

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

Er Chen¹, Christine Buerki¹, Fadia Saad¹, Marianne Laouri¹; ¹ Quorum Consulting Inc., San Francisco, CA; ² Med BioGene Inc., Vancouver, Canada; Correspondence: cbuerki@medbiogene.com

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).

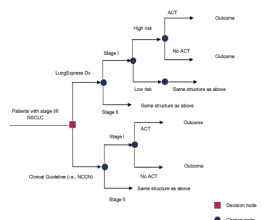


Figure 1. Risk classification and treatment decision

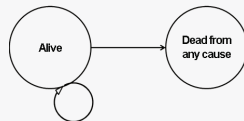


Figure 2. Markov model

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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 Kutikova L et al., Lung Cancer (2005)
 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.