An economic model to value companion diagnostics in non-small-cell lung cancer

Aim: An economic model was used to evaluate the potential economic impact and cost–effectiveness of companion diagnostic testing for patients with non-small-cell lung cancer (NSCLC). **Materials & methods:** A decision analysis model examined alternative patient management strategies for patients with advanced NSCLC who were not amenable to surgical treatment. A review of the literature provided the variables used to develop a timely base case and sensitivity analysis. A potential future scenario was also modeled. The model includes three options: conventional treatment (CT), new treatment (NT), and companion diagnostic (CD) strategy. **Results:** In the base case analysis based upon current data, the cost per life-year saved for CT, NT option and CD was US$43,367, US$47,394 and US$47,779, respectively. The cost per life-year saved for CT, NT option and CD in a potential future scenario with more expensive, effective targeted therapy was US$47,748, US$69,255 and US$66,369, respectively. **Conclusion:** In the future scenario, CDs have an incremental cost–effectiveness of US$56,829 per life-year saved when compared with NT as a first-line treatment. This is one demonstration of how CDs may be a cost-effective option for the treatment of patients with advanced NSCLC when the NT is extremely expensive but the outcome is significantly improved.

KEYWORDS: companion diagnostic ■ cost–effectiveness analysis ■ decision analysis ■ molecular therapies ■ non-small-cell lung cancer

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Lung cancer is among the most common neoplastic diseases encountered across the world and has among the highest rates of death amongst all cancer patients. The cost of treating lung cancer has also risen significantly, and as novel therapies emerge, the costs will most certainly rise as these novel agents are incorporated into clinical practice [1,2]. Most lung neoplasms (85%) are non-small-cell lung cancer (NSCLC) and patients with NSCLC often present at a mid to late stage, when treatment modalities are predominantly nonsurgical and palliative versus curative and directed towards symptom control and maintenance of a reasonable functional status and quality of life [1].

In view of the potential for significant adverse events with chemotherapy, and the high cost of potential targeted molecular therapies, companion diagnostics (CDs) could be potentially valuable in identifying those NSCLC patients most likely to benefit from a particular chemotherapeutic agent. A CD-guided patient management strategy, in which patients who possess a particular driver mutation associated with a better clinical outcome in response to a certain drug are identified in advance to target treatment towards those most likely to benefit, may represent a cost-effective option for emerging novel therapies for NSCLC and other diseases [3]. From an economic standpoint, the cost–effectiveness of a CD test for NSCLC is likely to depend upon such factors as the prevalence of a particular molecular mutation associated with therapeutic response, expected life expectancy, and the costs of available treatment and testing strategies.

Newer chemotherapeutic agents often benefit specific subgroups of patients who possess specific clinical, pathological and molecular characteristics [4]. As the ability to identify the cancer genome improves with the use of CD tests, clinicians may be increasingly able to identify those characteristics in advance and target therapy towards those patients most likely to benefit from a particular treatment. For example, the molecular marker for the *EGFR* driver mutation predicts a better overall prognosis and response to tyrosine kinase inhibitors erlotinib and gefitinib and has a frequency in a non-enriched US group of approximately 18% [5]. The *EML4–ALK* fusion oncogene (frequency: ~4%), and more recently *ROS1* (frequency: 1.7%) represent novel molecular targets predicting sensitivity to the drug crizotinib [6]. New markers are rapidly appearing, offering novel targets for therapy in a selected proportion of lung cancer patients with a higher likelihood of response than nonselective therapies.

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The goal of using a CD-guided strategy is to tailor the treatment strategy for each patient to improve expected survival, minimize the risk of potential side effects, and, from an economic standpoint, maximize the cost–effectiveness of scarce healthcare resources [7].

As with any patient management strategy, the attractiveness of CDs depends upon the net expected benefit that that test provides and the clinical decisions that ensue from the test result. In general, the main incremental benefit of a CD test for a particular disease is the selection and stratification of those patients who will most likely benefit from a particular therapeutic strategy [8]. From an economic standpoint, this approach has several ramifications regarding resource use and efficiency, because any approach that increases the efficient use of scarce resources will likely be cost effective by comparison. We therefore developed a general model to test the clinical and economic impact and cost–effectiveness of a CD strategy for patients with NSCLC.

Materials & methods

Model technique

A decision-analysis model was developed for a baseline population of NSCLC patients. The patient population had nonresectable, advanced disease (stages III–IV), in which the patient's status allowed for treatment beyond palliation. The model assumed the perspective of a managed care payer in the USA with a 1-year time horizon. A managed care perspective was used to set the 1-year time horizon for the model.

The method that we used to set up costs incurred in the model is consistent with the cost structure of fee-for-service Medicare. In order to make our results generalizable to other contexts, the model could be extended beyond the 1-year time horizon, as we demonstrate in an alternative future scenario. We chose not to include in our analysis societal costs such as time missed at work or quality-adjusted life-years. Researchers might want to broaden the context to a full societal perspective, and could do so with this model.

The patient population and perspective led to the inclusion of three clinical strategies in the model: conventional treatment (CT), new treatment (NT) option and a CD strategy. We defined CT to refer to the current standard of practice for late-stage NSCLC, which generally includes cisplatin-based (or platinum-based) combination therapy with docetaxel or pemetrexed [9]. The NT option was defined as the strategy that targets current and emerging molecular therapies for NSCLC. Current molecular therapies, for example, include the EGFR tyrosine kinase inhibitors such as erlotinib [10], and anaplastic lymphoma kinase inhibitors such as crizotinib [11]. We assumed that the CD tests for the presence of markers associated with the effectiveness of current molecular therapies. The model was designed to encompass novel CDs and molecular therapies that may be developed in the future.

One key clinical question that could require analytical modeling is not whether to employ the diagnostic test, but how best to select patients for testing. The CD strategy included the use of a test, such as an immunohistochemistry or genomic test, that guides the next step in the treatment process [10]. The model for NSCLC used in this study was generic in order to admit scenarios of both current and emerging chemotherapy drugs and tests. Our model investigated the effect of a paradigm shift where providers select one treatment strategy over another, in this case by choosing NT or CD instead of CT. While some patients may already receive diagnostic testing, we modeled the move from CT as the standard of care to NT or CD.

Our model incorporated costs and outcomes for a number of therapies, both in the CT and NT arms of the study. Costs and outcomes of CT included costs of docetaxel or pemetrexed, as well as other approved therapies as detailed in the 'Variable selection' section below. Costs and outcomes of NT included erlotinib, as well as other approved therapies. No single therapy was investigated in this study. Rather, any therapies that have the outcome and cost characteristics of the therapies used to populate this study can be investigated with the model we developed and analyzed.

Model structure & description

Figure 1 shows the decision-tree model employed in this analysis. The model depicts three main arms that correlate with the three strategies, CT, NT and CD, which are described above. Our model consolidated the many possible clinical pathways embedded in these three strategies into a small number of possible outcomes. TreeAge Pro 2009 was used to develop and depict the decision tree and perform the associated analyses [101].

In the CT strategy, we assumed that all patients would receive and remain on CT and that no diagnostic test for molecular markers

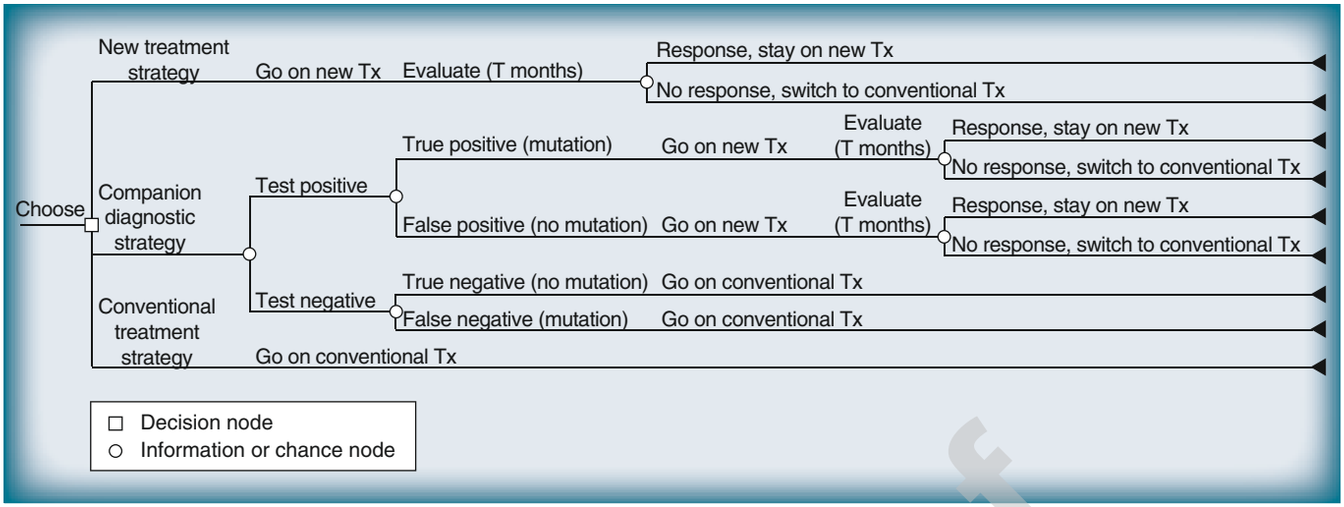

Figure 1. Decision tree model.
Tx: Treatment.

would be performed. The outcomes of this branch depended on the costs associated with the CT itself and all other medical costs incurred by patients throughout the course of care. To simplify the model structure, we incorporated such parameters as the re-evaluation of the effectiveness of chemotherapy, adverse events and mortality probabilities of chemotherapy, as opposed to designing separate branches.

The NT strategy referred to the use and administration of a novel molecular-based therapy to all patients who may potentially benefit without the use of a diagnostic test to identify potential driver mutations associated with increased likelihood of benefit. We structured into this arm a period of months following therapy, after which, patients are re-evaluated [12]. Patients would remain on this therapy if they demonstrated an objective beneficial response and would be switched to CT if they failed to respond or the tumor progressed. The expected outcomes from this strategy incorporated: the cost of NT; the cost of CT; the time at which patients are re-evaluated; the response rate of patients to the NT; the survival of responsive patients; and the survival of nonresponsive patients. As before, we also incorporated the probabilities of adverse events and mortalities directly into the model rather than creating separate 'sub-branches' for these potential sequelae. It is important to note that these drugs have not been approved by the US FDA for use in first-line NSCLC cancer treatment. Our model demonstrated how to evaluate the cost–effectiveness of diagnostics in a scenario where CT and molecular therapy would be equally available for all NSCLC cancer patients regardless of treatment line.

The CD strategy incorporated the use of a CD test, prior to the administration of any chemotherapy, to identify those patients who have a genetic or molecular mutation that has been associated with improved outcomes. We assumed, for the purposes of this analysis, that the results from this test would be dichotomous (i.e., positive or negative). Patients who tested positive initially received the NT. They were then evaluated to determine their response to NT. If they responded, NT was continued. If they did not respond, they were switched to CT. Patients who tested negative were assigned to CT and we further assumed that they would never receive the new molecular therapy that was tested for, regardless of eventual response.

The model is generalizable in that it can incorporate the results of tests that examine one marker or several markers in combination. This is important for CDs, which are not billed as such but rather by 'stacking' multiple billing codes for each aspect of the test. In other words, each activity that comprises the test is billed to the payer separately. The provider or laboratory cannot bill for the entire test with a single, unified procedure code. The variable selection used *EGFR* and *ALK* gene tests in developing the outcomes and costs input into the model (see 'Variable selection' section). However, our model was not specific to any marker or combination of markers.

The expected outcomes of the CD strategy depended on several variables. The CD, CT and NT costs, the time at which patients are re-evaluated, the response rate of patients to

Table 1. Probability variables from the literature used to populate the model.

Variable	Probability		Ref.
Sensitivity	0.92		[16]
Specificity	0.96†		[16]
Prevalence	0.19		[17]
Positive predictive value	0.84	Calculated based on assumed sensitivity, specificity and prevalence	
Negative predictive value	0.98	Calculated based on assumed sensitivity, specificity and prevalence	
New treatment – unselected response rate	0.34		[18]
New treatment – selected response rate	0.66		[18]

†We chose a specificity slightly below the one used in the article in order to perform sensitivity analysis.

the NT, the survival of responsive and non-responsive patients, and the prevalence of the mutation in the patient population, along with the sensitivity and specificity of the CD test, were all part of the model. The derivation of the associated variables is described in the next section.

Variable selection

The first type of variable required to populate the generic model was probability. The probability values and their sources in the literature are presented in Table 1. In our case of a CD, the meaning of sensitivity and specificity were in relation to the dichotomous presence or absence of the mutation. The prevalence of a generic mutation was based on a single driver mutation that was present in some but not all patients' cancers. The probability of response can be unselected (meaning for the entire population) or selected (meaning for those who test positive). Probability of response in the CT arm was included in the overall survival outcomes data.

The second type of variable needed to populate the model was costs. Cost variables and their sources in the literature are presented in Table 2. All costs were brought forward to 2011 using the Consumer Price Index (CPI)–Urban Medical inflation factor [102]. The test costs were derived from average costs reported in the references used in the paper. We chose the medical CPI as the index that best reflects the therapies and technologies analyzed in this study. We also note that our model is general enough to admit other inflation factors, such as the CPI–Urban and other medical trend factors.

Table 2. Cost variables from the literature used to populate the model.

Variable	Cost (US$)	Ref.
Conventional treatment – second line†	3979/month	[19]
New treatment – second line	3125/month	[19]
Test	470	[13]

†We used second-line costs for consistency because first-line costs were not available for the new treatment.

The final type of variable needed was survival. The survival values and their sources in the literature are presented in Table 3. In order to fit the 1-year time horizon of the model used in this study, 1-year survival data was extracted from the overall survival presented in the published studies.

These assumptions were entered into the model deterministically and did not follow the cost–effectiveness practice standards that would be required for a full cost–effectiveness analysis of a specific diagnostic and specific therapies. We would recommend that any analysis utilizing this model follow the appropriate guidelines for cost–effectiveness analysis, and consider such an analysis on specific tests and therapies to be a follow-up study to this analysis. Current literature suggested there is no evidence of an overall survival benefit from selecting treatment on the basis of *EGFR* status. We followed this assumption in selecting variables for our model.

Results

Deterministic results

The end points of our model included the expected outcomes of both cost and survival, resulting in a cost–effectiveness ratio for each strategy. The outcome measure of cost per year of life saved was calculated for each individual strategy. The cost per life-year saved for each strategy was used to calculate an incremental cost–effectiveness ratio (ICER). The ICER compares the relative cost–effectiveness of the NT, CD and CT strategies.

Table 4 shows the current base results. The strategies resulted in similar clinical outcomes (~0.4–0.5 life-years saved) and costs (~US$19,000–22,000). The resulting cost–effectiveness of the strategies were similar (~US$43,000–48,000 per life-year saved). As a result, the cheapest strategy, NT, dominated CT. The incremental cost–effectiveness of CD was approximately US$155,000 per life-year

saved. It is likely the CD ICER estimates were driven by potential alterations in costs of treatment rather than survival benefits.

Sensitivity analyses

We generated a more in-depth view of the importance of different variables with one-way sensitivity analysis. Intuitively, if one treatment is very cheap, or very expensive, the CD might not add economic value – we should just try the cheap therapy, especially if neither is clinically superior. That intuition comes through in the sensitivity analysis, where varying the cost of the new therapy changes the reference therapy (Figure 2). When the new therapy was cheap, the new therapy strategy was the reference strategy, dominating the CT strategy. The CD strategy had a high ICER, because it improved outcomes, but at a relatively high cost.

As the new therapy became more expensive, the CD strategy became more cost effective. At a certain point, the new therapy became expensive enough that the CT strategy was the reference therapy. The conventional strategy was the least costly, followed by the NT strategy, followed by the CD strategy. The incremental cost–effectiveness of the two more costly strategies was more reasonable, and the CD continued to decline. The incremental cost–effectiveness of the NT strategy rose until it became uneconomical.

Above a certain value, the NT for all strategy is more costly and less effective than the CD strategy. In this range, the CD strategy dominates the NT for all strategy. The CT strategy continued to be the reference, and the CD strategy rose again. The cost–effectiveness of the CD strategy was discontinuous, and it was a more cost-effective strategy for middle values of the NT compared with extremely high or low values.

Table 5 shows an additional sensitivity analysis based on the current base case. The cost of the NT was increased by 15%, resulting in increased costs for the NT and CD strategies. There were no changes in clinical outcomes. The order of strategies from least to most costly changed to CT, NT and CD, respectively. NT had an ICER of US$53,609 when compared with CT, and CD had an ICER of US$73,201 when compared with NT.

Table 3. Cost variables from the literature used to populate the model.

Variable	Months	Ref.
Conventional treatment	5.63	[20]
New treatment – unselected	5.26	[21]
New treatment – selected	7.66	[22]

Table 6 shows the variables used for a future scenario, the results of which are in Table 7. The future scenario represented a possible future where a small number of individuals would be expected to receive radically greater benefits from NT, and where that NT would be targeted through CDs. This hypothetical scenario was based on the desire to show how breakthrough therapies that extend survival well beyond those currently available would fit our model and change our results. It addressed the future perspective where novel therapies may be highly effective yet costly.

There was a very small, essentially negligible, difference in the effectiveness between these two strategies in Table 7. NT was slightly more effective; however, this difference was not shown when rounding to two decimal places. This led to the appearance of a high ICER for NT, which was due to the nonlinear effect of changing the inputs on the outputs in our model. Thus, the NT strategy became slightly less effective although the CD strategy showed remarkably greater clinical outcomes. The order of strategies from least to most costly was CT, NT and CD as in the current sensitivity analysis shown above. NT had an ICER of US$6,184,134 when compared with CT, and CD had an ICER of US$56,829 when compared with NT.

Other sensitivity analyses included changing the cost of the CD. We choose to highlight two point estimates in the manuscript. One is the test cost that we estimated from the literature. The second is a low estimate that is used to

Table 4. Cost–effectiveness results under the future scenario.

Strategy	Cost (US$)	LYS	Cost/LYS (US$)	ICER
New treatment	19,464	0.45	43,367	Reference
Companion diagnostic	22,070	0.47	47,394	US$154,512
Conventional treatment	20,930	0.44	47,779	Dominated (more expensive, less effective then reference)

ICER: Incremental cost–effectiveness ratio; LYS: Life-years saved.

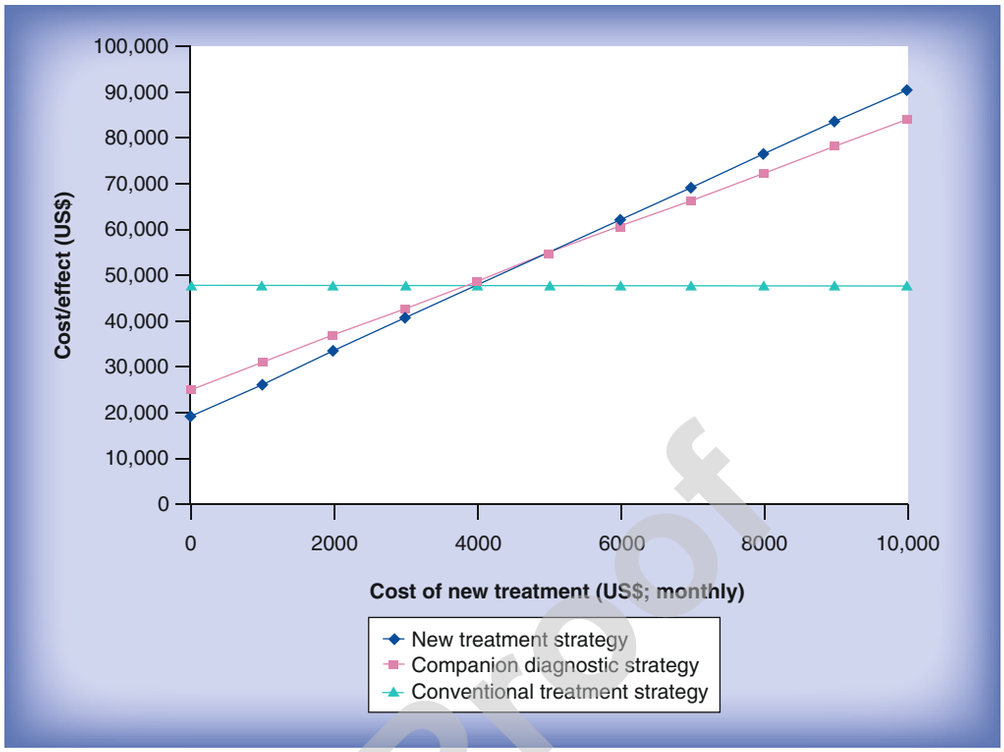

Figure 2. Sensitivity analysis of new treatment cost.

highlight the small impact of changes in test cost on the result. For example, US$114 was the average Medicare reimbursement for a generic immunohistochemistry test [13]. The ranks and magnitudes of the results were not changed for the range of test costs from US$114 to US$470, which did demonstrate the relative insensitivity of results to the cost of the CD test itself (results not shown).

Discussion

The model used is generalizable, and is able to inform future economic evaluations of CDs under many scenarios. The demonstration of the economic modeling approach, applied to a CD for NSCLC, and using published data where possible, shows the potential of economics modeling to inform the use of CD strategies in oncology. The information from a CD test is intuitively valuable if it leads to different, more personalized treatment based on the results of the test. The model demonstrates quantitatively the value of CD information. For example, one economic rationale for the CD is efficient use of costly novel therapies that may be developed, which is shown by the future scenario (Table 7).

The relative outcomes of the three strategies also come from the 1-year time horizon for our model. The NTs we used are noninferior to CTs (Table 3), so the outcomes are similar. There may be a justification for value in stratified treatment strategies in this case. We chose not to model such strategies, as our goal was to create a model that compared the strategies independently. The small additional benefit in survival of the CD in the current base case and sensitivity analyses comes from the prevalence of the mutation in a minority of the population. The responsive patients live nearly 50% longer; however, there are not enough to generate a large improvement over the CT strategy. That is a function of both the payer time horizon

Table 5. Current sensitivity analysis.

Strategy	Cost (US$)	LYS	Cost/LYS (US$)	ICER
Conventional treatment	20,930	0.44	47,749	Reference
New treatment	21,492	0.45	47,886	US$53,609
Companion diagnostic	22,726	0.47	48,802	US$73,201

ICER: Incremental cost–effectiveness ratio; LYS: Life-years saved.

in the USA and the severity of NSCLC in the modeled patient population.

As a result, relatively small changes in costs have large effects on cost–effectiveness results. When the NT is cheap, the NT strategy is the reference strategy, dominating the CT strategy. The CD strategy has a high ICER, because it improves outcomes at a relatively high cost. As the NT becomes more expensive, the CD strategy becomes more cost effective. At a certain point, the NT becomes expensive enough that CT is the reference strategy.

The economic modeling study also shows the amount of new data needed to populate a model of CDs. A clinical trial might compare the three strategies (CT, NT and CD) head-to-head. An ideal economic arm of the study would collect the total costs of therapy for the three groups. As the current sensitivity analysis demonstrates (Table 5), the total cost of treatment for the NT or CT, including adverse events and treatment switches, is the critical variable for deriving the economic value of CDs. Outcomes research should include all costs including adverse events and medical claims, in order to demonstrate the true economic value of CDs.

This evidence also informs the regulatory approach to CDs. The simultaneous approval of therapy and test advocated by the FDA is a match for the way that the model evaluated the CD [7]. The value of the test cannot be separated from the associated therapy. Furthermore, regulators, especially outside the USA, will likely request this kind of economic evaluation.

We also wish to contrast our results using a CD strategy with the patient enrichment strategy evaluated by other researchers. Based on the American Society of Clinical Oncology guidelines, all individuals are recommended the use of *EGFR* tests to aid treatment decision-making for NSCLC. There is a dispute as to how to utilize this information. A CD approach utilizes the test for all patients at a given stage to separate the recommended treatment. By contrast, the 'patient enrichment' strategy investigated by Atherly and Camidge used population data to try to find a population where the prevalence of the marker or markers is likely to be much higher, and to restrict the test to those subpopulations [14]. Since the tests and therapies modeled in this analysis are novel, we feel that the CD strategy is the one more likely to be used, as it may be difficult or impossible to restrict NSCLC or any cancer patients from a test that can potentially point to a highly effective therapy.

Table 6. Future scenario variables.

Variable	Value
Prevalence	40%
Population response	5%
False-positive response	5%
True-positive response	70%
New treatment monthly cost	US$7000
Survival for new treatment responders	11.5 months

This study demonstrates the need to model the diagnostic and the therapy as a single, bundled product. It also shows how such a model can be populated with data, and what results will be generated. Currently, stakeholders are debating whether drugs and the diagnostics that test for them should be regulated together or separately. They are also debating whether drugs and the diagnostics that test for them should be reimbursed and evaluated together or separately. Thus, our study shows the cost–effectiveness implications of the bundled strategy, which we feel will become more important as the bundled product model gains more currency. It may also help stakeholders envision and decide on bundled payments or value-based payments that consider the costs of an entire episode of care, rather than individual elements.

Conclusion

The economic evaluation of CDs differs somewhat from the standard comparative effectiveness evaluation of drugs. Our model, variables from the literature, assumptions and sensitivity analysis shows that CDs are valuable in a situation where a highly valid test can separate a patient population into two groups. The literature review-based data shows how CD extends the life of a selected population beyond that which is enjoyed by the average member of the population. The additional survival data alone is not enough for economic evaluation. The cost of the two types of treatment, including adverse events and supportive care, is also important.

Table 7. Future scenario.

Strategy	Cost (US$)	LYS	Cost/LYS (US$)	ICER
Conventional treatment	20,930	0.44	47,748	Reference
New treatment	30,464	0.44	69,255	US$6,184,134
Companion diagnostic	38,020	0.57	66,369	US$56,829

ICER: Incremental cost–effectiveness ratio; LYS: Life-years saved.

The numerical results of this study may not generalize to other clinical contexts or future NSCLC therapies.

The model we develop and present can encompass a range of future NSCLC therapies that may be developed. Our future scenario is one way of looking at how the results change when selection on the basis of a marker or markers generates significant overall survival benefit. This generic model shows one path forward for making the economic case for CDs.

Future perspective

CDs may be the technology that delivers the promise of personalized medicine for the treatment of NSCLC. While efforts towards prevention and early detection show some promise, NSCLC will continue to be a late-stage disease for many patients. The promise of new targeted therapies is the ability to turn the disease from terminal disease into a serious, but chronic, condition. For that reason, biopharmaceutical companies will continue to develop new targeted therapies. However, regulators and payers will continue to insist on showing the clinical effectiveness of these therapies, as well as the value proposition for their use.

We anticipate that an increasing number of these therapies will be approved for use in concert with CD tests. This will require a more collaborative approach by biopharmaceutical companies, especially those with a specialty in molecular therapies or diagnostics, but not both. It may also require a change in behavior by oncologists, such as limiting the number of treatments attempted [15]. The result will be a greater survival probability for lung cancer where the expense of care is incurred over a longer period. Careful economic analysis will be needed to show that the increased clinical benefit comes at an affordable cost.

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No writing assistance was utilized in the production of this manuscript.

Ethical conduct of research

The authors state that they have obtained appropriate institutional review board approval or have followed the principles outlined in the Declaration of Helsinki for all human or animal experimental investigations. In addition, for investigations involving human subjects, informed consent has been obtained from the participants involved.

Executive summary

Non-small-cell lung cancer care includes novel biopharmaceuticals

- Tyrosine kinase inhibitors and anaplastic lymphoma kinase inhibitors are two types of targeted molecular therapies.
- More molecular therapies will be developed.

Science of companion diagnostics shows that there are multiple types of non-small-cell lung cancer

- Different types of patients have radically different responses to therapies.
- Companion diagnostics can identify these responses ahead of time.

Personalized medicine for oncology

- Knowing who will benefit ahead of time allows clinicians to improve care.
- Knowledge of which patients will benefit ahead of time allows clinicians to restrict the use of expensive novel therapies to those who will benefit.

Economic case for companion diagnostics

- Companion diagnostics have a low cost relative to the overall cost of non-small-cell lung cancer therapy.
- The value of companion diagnostics is based on the improvements in care and the costs of suboptimal care that are avoided.

Conclusion

- Companion diagnostics are linked to the treatments they test for.
- Advancements in the science of companion diagnostics and biopharmaceuticals will require better economic data and additional comparative effectiveness analyses.

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