0.79	β (320, 85)	
Undefined	0.82	β (31, 7)	
Specificity	1.0	–	
Bronchoscopy + classifier			Silvestri *et al.*[9]
Sensitivity stratified per POM			
Low	1.0	β (2, 0.1)	
Intermediate	0.88	β (21, 3)	
High	0.89	β (77, 10)	
Undefined	1.0	β (7, 0.1)	
Specificity stratified per POM			Silvestri *et al.*[9]
Low	0.56	β (33, 26)	
Intermediate	0.48	β (29, 31)	
High	0.29	β (6, 15)	
Undefined	0.33	β (29, 31)	
^{18}F-FDG PET			Gould *et al.*[14]
Sensitivity	0.942	β (212, 13)	
Specificity	0.831	β (187, 38)	
TTNA (or TTNB)			Rivera *et al.*[7]
Sensitivity	0.90	β (90, 10)	
Specificity	0.97	β (97, 3)	

(Continues)

Table 1. Model parameters and assumptions (Continued)

Performance of diagnostic examinations	Base case	Distribution (a,b)	Reference
Distribution of surgical procedures			Vachani *et al.*[10] Feller-Kopman[11]
Lobectomy/segmentectomy	0.43	β (43, 57)	
Wedge resection	0.57	β (57, 43)	
Invasive procedures after BC + BGC positive results			Ferguson *et al.*[13]
TTNA (or TTNB)	0.69	β (69, 31)	
Surgical procedures	0.31	β (31, 69)	
Probability of pneumothorax (after BC)	0.03	N (0.03, 0.005)	Gould *et al.*[6]
Probability of pneumothorax (after TTNA/B)	0.15	β (15, 85)	Gould *et al.*[6]
Probability of death (after lobectomy/ segmentectomy)	0.015	β (1.5, 98.5)	Rivera *et al.*,[7] Yang *et al.*[16]
Probability of death (after wedge resection)	0.005	β (0.5, 99.5)	Gould *et al.*[6]
Probability of death for Stage I cancer (per year)	0.05	β (5, 95)	IELCAPI[17]
Probability of death for Stage II cancer (per year)	0.25	β (25, 75)	Wisnivesky *et al*[18]
Utilities			
Stage I cancer	0.58	β (0.64,0.47)	Trippoli *et al.*[19]
Stage II cancer	0.53	β (0.61,0.54)	Trippoli *et al.*[19]
Surgical procedures	0.56	β (0.63,0.50)	Trippoli *et al.*[19]
Pneumothorax	0.58	β (0.64,0.57)	Nafees *et al.*[20]
Baseline	1.003–0.003[1]Age		Sullivan *et al.*[21]
Costs			
Wedge resection	18,854	*n* (18,854,1885.4)	Supporting Information Appendix S1
Lobectomy/segmentectomy	22,660	*n* (22,660, 2,266)	Supporting Information Appendix S1
TTNA (or TTNB)	2,483	*n* (2,483, 248.3)	Supporting Information Appendix S1
Bronchoscopy	3,249	*n* (3,249, 324.9)	Supporting Information Appendix S1
BGC	2,865	*n* (2,865, 286.5)	Supporting Information Appendix S1
LDCT scan[2]	438	*n* (438, 43.8)	Supporting Information Appendix S1
F-FDG PET	1,438	*n* (1,438, 143.8)	Supporting Information Appendix S1

[1]Cohort characteristics refer to those of the AEGIS-1 and AEGIS-2 studies.[9]
[2]Follow-up consists of three LDCT scans within a time frame of 2 years.[6,7]
Abbreviations: BGC, bronchial-airway gene-expression classifier; BC, bronchoscopy; ^{18}F-FDG PET, ^{18}F-fluorocholine positron emission tomography; LDCT, low-dose computed tomography; POM, probability of malignancy; TTNA, transthoracic needle aspiration; TTNB, transthoracic needle biopsy.

negative result at TTNA/B or surgery directed patients to surveillance. A diagnosis of cancer at bronchoscopy or TTNA/B led to a curative surgery (Fig. 1*a*). Throughout the article, we referred to wedge resection or extent of resection (lobectomy and segmentectomy), for both diagnoses of suspected nodules and definitive management of malignancies, like surgery. Among patients directed to surgery, we assumed that 57% underwent wedge resection and the rest extent of resection (93% lobectomy and 7% segmentectomy[10–13]; Table 1).

In the location-based strategy, bronchoscopy plus BGC were used for patients with moderate/intense ^{18}F-FDG nodule uptake and central or central and peripheral lesions, and TTNA/B or surgery for those with only peripheral nodules. As before, a diagnosis of cancer was assumed to lead to a curative surgery. We assumed that physicians referred patients at intermediate risk of cancer to more invasive procedures for diagnostic confirmation, and their referrals did not change based on a positive BGC result. On the contrary, we assumed that all patients with a nondiagnostic result (true and false negatives) at bronchoscopy and negative result at BGC were referred to follow-up. All the other care decisions were unchanged from the standard strategy (Fig. 1*b*).

The simplified strategy uses a bronchoscopy plus BGC as diagnostic tool for all patients with moderate/intense ^{18}F-FDG nodule uptake, regardless of where the lesion is located, because of the high negative predictive value of the BGC analysis for the peripheral cancers.[9] The subsequent care management remained unchanged from the standard strategy (Fig. 1*c*).

By creating identical clones of our cohort and assigning them to different strategies, we compared diagnostic-related differences in outcomes. Because the recommended approach for the clinical management of undefined nodules in patients at low POM is the watchful waiting approach, and the recommended approach in patients at high POM is mostly a surgical approach, the use of the BGC in those two groups is limited. Thus, our base-case analysis focused on patients at

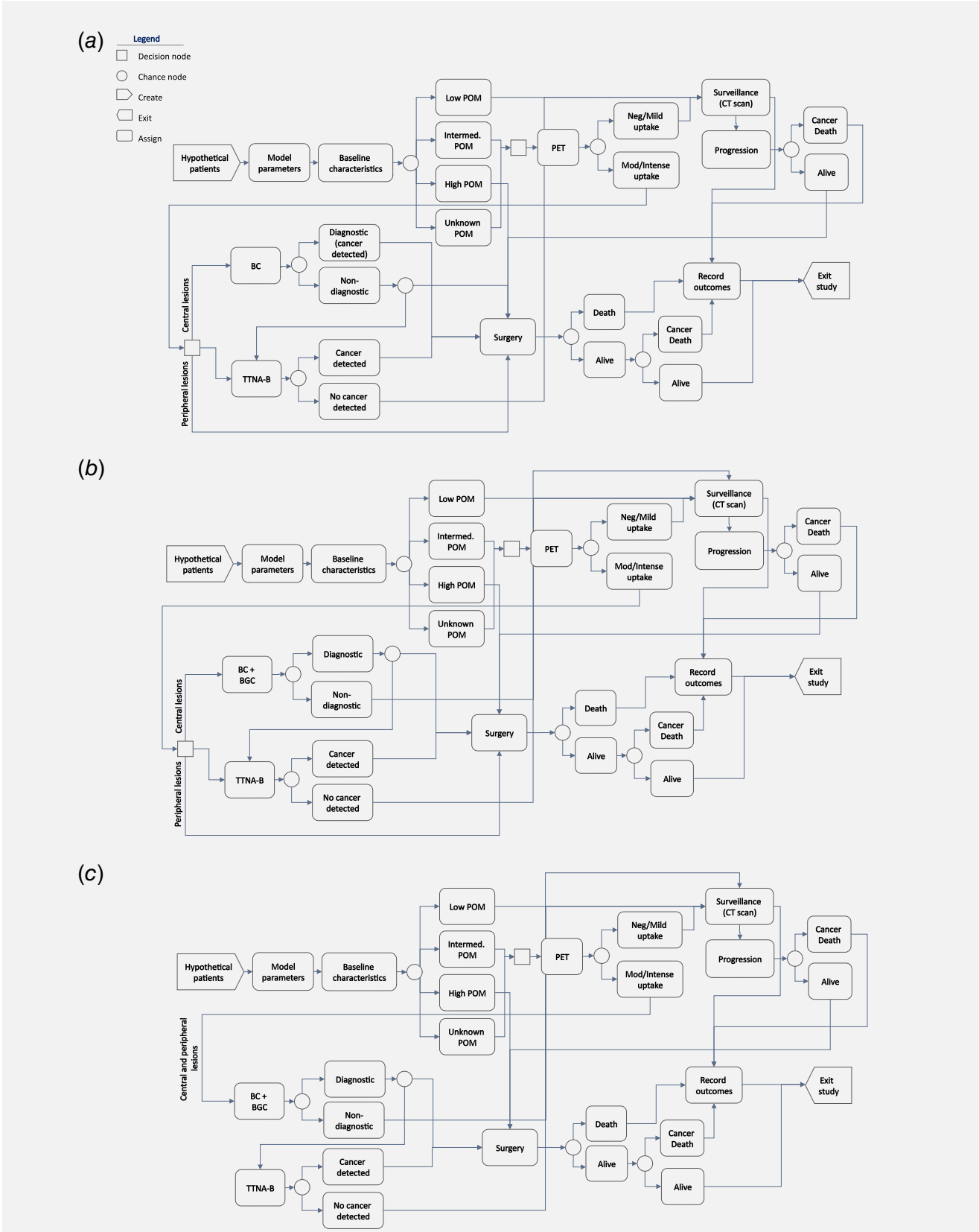

Figure 1. Legend on next page.

intermediate POM, who can achieve a greater benefit from the use of the BGC. We excluded from the base-case analysis the patients at unknown risk because of high prevalence of cancers and similarity to high POM group. Additional analyses on these subgroups are presented in the Supporting Information.

Data sources

We modeled sensitivity, specificity, positive and negative predictive values of bronchoscopy and bronchoscopy plus BGC based on the AEGIS studies.[9] Other data were derived from peer-reviewed literature[6,7,14–18] (Table 1).

Model outcomes

We estimated the number of procedures with high risk of adverse events (i.e., surgery and TTNA/B), cancer cases who went undetected and progressed to Stage II, and surgery-related and cancer-related deaths across the three strategies. Costs, quality-adjusted expected life years (QALYs) and incremental cost-effectiveness ratios (ICERs) were estimated; the results were also presented in a cost-effectiveness plane to facilitate comparisons. Because of the 2-year time horizon, costs and QALYs were not discounted. The analysis was conducted from a health care perspective.

Quality-of-life weights

Health-related quality-of-life weights associated with each health state in the model were derived from the peer-reviewed literature (Table 1),[19,20] and age-specific baseline quality-of-life estimates from the Medical Expenditure Panel Survey.[21] We penalized the QALYs lost due to mortality events based on patients' age-specific life expectancy per published US life tables.

Costs

Only direct medical costs were included. We used the 2017 national Medicare fee schedule to derive cost of most services because it is widely used by commercial payers as a reference or benchmark.[22,23] Whenever necessary, we adjusted unit costs for inflation by using the US Consumer Price Index to reflect 2017 US dollars.[24] Detailed information is provided in the Supporting Information.

Sensitivity analysis

One-way sensitivity analyses were performed by varying the model parameters by ±20% from the base case one at the time. Because BGC price was a key determinant of the incremental cost-effectiveness ratios, we varied it between $500 and $4,000. The results are reported as incremental net monetary benefit at a willingness-to-pay threshold of $100,000 per QALY.

We performed probabilistic sensitivity analyses by changing all model parameters simultaneously.[25] We sampled 10,000 independent sets of input parameters from their probability distributions and, for each set, we modeled a cohort of 10,000 hypothetical patients per strategy.[26,27] The results are reported using a cost-effectiveness plane (Supporting Information) and incremental cost-effectiveness acceptability curves.

Results

The median age (63, interquartile range [IQR] 55–71 years), smoking status (current or former smokers who quit within the past 15 years) and median pack-year history of cigarette smoking (43, IQR 24–63 pack-year) of our cohort were consistent with the eligibility criteria for the annual LDCT lung cancer screening covered by Medicare program and other commercial insurance in the US[28,29] (Table 1).

Base-case analysis

The base-case analyses, comparing the results of three alternative strategies for patients with solid nodules at intermediate POM are presented in Table 2. Cost-effectiveness frontiers are shown in Figure 2. Additional results, including patients from other POM categories, are presented in the Supporting Information.

The standard diagnostic strategy produced average quality-adjusted life expectancy of 12.13 QALYs and average 2-year costs of $11,111 per patient. Adopting the location-based strategy produced similar quality-adjusted life expectancy (12.129 QALYs) and average 2-year costs ($11,093) per patient, assuming the BGC cost of $2,865. The simplified strategy improved quality-adjusted life expectancy to 12.20 QALYs and increased average 2-year costs to $11,818. As a result, the location-based strategy was almost equivalent to the standard diagnostic strategy while the simplified strategy achieved higher quality-adjusted survival at higher costs. Compared to the standard or location-based strategies, simplified strategy produced an incremental cost-effectiveness ratio of $10,109 and $10,218 per QALY, respectively (Table 2, Fig. 2).

Use of the BGC was associated with reduced utilization of invasive procedures. With standard strategy, a total of 69.3% (95% confidence interval [CI], 57.0–81.8%) patients underwent these procedures. Adopting the location-based strategy reduced the use of both surgical procedures and TTNA/B, leading the overall

Figure 1. Model structure for the three diagnostic strategies to detect lung cancer in patients with suspected nodules. The diagrams show (*a*) standard, (*b*) location-based and (*c*) simplified diagnostic strategies in the model. The model assigns baseline characteristics (age, sex, smoking status, tobacco use, lesion location, POM) to a hypothetical cohort of people with an increased risk of cancer. Patients are assigned a diagnostic pathway and cancer status based on their POM. In each cycle, patients follow different health trajectories depending on whether they underwent surgery, surgical-related death, cancer-related death or background mortality; probabilities of each are a function of POM and cancer status in that cycle. If a patient survives in a given year, the quality-adjusted life-year and total cost accrued in that year will be recorded and patient characteristics will be updated for the next cycle. All patients are followed over 2 years. Abbreviation: POM, probability of malignancy; BC, bronchoscopy; TTNA-B, transthoracic needle aspiration or biopsy; BGC, bronchial gene-expression classifier; NB, within the non-diagnostic category are included. [Color figure can be viewed at wileyonlinelibrary.com]

Table 2. Results of base-case analyses in a population at intermediate probability of malignancy

Variable	Standard diagnostic strategy	Location-based diagnostic strategy	Simplified diagnostic strategy
Estimated distribution of procedures with high risk of adverse events, %			
Surgical procedures[1]	39.6 (32.1–48.1)	38.2 (30.8–46.3)	34.0 (26.3–42.5)
TTNA/B	29.7 (24.7–34.4)	27.8 (23.0–32.8)	24.9 (18.2–33.0)
Total	69.3 (57.0–81.8)	66.0 (54.1–78.6)	58.9 (46.2–73.2)
Cancer cases who went undetected and progressed to Stage II[2], %	4.65 (3.23–6.62)	5.56 (3.72–8.00)	7.18 (4.13–11.4)
Overall deaths within the 2-year follow-up[3], %			
Cancer-related death	2.65 (1.56–3.82)	2.70 (1.66–3.93)	2.75 (1.61–3.83)
Surgery-related death	0.60 (0.04–1.82)	0.57 (0.05–1.72)	0.51 (0.04–1.56)
Total	3.25 (1.90–4.94)	3.27 (1.98–4.88)	3.26 (1.91–4.63)
Cost-effectiveness results			
QALYs	12.130 (0.834–1.520)	12.129 (0.829–1.510)	12.200 (0.844–1.496)
Cost, $	11,111 (9,143–13,333)	11,093 (9,116–13,320)	11,818 (9,890–14,450)
Incremental QALYs	Reference	0.001 (−0.364 to 0.332)	0.070 (−0.362 to 0.340)
Incremental cost, $	Reference	−16 (−415 to 334)	708 (114–1,645)
ICER relative to standard diagnostic strategy, change in $/change in QALYs	Reference	Almost equivalent	10,109
ICER relative to location-based diagnostic strategy, change in $/change in QALYs	Almost equivalent	Reference	10,218

[1]Including wedge resection, lobectomy and segmentectomy.
[2]At the end of first round screening (before the two CT scans programmed in the watchful waiting approach).
[3]The background mortality is not included.
Abbreviations: QALYs, quality-adjusted life years; TTNA/B, transthoracic needle aspiration or biopsy.

proportion to 66% (95%CI, 54.1–78.6%). With the simplified strategy, the total estimate dropped to 58.9 (95%CI, 46.2–73.2%).

The proportion of cancers that went undetected at the end of the first screening round was 4.65% (95%CI, 3.23–6.62%) following the current guidelines, 5.56% (95%CI, 3.72–8.00%) with the location-based strategy and 7.18% (95%CI, 4.13–11.4%) with the simplified strategy. In the actual clinical setting, these patients are referred to follow-up and will undergo the second LDCT. However, in our model, we assumed that they progressed to Stage II to penalize BGC-based strategies for false negative results.

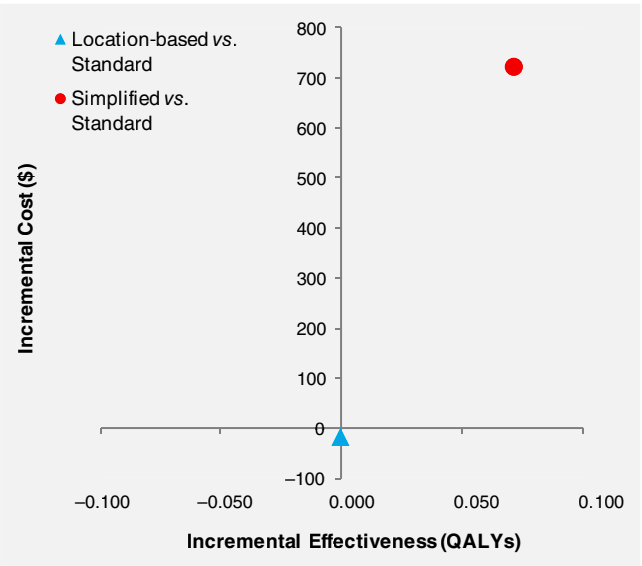

Figure 2. Base-case results of incremental cost-effectiveness of location-based and simplified diagnostic strategies *versus* standard diagnostic strategy. [Color figure can be viewed at wileyonlinelibrary.com]

Cancer-related deaths were 2.65% (95%CI, 1.56–3.82%) under the standard strategy, 2.70% (95%CI, 1.66–3.93%) under the location-based strategy and 2.75% (95%CI, 1.61–3.83%) under the simplified strategy. Surgery-related deaths were 0.60% (95%CI, 0.04–1.82%) under the standard strategy, 0.57% (95%CI, 0.05–1.72%) under the location-based strategy and 0.51% (95%CI, 0.04–1.56%) under the simplified strategy. Thus, overall deaths within the 2-year follow-up, excluding background mortality, were 3.25% (95%CI, 1.90–4.94%) following the current guidelines, 3.27% (95%CI, 1.98–4.88%) adopting the location-based strategy and 3.26% (95%CI, 31.91–4.63%) with the simplified strategy.

Sensitivity analysis

In one-way sensitivity analyses, none of the input parameters varied individually had a large effect on the ICERs other than the sensitivity and price of BGC. Lower sensitivity reduced costs and QALYs in both BGC-related strategies compared to

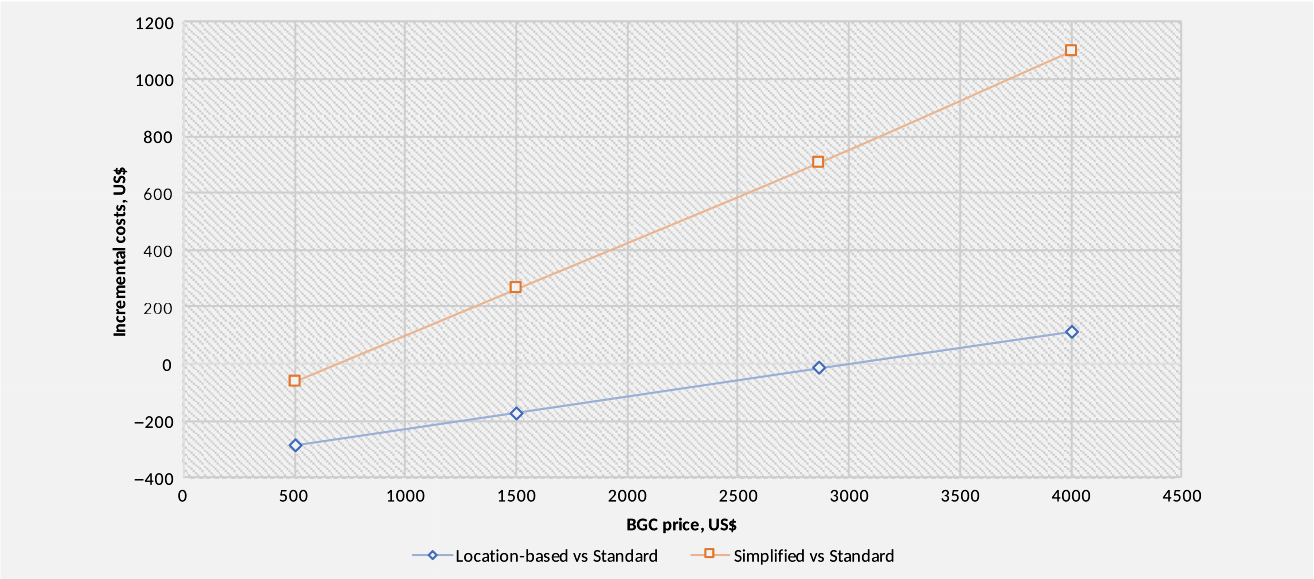

Figure 3. The graph shows the incremental costs (vertical axis; $) for different BGC prices (horizontal axis) when location-based strategy is compared to standard strategy (orange line) and when simplified strategy is compared to standard strategy (blue line). [Color figure can be viewed at wileyonlinelibrary.com]

the standard (Supporting Information). When the BGC price is $4,000, the simplified strategy increases the quality-adjusted life expectancy at about $1,100 per patient and the location-based strategy at about $100 compared to the standard strategy. If the BGC price is reduced to $500, then the simplified strategy could increase the quality-adjusted life expectancy at the same cost as the standard strategy. Reducing the BGC price at $500 made the location-based strategy cost-saving, by up to about $300 per patient (Fig. 3).

Figure 4 shows the cost-effectiveness acceptability curves of the probabilistic sensitivity analysis. When the willingness to pay per QALY was zero, the location-based strategy was the optimal diagnostic strategy, followed closely by the standard strategy. The simplified strategy had a greater probability to

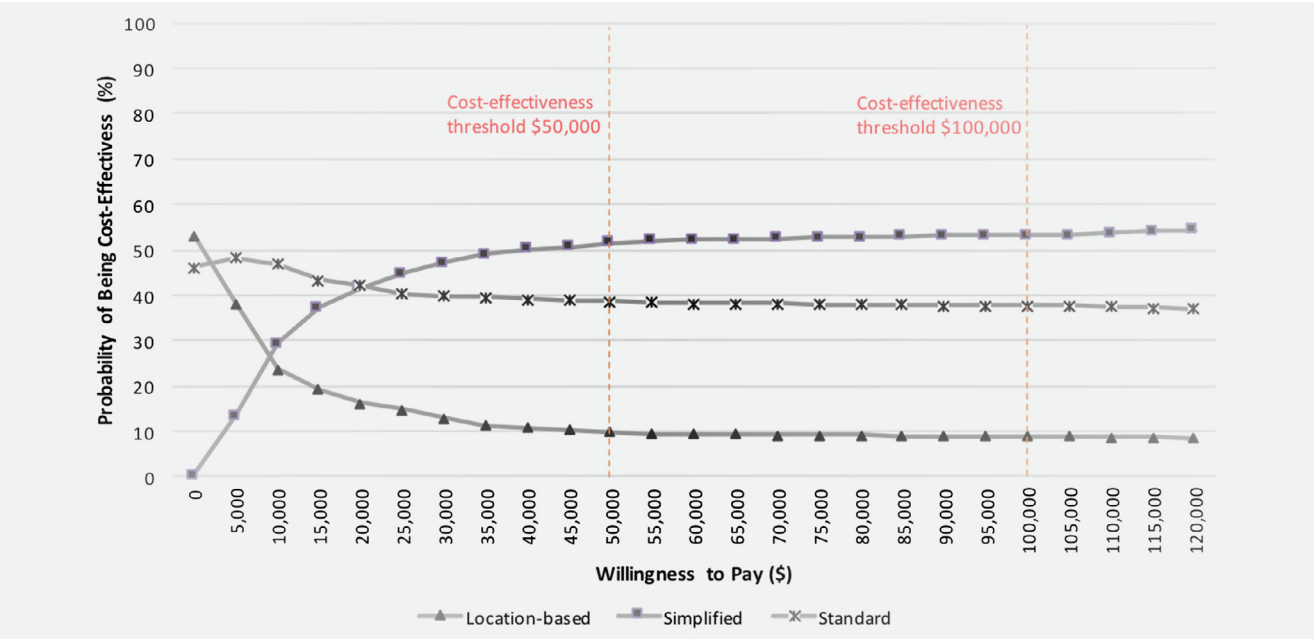

Figure 4. Cost-effectiveness acceptability curves (CEAC). The curves indicate the probability of each strategy to be cost-effective at a given willingness to pay (WTP) threshold. The dot lines indicate the common thresholds used for the US health care system. [Color figure can be viewed at wileyonlinelibrary.com]

be cost-effective compared to the others at willingness to pay thresholds of $20,000 or higher per QALY.

Discussion

For individuals with an indeterminate solid pulmonary nodule, which has risk of developing lung cancer between 5 and 60%, our analysis suggest that adding a bronchial genomic classifier to bronchoscopy for central and peripheral lesions improves quality-adjusted life expectancy, reduces unnecessary invasive procedures and represents good value for money relative to widely-accepted willingness-to-pay thresholds.[30] When used only for central lesions, the use of the classifier can be cost-saving if it is marketed at lower prices.

Compared to the standard, a simplified strategy increases the quality-adjusted life expectancy at an acceptable cost. This increase was mainly due to the net reduction of invasive procedures with high risk of complications in patients ultimately diagnosed with benign lesions. Even though this genomic test does not eliminate all of the unnecessary procedures (because of false-negative BGC results), the reduction is sizeable and might have significant clinical implications, especially since the lung cancer screening has become so widely used in the US.

Eight million Americans became eligible for annual LDTC lung cancer screening and it is extremely likely that this will increase the number of patients at intermediate risk under investigation. Among the nodules that LDCT detects, more than 90% are ultimately found to be benign.[5] As shown in the NELSON trial, the volumetric computed tomography might replace the LDCT to reduce the risk of unnecessary invasive interventions by lowering the rate of false positives to 60%, using a three rounds screening strategy.[31] However, in the real world, it is challenging to keep a high compliance with the screening for three consecutive rounds and even with a high adherence, the false positives are still a main problem. False-positive results can be partially resolved by ^{18}F-FDG PET, assuming that all intermediate-risk patients with an undetermined diagnosis are referred to this examination, as recommended by the guidelines.[6] However, a substantial number of these patients might still require invasive procedures. Adopting a location-based strategy, in which the classifier is used for all nonperipheral lesions, reduces the rate of invasive procedures by 3.3% while a simplified strategy in which the classifier is used regardless of where lesions are located could reduce the absolute rate of invasive approaches by more than 10%.

Although there is an evident benefit in decreasing the number of unnecessary and/or complicated procedures, in some cases relying on a false-negative classifier result might delay the correct diagnosis and subsequent treatment. As expected, the rate of undetected cancers after the first screening round increased with the location-based and simplified strategies (by 0.9 and 2.5%, respectively). However, we assumed that patients with negative results would be referred to surveillance, receiving two further annual LDCT scans. The high sensitivity of LDCT scans can ensure that an eventual growth of malignancies is not repeatedly perceived or misinterpreted as benign.[32] Although our study shows a slight increase in cancer-related mortality for the location-based and simplified strategies, the concomitant decrease in surgery-related deaths keeps the overall mortality roughly unchanged. Furthermore, it is important to note that we adopted a very conservative assumption by penalizing BGC-based strategies, for which all undetected cases progressed to Stage II within 1 year ignoring the high chance of detection in the follow-up screenings. Thus, it is likely that the difference between rates of undetected cancers and cancer-related mortality is even smaller than we observed.

Even though the location-based strategy also lowers the rate of unnecessary procedures, this was not sufficient to produce additional clinical benefits and the costs were comparable to those for the standard strategy. However, if the price of the classifier declines, the location-based strategy becomes cost-saving, with the potential to reduce health expenditures substantially (e.g., if the price of the classifier were set at $1,500 we could save almost $200 per person).

Our results are in line with those of several genomic classifiers for diagnosis and therapy of other conditions.[33–36] A previous cost-effective analysis on a BGC was performed but it was restricted to the location-based use of bronchoscopy plus classifier *vs.* bronchoscopy and did not estimate important clinical outcomes that might be a concern for implementation such as undetected cancer cases and cancer-related deaths.[11] We developed a more comprehensive model, reproducing entirely the current process for diagnosis and management of pulmonary nodules (standard strategy), and then analyzing the use of bronchoscopy plus BGC to replace not only the bronchoscopy (location-based strategy) but also TTNA/B as diagnostic examination (simplified strategy).

Our analysis has some limitations. First, we made several assumptions based on the current recommendations, and we did not account for the extent to which physicians and patients actually follow them. The clinical management of patients with pulmonary nodules might differ across diverse settings and in many situations, the operator experience, the availability of the equipment, patients' clinical history and preferences or other factors guide the decision. For example, in some circumstances, where TTNA might be associated with a greater risk of complications, bronchoscopy the with endobronchial ultrasound (EBUS) is a preferred approach to investigate undefined peripheral nodules.[37,38] However, because most assumptions affect all three strategies in a similar fashion, the conclusions are likely to apply beyond the particular model we analyzed. Second, because costs are derived from Medicare databases, accounting for commercial payers' costs would arguably lead to greater average unit costs than in our analysis. However, this would increase the costs for all strategies and should not affect the incremental results. Third, we restricted our analysis to direct medical costs and did not consider the effect of surgical interventions and cancer progression on indirect costs, nonmedical costs or costs accrued from prolonged life expectancy.

Finally, because the time horizon of our model is 2 years, we did not account for all the future medical costs relative to cancer progression and treatment. However, there is no reason to believe that the cost of treatment would be differential across the three strategies beyond year 2. This limitation does not apply to estimation of quality-adjusted life expectancy, because we have accounted for the age-specific life expectancy of patients and the impact of mortality on that in our model.

In summary, from a health care perspective, adding the classifier to bronchoscopy for the diagnosis of central or peripheral solid nodules could improve health outcomes in patients with indeterminate nodules at acceptable cost. The location-based use for central lesions can be cost-saving if the price of classifier declines.

Authors' contribution

Study concept: D'Andrea E and Najafzadeh M. Study design: D'Andrea E, Najafzadeh M and Choudhry NK; Model development and results analysis: D'Andrea E and Najafzadeh M. Interpretation of the results: all authors. Initial draft of the article: D'Andrea E; revision of the article: Najafzadeh M, Choudhry NK, Raby B and Weinhouse GL. Final version approval: all authors.

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