

Initial evaluation of the health economic impact of a 15-gene expression-based prognostic signature in early-stage NSCLC patient management

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Introduction

The 15-gene expression based prognostic signature (LungExpress Dx™) was developed using early-stage non-small-cell lung cancer (NSCLC) patient tumor specimens collected in the JBR.10 clinical trial to improve upon staging for identifying those patients who, following surgery, are at a higher or lower risk of mortality (Tsaao 2008).

In this initial study, patients classified by the 15-gene signature as higher risk significantly benefited from adjuvant chemotherapy (ACT), and those classified as lower risk did not benefit, and may have experienced a detrimental effect, from ACT (Tsaao 2008).

The prognostic utility of the 15-gene signature was subsequently validated in five independent patient cohorts totalling in aggregate 676 patients (Tsaao 2008; Der 2010).

This higher and lower risk stratification is independent of clinicopathological criteria, including stage, histology, gender and age, and may assist in guiding the post-surgical treatment of early-stage NSCLC patients (Der 2010).

Objective

The objective of this analysis is to conduct an initial evaluation of the clinical and economic impact of the 15-gene signature in early-stage NSCLC patient management by comparing it to clinical practice based on TNM staging.

Study Design

- Analysis:** Cost effectiveness analysis (CEA)
- Model structure:** Markov model
- Comparator:** 15-gene signature guided treatment versus NCCN/ASCO guided treatment
- Study population:** Stage I and stage II NSCLC patients with histologies of adenocarcinoma, squamous cell carcinoma and/or large cell carcinoma
- Perspective:** U.S. payor
- Time horizon:** Five years post surgery and life time (one-year cycle length)
- Annual discount rate:** 3%, applied to survival benefit and costs
- Outcome measures:** Life years (LY) and costs

Model Structure

Patients were triaged to either: (i) no adjuvant chemotherapy, or (ii) adjuvant chemotherapy, depending on the risk classification by TNM staging only (NCCN/ASCO guidelines) or TNM staging and the 15-gene prognostic signature (Figure 1).

Propensity to administer adjuvant chemotherapy based on TNM staging and the 15-gene signature was considered.

Clinical outcomes were modeled through Markov processes (Figure 2).

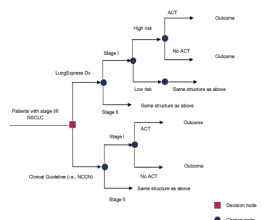


Figure 1. Risk classification and treatment decision

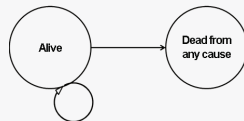


Figure 2. Markov model

Model Inputs and Assumptions

The 15-gene signature risk classification and clinical outcome data were estimated from the results of a recent validation study in patients with resected early-stage NSCLC who had not received adjuvant chemotherapy (Der 2010, Table 1).

The extent of chemotherapy benefit associated with patients treated in accordance with NCCN/ASCO guidelines was modeled from published meta-analysis (Pignon 2008, Table 1).

The extent of chemotherapy benefit associated with higher and lower risk patients as characterized by the 15-gene signature was estimated from the results of published adjuvant chemotherapy trials in NSCLC. The lowest reported hazard ratio (HR) was assumed to reflect benefit associated with higher risk patients, and the highest reported HR was assumed to reflect benefit associated with lower risk patients (Table 1).

Table 1. Clinical parameters

Parameter	Value	Data Source
Proportion of stage I patients	0.83	NCI SEER Survival Monograph
5-year survival (stage I, higher risk)	0.52	Der 2010
5-year survival (stage I, lower risk)	0.77	Der 2010
5-year survival (stage I)	0.63	Der 2010
5-year survival (stage II, higher risk)	0.42	Der 2010
5-year survival (stage II, lower risk)	0.66	Der 2010
5-year survival (stage II)	0.54	Der 2010
Proportion of higher risk (stage I)	0.52	Der 2010
Proportion of higher risk (stage II)	0.48	Der 2010
HR (ACT, higher risk)	0.49	Assumption based on Douillard 2006
HR (ACT, lower risk)	2.06	Assumption based on Pignon 2008
HR (ACT, stage I)	1.17	Pignon 2008
HR (ACT, stage II)	0.83	Pignon 2008
Propensity of ACT use (higher risk)	1	Assumption
Propensity of ACT use (lower risk)	0	Assumption
Propensity of ACT use (stage I)	0.125	Personal communication
Propensity of ACT use (stage II)	0.8	Kassam 2007, MBI market research report 2009

Costs were obtained from the published literature (Table 2).

Table 2. Cost parameters

Parameter	Value	Data Source
Test cost	\$ 3,850	Industry comparable price
ACT cost	\$14,724	Calculated based on Duh 2008
ACT adverse event cost	\$ 4,600	Pignon 2008, Weycker 2008
Treatment failure cost	\$75,000	Kutikova 2005

One-way sensitivity analyses were performed on the following parameters to account for their uncertainty (Table 3).

Table 3. Parameters tested in sensitivity analyses

Model Parameter	Base case	Input Value		
		Range	Low	High
Cost of test	\$3,820	20%	\$3,056	\$4,584
Cost of Treatment Failure	\$75,000	20%	\$60,000	\$90,000
Cost of Cancer Surveillance	\$1,000	20%	\$800	\$1,200
Cost of ACT	\$14,724	20%	\$11,780	\$17,670
Cost of ACT-related AE	\$4,600	20%	\$3,680	\$5,520
Proportion of stage I patients	83%	20%	66%	100%
HR (ACT- higher risk)	0.49	2008	0.33	0.73
HR (ACT- lower risk)	2.06	Tsaao 2008	2.06	3.67
Propensity of ACT use (higher risk, stage I)	1	20%	0.8	1
Propensity of ACT use (lower risk, stage II)	0	20%	0	0.2
Propensity of ACT use (no test, stage I)	0.125	20%	0.1	0.15
Propensity of ACT use (no test, stage II)	0.8	20%	0.6	1

References

- Der S et al., ACR-NSCLC (2010)
 Douillard JY et al Lancet Oncol. (2006)
 Duh MS et al., Curr Med Res Opin. (2008)
 Kassam F et al., J Thorac Oncol. (2007)
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- NCI. Cancer of Lung (2002)
 NCCN. NCCN Clinical Practice Guidelines NSCLC. (2009)
 MBI Market research (2009)
 Tsaao MS et al., ASCO (2008)
 Pignon JP et al., J Clin Oncol. (2008)
 Weycker D et al., Ann Oncol. (2008)

Results

Approximately 52% of patients were reassigned to a new risk category when the 15-gene signature was applied instead of TNM staging.

Overall, in stage I and stage II patients combined, the application of the 15-gene signature led to an increase of 0.32 life years (LY) at 5 years post-surgery and 2.57 LY at 20 years while being cost saving at both time points (Table 4).

Table 4. Cost-effectiveness of the 15-gene signature guided treatment vs. NCCN/ASCO-guided treatment (stage I and II)

	5-Year Horizon			20-Year Horizon		
	w/ testing	w/o testing	Difference	w/ testing	w/o testing	Difference
LIFE YEAR GAINED (LYG)						
Not discounted	4.32	4	0.32	11.47	8.9	2.57
Discounted	4.14	3.84	0.3	11.07	8.6	2.46
COST (\$)						
Not discounted	29,157	32,365	-3,208	69,564	74,196	-4,633
Discounted	28,005	31,033	-3,208	67,895	71,737	-3,842
INCREMENTAL COST-EFFECTIVENESS RATIO (ICER) (\$/LYG)						
Not discounted	Dominating			Dominating		
Discounted	Dominating			Dominating		

A subgroup analysis for stage I and stage II separately indicates that the 15-gene signature strategy would also be dominating in both stage I and stage II patients (Table 5 and 6).

Table 5. Cost-effectiveness of the 15-gene signature guided treatment vs. NCCN/ASCO-guided treatment (stage I)

	5-Year Horizon			20-Year Horizon		
	w/ testing	w/o testing	Difference	w/ testing	w/o testing	Difference
LIFE YEAR GAINED (LYG)						
Not discounted	4.36	4.02	0.34	11.83	9.02	2.81
Discounted	4.18	3.86	0.32	11.41	8.72	2.69
COST (\$)						
Not discounted	28,179	30,827	-2,648	68,199	72,791	-4,592
Discounted	27,068	29,544	-2,476	66,711	70,366	-3,655
INCREMENTAL COST-EFFECTIVENESS RATIO (ICER) (\$/LYG)						
Not discounted	Dominating			Dominating		
Discounted	Dominating			Dominating		

Table 6. Cost-effectiveness of the 15-gene signature guided treatment vs. NCCN/ASCO-guided treatment (stage II)

	5-Year Horizon			20-Year Horizon		
	w/ testing	w/o testing	Difference	w/ testing	w/o testing	Difference
LIFE YEAR GAINED (LYG)						
Not discounted	4.11	3.91	0.2	9.7	8.31	1.39
Discounted	3.95	3.76	0.19	9.37	8.04	1.33
COST (\$)						
Not discounted	33,931	39,873	-5,943	76,226	81,060	-4,833
Discounted	32,581	38,302	-5,721	73,674	78,428	-4,754
INCREMENTAL COST-EFFECTIVENESS RATIO (ICER) (\$/LYG)						
Not discounted	Dominating			Dominating		
Discounted	Dominating			Dominating		

Multiple one-way sensitivity analyses suggests that the model results were robust even when the model parameter uncertainties were considered. While all parameters result in a dominating ICER when the input was varied by $\pm 20\%$, it was noted that the chemotherapy benefit in the higher risk patient population had the greatest impact on the result.

Conclusions

Based upon this initial analysis, integrating the 15-gene signature into current clinical practice to assist in guiding treatment decisions appears to be a cost-saving strategy for the management of early-stage NSCLC patients.

The chemotherapy impact on higher and lower risk groups as classified by the 15-gene signature needs to be independently validated in additional studies to further inform the model.