Cost-effectiveness of precision diagnostic testing for precision medicine approaches against non-small-cell lung cancer: a systematic review

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Abbreviations

**ALK**  
anaplastic lymphoma kinase

**ARMS**  
amplification refractory mutation system

**ASCO**  
American Society for Clinical Oncology

**AUDS**  
Australian dollars

**CADS**  
Canadian dollars

**CEA**  
cost-effectiveness analysis

**CET**  
cost-effectiveness threshold

**CHEERS**  
Consolidated Health Economic Evaluations Reporting Standards

**CHFS**  
Swiss francs

**CN**  
China

**EGFR**  
epidermal growth factor receptor

**FISH**  
fluorescent in situ hybridization

**HK$**  
Hong Kong dollars

**HRM**  
high-resolution melt

**ICER**  
incremental cost-effectiveness ratio

**IHC**  
immunohistochemistry

**IO**  
immuno-oncology

**ISPOR**  
International Society for Pharmacoeconomic Outcomes Research

**LYG**  
dlife year gained

**MET**  
mesenchymal epithelial transition factor

**MTS**  
multiplex targeted sequencing

**NGS**  
next-generation sequencing

**NICE**  
National Institute for Health and Care Excellence

**NMB**  
et monetary benefit

**NSCLC**  
non-small-cell lung carcinoma

**OWSA**  
One-way sensitivity analysis

**PAP**  
patient access program

**PD-L1**  
programmed death-ligand 1
Abstract

Precision diagnostic testing (PDT) employs appropriate biomarkers to identify cancer patients that may optimally respond to precision medicine (PM) approaches, such as treatments with targeted agents and immuno-oncology drugs. To date, there are no published systematic appraisals evaluating the cost effectiveness of PDT in non-small-cell lung cancer (NSCLC).

In order to address this gap, we conducted Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) searches for the years 2009–2019. Consolidated Health Economic Evaluation Reporting Standards were employed to screen, assess and extract data. Employing base costs, life years gained or quality-adjusted-life-years, as well as willingness-to-pay (WTP)
threshold for each country, net monetary benefit was calculated to determine cost-effectiveness of each intervention.

Thirty-seven studies (50%) were included for analysis; a further thirty-seven (50%) were excluded, having failed population-, intervention-, comparator-, outcomes-, and study-design criteria. Within the thirty-seven studies included, we defined sixty-four scenarios. Eleven scenarios compared PDT-guided PM to non-guided therapy [epidermal growth factor receptor (EGFR), n=5; programmed death-ligand 1 (PD-L1), n=6]. Twenty-eight scenarios compared PDT-guided PM to chemotherapy alone [anaplastic lymphoma kinase, n=3; EGFR, n=17; PD-L1, n=8]. Twenty-five scenarios compared PDT-guided PM to chemotherapy alone, while varying the PDT approach.

Thirty-four scenarios (53%) were cost-effective, twenty-eight (44%) were not cost-effective, and two were marginal, dependent on their country’s WTP threshold. When PDT-guided therapy was compared to a therapy-for-all patients approach, all scenarios (100%) proved cost-effective.

Seven of thirty-seven studies had been structured appropriately to assess PDT-PM cost-effectiveness. Within these seven studies, all evaluated scenarios were cost-effective. However, 81% of studies had been poorly designed. Our systematic analysis implies that more robust health economic evaluation could help identify additional approaches towards PDT cost-effectiveness, underpinning value-based care and enhanced outcomes for patients with NSCLC.

1. Introduction

The World Health Organization (WHO) lists lung cancer as the most common cancer and leading cause of cancer death (1.76 million globally).[1] In the US, lung cancer was projected to cause 140,730 cancer deaths in 2020 (almost a quarter of total cancer deaths), with projected lung cancer deaths in the EU at 182,600 in 2020.[2,3] Relative survival of lung cancer is poor, at 39% and 13% for 1 and 5 years survival respectively. Non-small-cell lung cancer (NSCLC) accounts for 85% of lung cancer cases.[4,5]

Since 2009, several classes of drugs for NSCLC have been approved for use, all with accompanying precision diagnostic tests (PDTs). These include tyrosine kinase inhibitors (TKIs) against epidermal growth factor receptor (EGFR) (gefitinib, erlotinib, afatinib, dacomitinib and
osimertinib), TKIs against anaplastic lymphoma kinase (ALK) (crizotinib, ceritinib, alectinib, brigatinib, and lorlatinib), v-raf murine sarcoma viral oncogene homolog B1 (BRAF) (dabrafenib/trametinib), c-ros oncogene 1 (ROS1) (crizotinib or entrectinib), mesenchymal epithelial transition factor (MET) (capmatinib or tepotinib), rearranged during transfection proto-oncogene (RET) (selpercatinib), and neurotrophic tropomyosin receptor kinase (NTRK) (entrectinib or larotrectinib), and immuno-oncology (IO) drugs (pembrolizumab, nivolumab, atezolizumab, and durvalumab). American Society of Clinical Oncology (ASCO) and Ontario Health guidelines state that the 60% of stage IV NSCLC patients with actionable mutations (EGFR, ALK, BRAF, ROS1, MET, RET, and NTRK) should be offered the corresponding precision medicine that targets these abnormalities, and the remaining 40% without driver mutations should be offered immunotherapy, dependent on PD-L1 tumour proportion score (TPS) test result.[6,7] However, the costs of these new agents are proving unsustainable, in both unregulated markets and socialised healthcare systems;[8,9] But, this challenge has to be set against improved patient outcomes observed using these new targeted agents.[10] Quantifying the impact requires a value assessment of a PM intervention to both the patient and the payer. [11,12]. This requires some form of health economic evaluation, as part of a health technology assessment process.

In order to understand the health economic evaluation landscape of PDT-guided PM, we undertook a systematic review of the evidence available for value-based policymaking in this domain. Our hypothesis is that PDTs, while a fraction of the cost of their associated PM, provide substantial value in terms of health benefits.

2. Methods

The review is registered with PROSPERO (registration number: CRD42020171234) as per Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) guidelines.[13] The methodology followed was similar to a previous paper by the authors.[14]

2.1. Search Strategy

Utilizing the PICOS framework (population, intervention, comparator, outcome, study design), we formulated the research question “What is the cost-effectiveness of precision diagnostic testing for guiding therapy in non-small-cell lung cancer?” PICOS was employed to develop a search limited to studies that performed economic evaluation of patients diagnosed with NSCLC, who were subsequently stratified for treatment selection based on a PDT result. The search was conducted
for studies reported between 1 January 2009 and 31 December 2019. We searched MEDLINE, EMBASE, Cochrane Library, SCOPUS, Web of Science, NHS EED, and Econlit. Meeting presentations were also searched for the same period in the ASCO and International Society for Pharmacoeconomics and Outcomes Research (ISPOR) websites (see Table 1).

2.2 Search terms for MEDLINE and EMBASE

MEDLINE and EMBASE (OvidSP): 2009 to 2019 week 52

Searched 1st January 2020.

1. exp Lung Neoplasms/

2. ((lung or bronchial or nsclc) adj3 (adenocarcinoma$ or adenoma$ or cancer$ or carcinoma$ or lesion$ or malignant$ or meta-sta$ or metast$ or neoplas$ or oncolog$ or sarcoma$ or tumo?r$)).ti,ab,ot,hw.

3. NSCLC.ti,ab,ot.

4. or/1-3

5. *Polymorphism, Genetic/ or *Mutation/ or *Genotype/

6. (EGFR or KRAS or ALK or PD-L1 or MSI or TMB or PD-1).mp. [mp=title, abstract, original title, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]

7. (((HRM test or HRMA test or sanger sequencing or pyrosequencing or high resolution) adj3 melt) or next generation sequencing).mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]

8. (DNA profil* or Mutligene assay or expression profil* or DNA mutational analysis or genetic testing or germ-line mutation or nucleotide sequence or genetic screening or germline mutation or ((germline or germ-line) adj8 mutation)).mp. or ((genetic* adj test*) or (mutation* adj analysis)).tw. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word,
9. (immunohistochemistry or ihc).mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]

10. biomarker.mp.

11. ((genom$ or precision or personali$ or stratif$ or individuali$ or target$ or P4) adj (medic$ or treatment or therap$)).ti,ab,ot,hw.

12. 5 or 6 or 7 or 8 or 9 or 10 or 11

13. (Immunotherapy or Atezolizumab or Tecentriq or Durvalumab or Imfinzi or Nivolumab or Opdivo or Pembrolizumab or Keytruda).mp.

14. (Anti-EGFR therapy or EGFRi or Erlotinib or Tarceva or Afatinib or Gilotrif or Gefitinib or Iressa or Osimertinib or Tagrisso or Dacomitinib or Vizimpro).mp.

15. (Entrectinib or Rozlytrek or Crizotinib or Xalkori or Ceritinib or Zykadia or Alectinib or Alecensa or Brigatinib or Alunbrig or Lorlatinib or Lorbrona).mp.

16. (Trametinib or Mekinist or Dabrafenib or Tafinlar).mp.

17. (angiogenesis inhibitors or Bevacizumab or Avastin or Ramucirumab or Cyramza).mp.

18. (Chemotherapy or Cisplatin or Carboplatin or Paclitaxel or Taxol or Abraxane or docetaxel or Taxotere or Gemcitabine or Gemzar or Vinorelbine or Navelbine or Etoposide or VP-16 or Pemetrexed or Alimta).mp.

19. surgery.mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]

20. Radiotherapy.mp.

21. or/13-20
22. Costs.mp. and Cost-Analysis/
23. Cost-Benefit Analysis/
24. exp Models, Economic/
25. Quality-Adjusted Life Year*.mp.
26. Economic Evaluation/
27. Cost-Effectiveness Analysis/
28. Cost Utility Analyses/
29. Statistical Model/
30. (econom* or pharmacoeconomic* or pharmaco-economic*).ti.
31. (economic evaluation* or economic review*).tw.
32. (cost* adj2 (util* or effective* or benefit? or analy*)).tw.
33. (health adj2 utilit*).tw.
34. (euroqol or eq5d or eq-5d or hui or hui1 or hui2 or hui3).mp.
35. ((utility* adj2 (valu* or measure*)) or (time adj2 trade) or (standard adj2 gamble)).mp.
36. ((cost* or economic*) adj2 model*).tw.
37. (sensitivity analys$ or "willingness to pay" or quality-adjusted life year$ or quality adjusted life year$ or quality-adjusted life expectanc$ or quality adjusted life expectanc$).ti,ab.
38. (economic$ or cost or costs or costly or costing or costed or price or prices or pricing or priced or discount or discounts or discounted or discounting or ration$ or expenditure or expenditures or budget$ or afford$ or pharmacoeconomic or pharmaco-economic$).ti,ab.
39. exp economics, hospital/
40. economics, medical/
41. economics, nursing/
42. economics, pharmaceutical/
43. (expenditure$ not energy).ti,ab.
44. (value adj1 money).ti,ab.
45. budget$.ti,ab.
46. (cba or cea or cua).ti,ab.
47. exp "fees and charges"/
48. (fee or fees or charge$ or preference$).tw.
49. (fiscal or funding or financial or finance).tw.
50. exp Health Care Costs/
51. (cost$ adj1 (util$ or effective$ or efficac$ or benefit$ or consequence$ or analy$ or minimi$ or saving$ or breakdown or lowering or estimate$ or variable$ or allocation or control or illness or sharing or life or lives or affordabl$ or instrument$ or technolog$ or day$ or fee or fees or charge or charges)).ti,ab.
52. ((value or values or valuation) adj3 (money or monetary or life or lives or costs or cost$)).ti,ab.
53. (unit cost or unit-cost or unit-costs or unit costs or drug cost or drug costs or hospital costs or health-care costs or health care cost or medical cost or medical costs).ti,ab.
54. cost$.ti,ab.
55. exp decision support techniques/
56. markov$.ti,ab. or markov chains/
57. monte carlo.ti,ab. or monte carlo method/
58. (decision adj2 (tree$ or analy$ or model$)).ti,ab. or decision tree/
59. (survival adj3 analys$).ti,ab.
60. "deductibles and coinsurance"/
61. exp Health expenditures/
2.3. Study Selection

Articles were screened for eligibility based on criteria listed in Table S.1. (Appendix p2). Titles and abstracts of all articles were reviewed for eligibility and only accepted if these criteria were met. Four reviewers (RH, DF, DS, and ML) independently evaluated the full text of potentially eligible articles to determine whether to include or exclude. A lack of consensus over eligibility was resolved between the four reviewers. If doubts remained about study suitability (e.g., abstracts lacking peer review), they were excluded.

Integrity of each study was assessed according to a checklist developed by the ISPOR Consolidated Health Economic Evaluations Reporting Standards (CHEERS) Task Force Report.[15] This underpinned development of a quality rating for each study, thus allowing rigorous evaluation of the robustness of the data generated. Quality assessment was performed by one reviewer, checked by a second reviewer and any disagreement resolved by third/fourth reviewers. Quality ratings were assigned in five categories (Table S.2., Appendix p2).

The Study Selection Workflow is outlined in Figure S.1. (Appendix p1). Our initial database search and other electronic searches (ASCO, ISPOR) identified 18,723 records. MEDLINE and EMBASE results were further searched based on health economic filters, as there is a paucity of
these represented in the identified records. A total of 18,614 records were excluded, and the remaining 110 records were imported into reference management software, where duplicate records (n=36) were removed. A total of seventy-four articles were screened for eligibility. After full text examination, ten articles were either reviews or systematic reviews, which were retained for reference, while seven articles did not mention the terms life-years gained (LYG), quality-adjusted-life-years (QALY), or incremental cost-effectiveness ratio (ICER). Seven other articles did not include CEAs, cost benefit analysis, or cost utility analysis. On further examination, twelve were abstracts without enough detailed information, and one was an intervention without deployment of a PDT. In total, thirty-seven eligible studies remained, which involved economic evaluation of PDTs for guiding therapeutic intervention in NSCLC.

2.4. Data Extraction

We extracted empirical and methodological data and imported these data into Microsoft Excel. Extracted features included: author, year, country of study, NSCLC stage/advanced/not described, therapy, biomarker utilised, LYG, QALY, the current ICER (cost per LYG) and/or ICER (cost per QALY), willingness-to-pay (WTP) cost effectiveness threshold (CET), and net monetary benefit (NMB) statistic (calculated based on LYGs or QALYs, costs, and WTP). We also extracted author, PM cost, PDT cost (and calculated the PDT:PM cost ratio), perspective (healthcare payer, health insurance or hospital), modelling approach, time horizon (duration of therapy), discounting applied, one-way sensitivity analysis (OWSA), probabilistic sensitivity analysis (PSA), and the trial upon which the economic evaluation was based. While most studies only listed one scenario of PDT intervention compared to standard-of-care (or another PDT), some studies listed as many as 10 different scenarios, where the scenario involved variation in the PDT, therapy, or country. If there were insufficient data (e.g., abstract reports from conferences), we emailed the original authors for further details.

2.5. Data Synthesis

Data capture and quality analysis for each study of cost-effectiveness were represented in the data extraction and as a narrative summary. Modelling techniques used in the different studies were compared, and their robustness analysed.
2.6. Sub-Analysis
Net monetary benefit (NMB) was calculated in each instance where a PM-guided by a PDT was compared to the same PM drug administered to all patients without PDT guidance.

2.7. Mathematical Formulae employed
In cases where more than one therapy and test combination were modelled, the reported ICER might not be compared to the base case, e.g., best supportive care (BSC) or LYGs and QALYs reported, but no corresponding ICER calculated. In these instances, we calculated the ICER based on reported costings and QALYs for the PDT using the following formula:

\[
\text{ICER} = \frac{\Delta \text{Costs}}{\Delta \text{QALYs or } \Delta \text{LYGs}}
\]

For the studies that compared PDT-guided therapy with unselected PDT therapy for all-comers and with chemotherapy, we conducted a sub-analysis using the net monetary benefit (NMB) (a summary statistic that represents an intervention’s value in monetary terms) with the formula:

\[
\text{NMB} = (\text{QALY or LYG } \times \text{WTP}) - \text{Cost}
\]

The WTP CET employed for each scenario corresponded to that reported in the study; if more than one or a range of WTP CETs were described, we conservatively chose the lowest. Additionally, if no WTP CET was disclosed, then the WTP CET from the same country in another captured study was employed, or 1 x GDP per capita of that country was used.

3. Results
The thirty-seven studies were reported from Asia, Australia, Europe, and North America, all of which were at least upper middle-income countries. Publications spanned the period 2009 - 2019. Where a negative ICER was reported or calculated, it was always due to negative costs, not negative LYGs or QALYs. The reader should refer to the NMB statistic before drawing conclusions, as a negative value here will always determine that the intervention was not cost-effective.

3.1. Health Outcomes for each precision medicine (PM)/precision diagnostic testing (PDT) combination

3.1.1. TKI treatment guided by EGFR status versus TKI treatment for all patients
Four of five ICERs were negative (Table 2.a), generated from increased QALYs and less costly therapy; one of the ICERs was positive.[16–20] Negative ICERs can be equated with an intervention that can either be cost-effective or not, which may lead to confusion. The simpler Net Monetary Benefit (NMB) was calculated for each scenario; here a negative NMB indicates a non-cost-effective strategy. All four erlotinib studies produced positive NMBs. The one gefitinib study evaluated revealed an NMB equal to a S$5,800 increase per patient in value, when the EGFR test is employed to guide gefitinib therapy, as opposed to an unselected approach.

3.1.2. Immunotherapy treatment guided by PD-L1 positivity versus immunotherapy treatment for all patients

ICERs generated by the PD-L1 testing strategy were described as dominated (i.e. yielded worse health outcomes and were more costly) when compared to the no testing strategy, when pembrolizumab treatment was considered. However, the corresponding incremental QALYs and costs reported increased health benefits, and were less expensive, respectively.[21] Nivolumab therapy accompanied by PD-L1 testing generated ICERs well below the CHF100,000 WTP CET (Table 2b).[22]

Sub-analysis of the nivolumab study indicated a net monetary benefit (NMB) of CHF86 per patient at PD-L1 > 1% and a NMB of CHF2,779 per patient at PD-L1 > 10%, where the PD-L1 test guides nivolumab therapy when compared to an unselected approach (Figure 1a). Analysis of the pembrolizumab study revealed a NMB of US$32,604 per patient at PD-L1 > 1% and a NMB of US$56,889 per patient at PD-L1 > 50% in the US (Figure 1b). For China, the results indicated a NMB of US$27,039 per patient at PD-L1 > 1% and a NMB of US$52,120 per patient at PD-L1 > 50% (Figure 1c).

In summary, precision medicine treatments (erlotinib, gefitinib, or immunotherapy) guided by a precision diagnostic test (EGFR or PD-L1) increased the clinical and monetary value of PM for both the patient and healthcare payer, when compared to an unselected treatment approach for “all” patients.

3.1.3. TKI treatment guided by EGFR or ALK status versus chemotherapy treatment
Of the fourteen studies (twenty scenarios) evaluated, thirteen scenarios generated ICERs which breached their respective WTP CETs (Table 2c), and this is reflected in their corresponding negative NMB values (Table 1.c).

### 3.1.4. Immunotherapy treatment guided by PD-L1 positivity versus chemotherapy treatment

Table 1d shows six scenarios which generated ICERs below their WTP CETs (Table 2d), which correlated with positive NMB values; the remaining two scenarios had ICERs which breached their WTP CETs.

### 3.1.5. Treatment guided by genetic status using different testing scenarios

Twelve scenarios breached their WTP CETs, two scenarios were dominated (clinically inferior and more expensive than the standard-of-care), while the remaining eleven scenarios were within their CETs (Table 2e). The NMB indicated thirteen scenarios that were not cost-effective, ten scenarios that were cost-effective, and two scenarios which were marginal at zero.

### 3.2. Analyses for each PM-PDT cost evaluated

The annual cost of each study’s PM was identified, and this was employed as a denominator to assess the fraction of test cost relative to precision therapy (Appendix p3-11). The proportion of PDT cost to therapy cost ranged from 0.03% [US$32 immunohistochemistry (IHC) test to detect ALK mutations to guide crizotinib therapy at US$86,966 in China] to 4.24% [US$550 ARMS (amplification refractory mutation system) PCR test to detect EGFR to guide gefitinib therapy at US$12,893 in Mexico]. IHC tests were consistently the least expensive, while costs increased with the complexity of the test employed.

### 3.3 Decision Model for each PM-PDT combination evaluated

The modelling approaches principally followed the Markov process (twenty-two of the thirty-seven articles, see Appendix p3-11). Five articles had a partition survival modelling (PSM) perspective, and four articles solely employed a decision analytic method. The remaining studies included a state-transition model, a microsimulation with a state-transition model, a microsimulation alone, a discrete event simulation, a decision Monte Carlo, and an article which did not report its modelling approach.

### 3.4. Sensitivity Analyses for each PM-PDT combination evaluated
3.4.1. TKI treatment guided by EGFR status versus TKI treatment for all patients
The one-way sensitivity analyses (OWSAs) and probabilistic sensitivity analyses (PSAs) conducted indicated in four out of five cases that PDTs employed to guide therapy were the dominant strategy in France, Singapore, South Korea, and USA, demonstrating clinical benefit and cost-effectiveness for the patient (Appendix p3).[16–20]

3.4.2. Immunotherapy treatment guided by PD-L1 positivity versus immunotherapy treatment for all patients
For immunotherapy guided by PD-L1, the OWSAs indicated that PDT deployment or patient’s health status had the greatest effect on the ICER, while the PSAs determined that PD-L1 testing increased cost-effectiveness of the therapy in China, Switzerland, and USA (Appendix p4).[21,22]

3.4.3. TKI treatment guided by EGFR or ALK status versus chemotherapy treatment

3.4.3.1. Afatinib, Erlotinib, and Gefitinib treatment guided by EGFR Status
Reviewing the OWSA results, it was evident that both increasing mutation prevalence of EGFR and the health status of the patient had the greatest impact on the ICER, while the PSA determined in 4 of 7 studies that in China (with patient access programs), Germany, and Japan, that EGFR-guided therapy was cost-effective, whereas the Mexican, Thai, and USA studies were not cost effective (Appendix p5).[23–29]

3.4.3.2. Osimertinib treatment guided by EGFR-T790M Status
Overall, the OWSA results showed that the patient’s health status and the cost of osimertinib had the greatest effect on the ICER, while the PSA was inconclusive, with China and the UK studies cost-effective, while Canadian, Chinese, and USA studies were not cost-effective. (Appendix p5 and p6).[30–34]

3.4.3.3. Alectinib, Ceritinib, and Crizotinib treatment guided by ALK Status
The OWSAs demonstrated that cost of therapy and patient’s health status influenced the ICER the most; where a PSA was conducted in the Chinese study, it was likely that ceritinib was cost-effective, while alectinib was not (Appendix p6).[35,36]

3.4.4. Immunotherapy treatment guided by PD-L1 positivity versus chemotherapy treatment
The OWSAs performed showed that OS had a major impact on the ICER in four of five studies; in the four cases where PSA was conducted, the Swiss study was likely to be cost-effective; Hong Kong and USA studies were inconclusive, while the USA study was not cost-effective (Appendix p8).[37–41]

3.4.5. Treatment guided by genetic status using different testing scenarios
Although the OWSA in Canada, China, and USA revealed that several ICER values were most sensitive to OS, PFS and drug costs, this was not true for all studies, with certain ICER values in Australia and France more impacted by high-risk patients, inpatient care or costs alone. Most of the PSAs performed suggested that these were not cost-effective strategies, although the 14-gene assay and ALK testing were cost-effective (Appendix p9-11).

4. Discussion
To our knowledge, there is no systematic review of economic evaluations of NSCLC which focuses specifically on Precision Diagnostic Testing (PDT) guided precision medicine. In our analysis, we identified sixty-four CEA scenarios, evaluated within thirty-seven studies, which satisfy our criteria “What is the cost-effectiveness of precision diagnostic testing for guiding therapy in non-small-cell lung cancer?”; thirty-four (53%) of these scenarios were deemed cost-effective. However, only eleven of the sixty-four scenarios followed the correct analysis format to assess whether a PDT adds value to a precision medicine approach. That is, only these eleven scenarios compare precision medicine and PDT against precision medicine administered to the patient cohort without prior use of the test to select patients. Of these, seven scenarios (63.6%) agreed with our hypothesis of PDT-guided treatment conferring measurable increased benefit.

Four scenarios presented conflicting results of data from Wan et al.[21] we believe that the authors may have mislabelled these studies as dominated (clinically inferior and more expensive) rather than dominant (less costly and better health outcomes), which corresponds to the incremental costs and QALYs indicated in their results. The data that we have presented for these seven positive studies, and our conclusions, are supported by the authors of a recent systematic review of economic evaluation which only focussed on IO drugs. This study found that in NSCLC, molecular testing to help guide IO interventions provides more clinical benefit than the pharmaceutical agent alone.[42]
Overall, the LYGs or QALYs gained for EGFR-directed therapy were greater in the Asian studies than in North American or European populations, which is to be expected as the prevalence of EGFR mutations are greater in Asia. In 59% (24 of 41) cases, the EGFR-guided therapy fails cost effectiveness criteria regardless of test type, this is also true for ALK testing in 38% (5 of 13) of cases, and also occurs in 14% (2 of 14) of PD-L1 testing (all IHC-based testing).

A number of the testing scenarios involving NGS have difficulty capturing more than one actionable mutation with standard CEAs, as current Markov or state transition models aggregate patient data into distinct health groups [e.g., progression-free survival (PFS), progressive disease (PD) and death], neglecting heterogeneity amongst the patient cohort, and PSM is incapable of returning to PFS from a PD state, where in some cases there is a distinct possibility of a ‘cure’. Dynamic simulation modelling such as discrete event simulation (DES) has recently been suggested as a model which can track individual patient pathways incorporating results, testing and consequential therapies.[43]

Our analyses strongly suggest that health economic evaluation should be performed routinely from the start of and alongside clinical trials. This is particularly true for precision oncology, where therapeutic costs are high and improved patient outcomes achieved through application of a relatively inexpensive PDT would be beneficial, both from a clinical and a health economic viewpoint. Previously, we have demonstrated a paucity of CEA studies for precision medicine-guided care in colorectal cancer; that same dearth of application of CEA is evident for NSCLC, with only seven of thirty-seven studies (18.9%) adequately designed to analyse the cost effectiveness and value of PDTs.[14]

4.1. Strengths and Weaknesses

The principal strength of this systematic review is that we employ the net monetary benefit (NMB) summary statistic rather than the ICER to assess cost effectiveness. NMB incorporates both costs and QALYs at a willingness-to-pay threshold particular to that country, allowing cost effectiveness to be easily captured, thus generating more robust data. Secondly, we demonstrate that while precision medicine is a driver of costs, PDTs are a driver of value. PDTs, at a fraction of the cost of a precision therapy, add value beyond the therapy, by selecting patients who will accrue greater health benefits and reducing costs by excluding patients who will not benefit from a particular precision medicine approach.
Weaknesses of the data presented in this systematic review are that the majority of studies published are inappropriately structured to best assess effective PDT deployment in PM, which may reflect the lack of involvement of health economists and diagnostic stakeholders in setting the PM agenda.

Secondly, the generalisability of the results of this study is difficult to achieve, as WTP CETs vary not only between, but also within countries where such studies are performed. WHO proposes that it is reasonable to spend income to achieve a QALY that is equivalent to the GDP per capita of a country, a recommendation followed in the UK by National Institute for Health and Clinical Excellence (NICE) with its £30,000 WTP CET, but this is adapted for end-of-life disease such as metastatic NSCLC at £50,000, and modified again for small patient subgroups, a hallmark of precision medicine, with values of £75,000 upwards.[44–46] Such high WTP CETs could significantly impact on the costs of a country’s healthcare system, if only the value of an intervention is considered. It would be advisable to also conduct a Budget Impact Analysis which would more robustly assess the intervention’s affordability.[47]

Thirdly, all these CEAs are based on randomised controlled trials (RCTs) which involve highly selected patient populations. For precision medicine RCTs, the small patient populations and more complex clinical pathways may increase uncertainty in CEA modelling results. Adding CEA of real-world data as an adjunct to RCT data would improve confidence in a treatment’s effectiveness.[48]

Fourthly, the CEAs do not capture capital costs (testing equipment), personnel and their training, and reporting tool costs.

Fifthly, patient waiting times between test and therapy and the impact of first and potentially further surgical biopsies are not reported, two important aspects of PDT deployment. The turnaround times from sequential single gene testing to NGS is important in advanced NSCLC, where appropriate speed of test turnaround may be crucial to a patient’s survival (and likely QALY impact). These are not modelled in the studies described. Liquid biopsies also add to the speed of tumour profiling, with the additional bonus of being relatively painless to sample the patient.[49]
5. Conclusion

Over half of the scenarios analysed presented ICERs below the WTP CET, suggesting a potential publication bias, which can only be addressed by increased diligence and transparency in the health economics/precision oncology evaluation. Only seven of thirty-seven cost-effectiveness analysis studies performed to assess the benefit of PM approaches in NSCLC care were appropriately designed to assess the value of combining PDTs with PM, highlighting the need for greater emphasis on precise health economic analysis to inform value-based patient care. Despite this, employing molecular tests to guide NSCLC therapy appears to be cost effective in the majority of cases. Thus, cost-effective deployment of PDTs can add substantial value to the PM approach, well in excess of the cost of the test itself and should inform a more robust approach for future PM delivery for NSCLC patients.

Author contributions

RH, PK, DF, DS and ML were involved in the conception and design of the study. RH, DF, DS, and ML created the search strategy and performed the article inclusion. RH performed the data extraction. RH, DF, DS, and ML performed the quality assessment. All authors contributed to data interpretation, critically revised the article, and approved the final version.

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Conflict of Interest

ML reports honoraria received from Pfizer, EMD Serono, Roche and Carnall Farrar for presentations unrelated to this work. ML reports an unrestricted educational grant from Pfizer for activity unrelated to this work. All other authors have no conflicts of interest to declare.
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Supplemental data

Figure S.1. PRISMA flow diagram

Table S.1. Screening Criteria and Study Design for Systematic Review

Table S.2. CHEERS criteria and Quality Rating

Table S.3a. Methodological characteristics and quality rating of TKI treatment guided by EGFR status versus TKI treatment for all patients

Table S.3b. Methodological characteristics and quality rating of immunotherapy guided by PD-L1 positivity versus immunotherapy for all patients

Table S.3c. Methodological characteristics and quality rating of TKI treatment guided by EGFR or ALK status versus chemotherapy

Table S.3d. Methodological characteristics and quality rating of assessment of immunotherapy guided by PD-L1 positivity versus chemotherapy
Table S.3e. Methodological characteristics and quality rating of treatment guided by genetic status using different testing scenarios
| Search term | Database | Identified | Screened | Duplicates | Eligible |
|------------|----------|------------|----------|------------|----------|
| see MEDLINE | MEDLINE  | 4,782      | 11       | 22         |          |
| see EMBASE | EMBASE   | 13,698     | 38       | 5          | 5        |
| cost effectiveness analysis of testing for lung cancer therapy | PUBMED | 34 | 32 | 21 |
| cost effectiveness analysis of testing for lung cancer therapy | Cochrane | 28 | 10 | 3 | 1 |
| cost effectiveness analysis + testing + lung cancer therapy | SCOPUS | 33 | 32 | 9 | 5 |
| cost effectiveness analysis + testing + lung cancer therapy | Web of Science | 33 | 18 | 8 | 2 |
| testing + lung cancer therapy | NHS EED | 38 | 0 | 0 | 0 |
| cost effectiveness analysis + testing + lung cancer therapy | EconLit | 1 | 1 | 0 | 0 |
| cost effectiveness analysis of testing for lung cancer therapy | ASCO | 6 | 4 | 0 | 0 |
| cost effectiveness analysis of testing for lung cancer therapy | ISPOR | 21 | 18 | 0 | 1 |
| Systematic reviews of economic evaluations in PM or lung cancer | Hand searches | 49 | 49 | 11 | 17 |
Table 1. Search results from 10 databases and hand searching.

ASCO – American Society for Clinical Oncology; ISPOR – International Society for Pharmacoeconomic Outcomes Research; NHS EED - NHS Economic Evaluation Database

Table 1a. Study characteristics and outcomes of TKI treatment guided by EGFR status versus TKI treatment for all patients

| Author               | Year | Country | NSCLC stage | Therapy | Biomarker (methodology) | Change in LYG | Change in QALY | ICER (LYG)       | ICER (QALY) | WTP CET a | NMB     |
|----------------------|------|---------|-------------|---------|-------------------------|---------------|---------------|----------------|-------------|-----------|---------|
| Borget et al.[16]    | 2012 | France  | IIIB/IV     | Erlotinib | EGFR DNA sequencing     | 0.150         | 0.081         | -€38,767 b    | -€71,790 b  | €38,000 c  | €8,893  |
| de Lima Lopes et al.[17] | 2012 | Singapore | Advanced | Gefitinib | ARMS PCR Dxs EGFR29    | NR            | 0.040         | -S$75,000 b   | S$75,000 c  | S$5,800   |
| Hornberger et al.[18] | 2015 | USA     | IIIB/IV     | Erlotinib | EGFR Veristrat®        | 0.091         | 0.050         | -US$1,473 b   | -US$2,680 b  | US$72,346  | US$3,751|
| Lim et al.[19]      | 2016 | South Korea | IIIB/IV | Erlotinib | EGFR DNA sequencing     | NR            | 0.075         | -US$8,733 b   | US$14,691 c  | US$1,749  |         |
| Year | Country | Stage | Treatment | EGFR Veristrat® | CET | LYGs | WTP CET | ICER | GDP per capita |
|------|---------|-------|-----------|----------------|-----|------|---------|------|---------------|
| 2013 | USA     | Advanced | Erlotinib | 0.108 0.090 | US$75,926<sup>b</sup> | US$91,111 | US$125,000 | US$3,050 |

a – WTP CET is particular to each country; b – ICER not reported and calculated from reported costs and LYGs and/or QALYs; c – WTP CET not reported and the WTP CET from the same country was employed or 1 x GDP per capita of that country.

Negative ICER can infer favourable or unfavourable treatment options depending on where it lies on the cost effectiveness plane.

Negative NMB implies intervention is not cost effective compared to standard of care.

ARMS PCR - Amplification Refractory Mutation System polymerase chain reaction; CET – cost-effectiveness threshold; € - euros; EGFR – Epidermal Growth Factor Receptor; GDP – gross domestic product; ICER – incremental cost effectiveness ratio; LYG – life years gained; NMB – net monetary benefit; NR – not reported; NSCLC – non-small cell lung cancer; QALY - quality-adjusted life-year; S$ - Singapore dollars; US$ - United States dollars.
### Table 1b. Study characteristics and outcomes of immunotherapy guided by PD-L1 positivity versus immunotherapy for all patients

| Author            | Year | Country | NSCLC stage | Therapy  | Biomarker (methodology) | Change in LYG (methodology) | Change in QALY (methodology) | ICER (LYG) | ICER (QALY) | WTP CET\(^a\) | NMB |
|-------------------|------|---------|-------------|----------|-------------------------|-----------------------------|-----------------------------|-------------|-------------|----------------|------|
| Matter-Walstra et al.[22] | 2016 | Switzerland | NR | Nivolumab | PD-L1 > 1%, IHC | 1%(\%)0.1530.100 | CHF45,366\(^b\) | CHF65,774 | CHF100,000 | CHF86 | CHF2,779 |
|                   |      |          |             |          | PD-L1 > 10%, IHC      | 10%(\%)0.1180.090 | CHF31,229\(^b\) | CHF37,860 |              |              |      |
|                   |      |          |             |          | IHC                    |                            |                             |             |             |                 |      |
|                   |      |          |             |          | IHC - 22C3 pharmDx     |                            |                             |             |             |                 |      |
| Wan et al.[21]    | 2019 | China    | Advanced    | Pembrolizumab | US: PD-L1 > 1% | NR | US(1%)0.270 | NR | Dominated | US: US$100,000 | US$56,889 |
|                   |      |          |             |          | US: PD-L1 > 50%       | NR | US(5%)0.140 | NR | Dominated | US: US$27,039 | US$52,120 |
|                   |      |          |             |          | CN: PD-L1 > 1%        | NR | CN(1%)0.160 | NR | Dominated | CN: US$27,351 | US$52,120 |
|                   |      |          |             |          | CN: PD-L1 > 50%       | NR | CN(5%)0.050 | NR | Dominated |              |      |
|                   |      |          |             |          | IHC - 22C3 pharmDx     |                            |                             |             |             |                 |      |

\(^a\) WTP CET is particular to each country; \(^b\) ICER not reported and calculated from reported costs and LYGs and/or QALYs; \(^c\) percentages in brackets refers to PD-L1 expression cut-off.

Negative ICER can infer favourable or unfavourable treatment options depending on where it lies on the cost effectiveness plane.

A dominated strategy is one which is clinically inferior and more expensive.
CN – China; CET – cost-effectiveness threshold; CHF – Swiss francs; ICER – incremental cost effectiveness ratio; IHC – immunohistochemistry; LYG – life years gained; NMB – net monetary benefit; NR – not reported; NSCLC – non-small cell lung cancer; PD-L1 – Programmed Death Ligand 1; QALY - quality-adjusted life-year; WTP – willingness-to-pay; US – United States; US$ - US dollars.
Table 1c. Study characteristics and outcomes of TKI treatment guided by *EGFR* or *ALK* status versus chemotherapy treatment

| Author          | Year | Country | NSCLC stage | Therapy | Biomarker (methodology) | Change in LYG | Change in QALY | ICER (LYG) | ICER (QALY) | WTP CET<sup>a</sup> | NMB   |
|-----------------|------|---------|-------------|---------|-------------------------|----------------|----------------|------------|-------------|---------------------|-------|
| Arrieta et al.[23] | 2016 | Mexico  | Advanced    | Gefitinib | *EGFR* ARMS PCR DxS *EGFR*<sup>29</sup> | 0.086          | NR             | US$55,349   | NR          | US$10,929<sup>c</sup> | -US$46,820<sup>d</sup> |
| Limwattananon et al.[24] | 2018 | Thailand | IIIB/IV     | Gefitinib | *EGFR* Test NR Afatinib  | 0.111          | 0.148          | US$82,964<sup>b</sup> | Dominated  | US$4,500            | -US$8,543        | US$8,001       | -US$10,872   |
| Narita et al.[25] | 2015 | Japan   | IIIB/IV     | Gefitinib | *EGFR* ARMS PCR DxS *EGFR*<sup>29</sup> | NR             | 0.113          | NR          | ¥3,380,00   | ¥5,000,000          | ¥225,000         |
| Zhu et al.[26]  | 2013 | China   | Advanced    | Gefitinib<sup>e</sup> | *EGFR* ARMS PCR DxS *EGFR*<sup>29</sup> | 0.750          | 0.740          | US$34,867<sup>b</sup> | US$57,066  | US$18,951            | -US$12,126        |
| Handorf et al.[27] | 2012 | USA     | IV          | Erlotinib | *EGFR* FISH             | NR             | 0.059          | NR          | US$10,658   | US$100,000          | -US$573          |
| Schremser et al.[28] | 2015 | Germany | IV          | Erlotinib | *EGFR* DNA sequencing of exons 18–21 | NR             | 0.013          | NR          | €15,577     | €70,500             | €716              |
| Study                          | Year | Country | Stage    | Drug          | Mutation Test          | Cost 1 | Cost 2       | Cost 3        | Cost 4       | Cost 5       | Cost 6      |
|-------------------------------|------|---------|----------|---------------|------------------------|--------|--------------|--------------|--------------|--------------|-------------|
| You et al. [29]               | 2019 | China   | Advanced | Afatinib      | EGFR                   | NR     | 0.150        | NR           | US$33,749    | US$26,508    | US$1,093    |
| Bertranou et al. [30]         | 2018 | UK      | Advanced | Osimertinib   | EGFR-T790M cobas mutation test | NR     | 1.541        | NR           | £41,705      | £50,000      | €12,768     |
| Ezeife et al. [31]            | 2018 | Canada  | Advanced | Osimertinib   | EGFR-T790M              | 1.040  | 0.790        | CAD$169,610b | CAD$223,133  | CAD$50,000   | -CAD$136,894|
| Guan et al. [32]              | 2019 | China   | IIIB/IV  | Osimertinib   | EGFR-T790M cobas mutation test | 1.064  | 0.846        | US$19,708b  | US$24,976    | US$30,000    | US$5,081    |
| Wu et al. [33]                | 2017 | China   | Advanced | Osimertinib   | US: EGFR-T790M          | 0.877  | 0.704        | US$178,072b | US$222,030   | US -$100,000| -US$85,769  |
|                             |      |         |         |               | CN: EGFR-T790M          | 0.877  | 0.642        | US$222,294b | US$30,472    | CA -$23,815 | -US$4,623  |
| Wu et al. [34]                | 2019 | China   | Advanced | Osimertinib   | US: EGFR-T790M          | 1.100  | 0.851        | US$242,344b | US$312,903   | US$150,000  | -US$138,928|
|                             |      |         |         |               | CN: EGFR-T790M          | 1.100  | 0.757        | US$28,596b  | US$41,512    | US$28,410   | -US$8,746  |
|                             |      |         |         |               | cobas mutation test     |        |              |              |              |              |
| Djalaov et al. [35]           | 2014 | Canada  | IV       | Crizotinib    | ALK                    | 0.640  | 0.379        | CAD$148,011 | CAD$250,632  | CAD$100,000 | -CAD$57,143|
| Li, Lai, and Wu [36]          | 2019 | China   | IIIB/IV  | Alectinib     | ALK - FISH             | 0.890  | 1.000        | US$69,922   | US$62,231    | US$28,410   | -US$33,821 |
|                             |      |         |         |               | Ceritinib              | 0.810  | 1.090        | US$18,722   | US$13,905    |           | US$15,802  |
a – WTP CET is particular to each country; b – ICER not reported and calculated from reported costs and LYGs and/or QALYs; c – WTP CET not reported and the WTP CET from the same country was employed or 1 x GDP per capita of that country; d - NMB calculated with LYGs rather than QALYs; e – 10-year scenario.

Negative NMB implies intervention is not cost effective compared to standard-of-care.

A dominated strategy is one which is clinically inferior and more expensive.

**ALK** - Anaplastic Lymphoma Kinase; ARMS PCR - Amplification Refractory Mutation System polymerase chain reaction; £ - British pounds; CAD$ - Canadian dollars; CET – cost effectiveness threshold; CN – China; € - euros; EGFR – Epidermal Growth Factor Receptor; *EGFR-T790M* – *EGFR* gatekeeper mutation; FISH - fluorescence in situ hybridization; ICER – incremental cost effectiveness ratio; IHC – immunohistochemistry; LYG – life years gained; PAP – patient assistance programme; NMB – net monetary benefit; NR – not reported; NSCLC – non-small cell lung cancer; QALY - quality-adjusted life-year; WTP – willingness-to-pay; UK – United Kingdom; US – United States; US$ - US dollars; ¥ - Japanese Yen.

### Table 1d. Study characteristics and outcomes of immunotherapy guided by PD-L1 positivity versus chemotherapy

| Author          | Year | Country  | NSCLC stage | Therapy  | Biomarker (methodology) | Change in LYG | Change in QALY | ICER (LYG) | ICER (QALY) | WTP CET$^a$ | NMB      |
|-----------------|------|----------|--------------|----------|-------------------------|----------------|----------------|-------------|-------------|-------------|----------|
| Aguiar et al.[37] | 2017 | USA      | Advanced     | Pembrolizab | PD-L1 > 1% | 0.690 | 0.350 | US$49,007 | US$41,187 | US$98,421 | US$80,735 | US$100,000 | US$981 |
|                 |      |          |              |          | PD-L1 > 50% | 0.809 | 0.409 | US$98,421 | US$80,735 | US$100,000 |           |
|                 |      |          |              |          | 22C3 pharm Dx IHC |                |                |            |             |             |          |
| Bhadhuri       | 2019 | Switzerland | IV          | Pembrolizab | PD-L1 > 50% | 1.700 | 1.340 | CHF45,531 | CHF57,402 | CHF100,000 | CHF56,940 |
| Authors       | Year | Location | Disease Stage | Treatment | PD-L1 > 1% | PD-L1 > 20% | PD-L1 > 50% | CET (WTP) | US$ (CET) | CHF (CET) | HK$ (CET) | US$ (WTP) | CHF (WTP) | HK$ (WTP) | US$ (WTP) |
|--------------|------|----------|---------------|-----------|-------------|-------------|-------------|-----------|-----------|----------|-----------|-----------|----------|----------|-----------|
| et al.[38]   |      |          |               |           |             |             |             |           |           |          |           |           |          |          |           |
| Huang et al.[39] | 2017 | USA      | IV            | Pembrolizumab | PD-L1 > 50% |             |             | 1.300     | 1.050     | US$78,344 | US$97,621 | US$100,000 | US$2,561  |
| Loong et al.[40] | 2019 | Hong Kong | Advanced      | Pembrolizumab | PD-L1 > 50% |             |             | 0.360     | 0.280     | HK$697,462 | HK$865,189 | HK$1,017,819 | HK$35,912  |
| She et al.[41] | 2019 | USA      | Advanced      | Pembrolizumab | PD-L1 > 1%   | PD-L1 > 20% | PD-L1 > 50% | 0.690     | 0.390     | US$101,764 | US$179,530 | US$150,000 | -US$12,387 |
|              |      |          |               |           |             |             |             | 0.820     | 0.460     | US$90,966  | US$160,626 | US$136,229 | -US$5,562  |
|              |      |          |               |           |             |             |             | 1.130     | 0.630     | US$76,390  | US$8,290    |             |          |

a – WTP CET is particular to each country.

Negative NMB implies intervention is not cost effective compared to standard-of-care.

CET – cost effectiveness threshold; CHF - Swiss francs; HK$ - Hong Kong dollars; ICER – incremental cost effectiveness ratio; IHC – immunohistochemistry; LYG – life years gained; NMB – net monetary benefit; NSCLC – non-small cell lung cancer; PD-L1 – Programmed Death-Ligand 1; QALY - quality-adjusted life-year; WTP – willingness-to-pay; US – United States; US$ - US dollars.
Table 1e. Study characteristics and outcomes of treatment guided by genetic status using different testing scenarios

| Author         | Year | Country | NSCLC stage | Therapy | Biomarker (methodology) | Change in LYG | Change in QALY | ICER (LYG) | ICER (QALY) | WTP CETa | NMB       |
|----------------|------|---------|-------------|---------|-------------------------|---------------|---------------|------------|-------------|-----------|-----------|
| Carlson et al. | 2009 | USA     | IIIB/IV     | Erlotinib | EGFR - FISH - IHC       | 0.120         | 0.060         | US$76,742b | US$153,483b | $150,000 | -US$209   |
|                |      |         |             |         |                         | 0.080         | 0.040         | US$78,367  | US$162,018  |           |           |
|                |      |         |             |         |                         |               |               | US$78,367  | US$162,018  |           |           |
| Westwood et al. | 2014 | UK      | IIIB/IV     | EGFR-TKI | 1. Sanger seq. and fragment length analysis/PCR of -ve samples | NR            | -0.007        | NR         | -£33,347    | £30,000   | -£436     |
|                |      |         |             |         | 2. HRM analysis         | NR            | -0.007        | NR         | -£30,143    |           |           |
|                |      |         |             |         | 3. Sanger seq. or Therascreen PCR kit for samples with insufficient tumour cells | NR            | -0.001        | NR         | -£45,629    |           |           |
|                |      |         |             |         | 4. Therascreen PCR kit   | NR            | 0.000         | NR         | Dominated   |           |           |
|                |      |         |             |         | 5. Sanger seq. or Roche cobas for | NR            | 0.001         | NR         | Dominated   |           |           |
|                |      |         |             |         |                         |               |               |            |             |           |           |

Notes: EGFR = Epidermal Growth Factor Receptor; WTP CETa = willingness to pay cost-effectiveness threshold; NMB = net monetary benefit; NR = not reported.
samples with insufficient tumour cells
6. Direct sequencing or WAVE-HS
7. Direct sequencing of exons 19–21
8. Roche cobas
9. Fragment length analysis combined with pyrosequencing
10. Single-strand conformation analysis

| Study                  | Year | Country | Stage   | Initial Treatment    | Targeted Mutations                          | Pvalues | Cost  | Cost  | Cost  | Cost  |
|------------------------|------|---------|---------|----------------------|---------------------------------------------|---------|-------|-------|-------|-------|
| Lieberthal et al.[52]  | 2013 | USA     | Advanced Targeted therapy | *EGFR* and *ALK* various mutations         | 0.020                                        | NR      | $154,512 | NR    | NR    | -US$606e |
| Doble et al.[53]       | 2017 | Australia | Advanced Targeted therapy | Driver mutations other than *EGFR* or *ALK* MTS | 0.008, 0.009                                  | AUD$485,199, AUD$489,338  | AUD$100,000 | AUD$3,403 |
| Romanus et al.[54]     | 2015 | USA     | IV      | Erlotinib or crizotinib | *EGFR*, *ALK*, and other Overexpression     | 0.04, 0.03 | US$102,000, US$136,000 | US$155,000 | US$568 |
| Study         | Country | Stage   | Treatment | Assay (Method) | Sensitivity | IHC | HER2 | ALK | BRAF | EGFR | Costs   | Other Costs |
|--------------|---------|---------|-----------|----------------|-------------|-----|------|-----|------|------|----------|-------------|
| Loubière et al. [55] | France | Advanced | Gefitinib, erlotinib or crizotinib | EGFR, ALK, BRAF, HER2, and KRAS IHC, FISH and sequencing | 0.197 | NR | €13,320 | NR | €38,000 | €4,884 | €4,962 |
| Roth et al. [56] | USA     | I/II    | Chemotherapy | 14-Gene Risk Score Assay | 0.150 | 0.080 | US$11,952 | US$23,154 | US$50,000 | US$2,191 |
| Steuten et al. [57] | USA     | IIIB/IV | Targeted therapy | EGFR, ALK, BRAF, RET, ROS1, HER2, and MET multigene panel sequencing | 0.060 | NR | US$148,478 | NR | US$100,000 | -US$2,813 |
| Lu et al. [58] | China   | Advanced | Crizotinib (PAP) | ALK- multiplex PCR, ALK- NGS panel | 0.056 | 0.040 | US$10,304 | US$14,384 | $32,000 | US$703 |
| Lu et al. [59] | China   | IIIB/IV | Crizotinib (PAP) | ALK- Ventana (DSF3) CDx ALK- IHC plus FISH ALK - qRT-PCR | 0.051 | 0.029 | US$9,667 | US$193 | US$435 |

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a – WTP CET is particular to each country; b – ICER not reported and calculated from reported costs and LYGs and/or QALYs; c - Cost-effectiveness of each test methodology compared with direct sequencing of all EGFR exon 18–21 mutations; d - NMB calculated with LYGs rather than QALYs.

A dominated strategy is one which is clinically inferior and more expensive.

Negative NMB implies intervention is not cost effective compared to standard-of-care.

ALK - Anaplastic Lymphoma Kinase; AUD$ - Australian dollars; BRAF - v-Raf murine sarcoma viral oncogene homolog B; £ - British pounds; CAD$ - Canadian dollars; CET – cost effectiveness threshold; EGFR – Epidermal Growth Factor Receptor; EGFR-TKI – EGFR tyrosine kinase inhibitor; € - euro; FISH - fluorescence in situ hybridization; HER2 - human epidermal growth factor receptor 2; HRM – high-resolution melt; ICER – incremental cost effectiveness ratio; IHC – immunohistochemistry; KRAS - Kirsten rat sarcoma viral oncogene homolog; LYG – life years gained; MET - mesenchymal epithelial transition factor; MTS - multiplex targeted sequencing; NMB – net monetary benefit; NGS – next-generation sequencing; NR – not reported; NSCLC – non-small cell lung cancer; PAP – patient assistance programme; PCR – polymerase chain reaction; QALY - quality-adjusted life-year; qRT-PCR - quantitative reverse transcription PCR; RET - rearranged during transfection proto-oncogene; ROS1 - c-ros oncogene 1; UK – United Kingdom; US – United States; WAVE-HS – sequencing methodology.
FIGURE LEGENDS

Figure 1. Sub-analysis of health economic impact of precision medicine

CHF – Swiss francs; CN – China; PD-L1 – Programmed Death Ligand 1; PD-L1 > 1%, > 10%, and >, 50% figures refer to tumour proportion score; US$ - US dollars.
a. Nivolumab and PD-L1 study, a Swiss perspective

b. Pembrolizumab and PD-L1 study, a US perspective

c. Pembrolizumab and PD-L1 study, a Chinese perspective