

INTRODUCTION

- Globally, lung cancer is the most common cancer (2.09 million cases, 2018) and the leading cause of cancer death (1.76 million deaths in 2018).¹
- In the US, lung cancer is projected to cause 140,730 cancer deaths in 2020 (almost a quarter of total cancer deaths).²
- Precision Medicine (PM) guided by precision diagnostic tests (PDTs) can help increase overall survival (Table).

Drug Class	Tyrosine Kinase Inhibitor (TKI)		Immune-Oncology (IO)	
	Epidermal growth factor receptor (EGFR)	Anaplastic lymphoma kinase (ALK)	Programmed cell death protein 1 (PD-1)	Programmed death-ligand 1 (PD-L1)
	Crizotinib	Gefitinib	Nivolumab	Atezolizumab
	Ceritinib	Erlotinib	Pembrolizumab	Durvalumab
	Alectinib	Afatinib		
	Brigatinib	Dacomitinib		
	Lorlatinib	Osimertinib		

Table. FDA-approved Precision Medicines for non-small cell lung cancer (NSCLC).

- Evaluating PMs as costs escalate is required to ensure value-based pricing (VBP).
- The first step in quantifying this value chain is assessing the economic impact of PM by cost-effectiveness analysis (CEA).

AIM OF STUDY

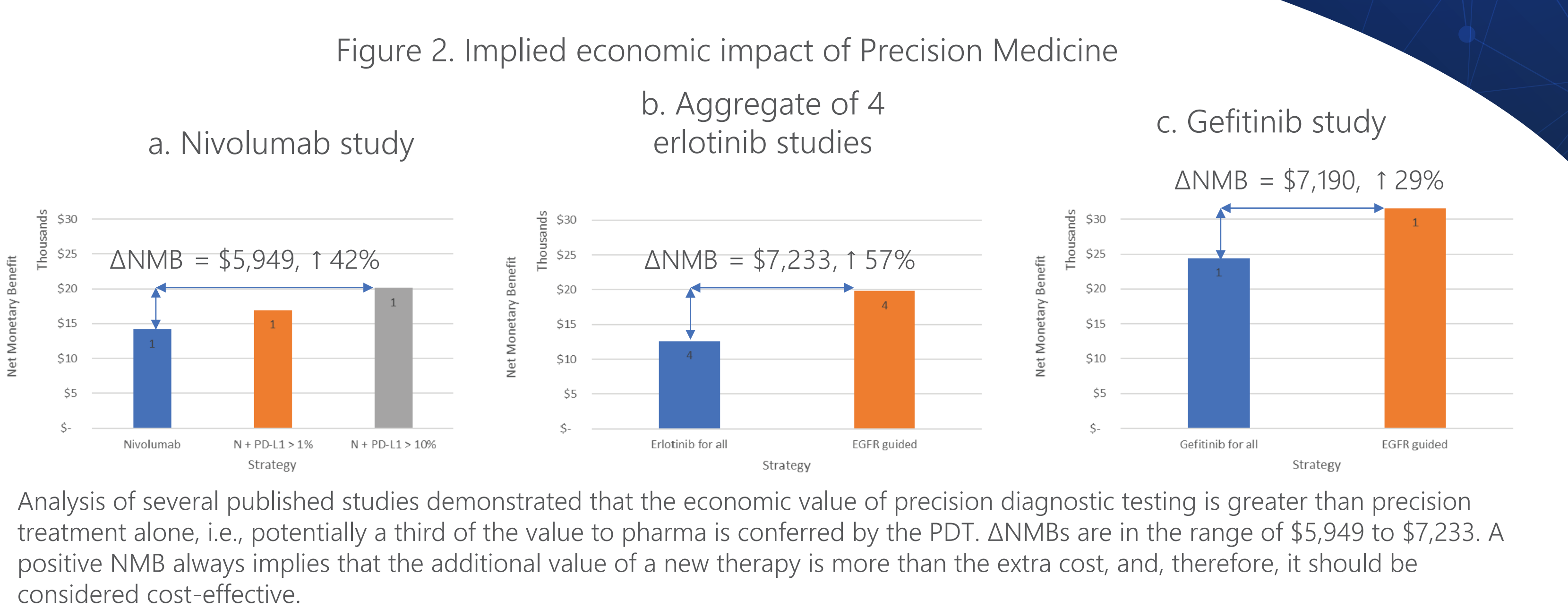
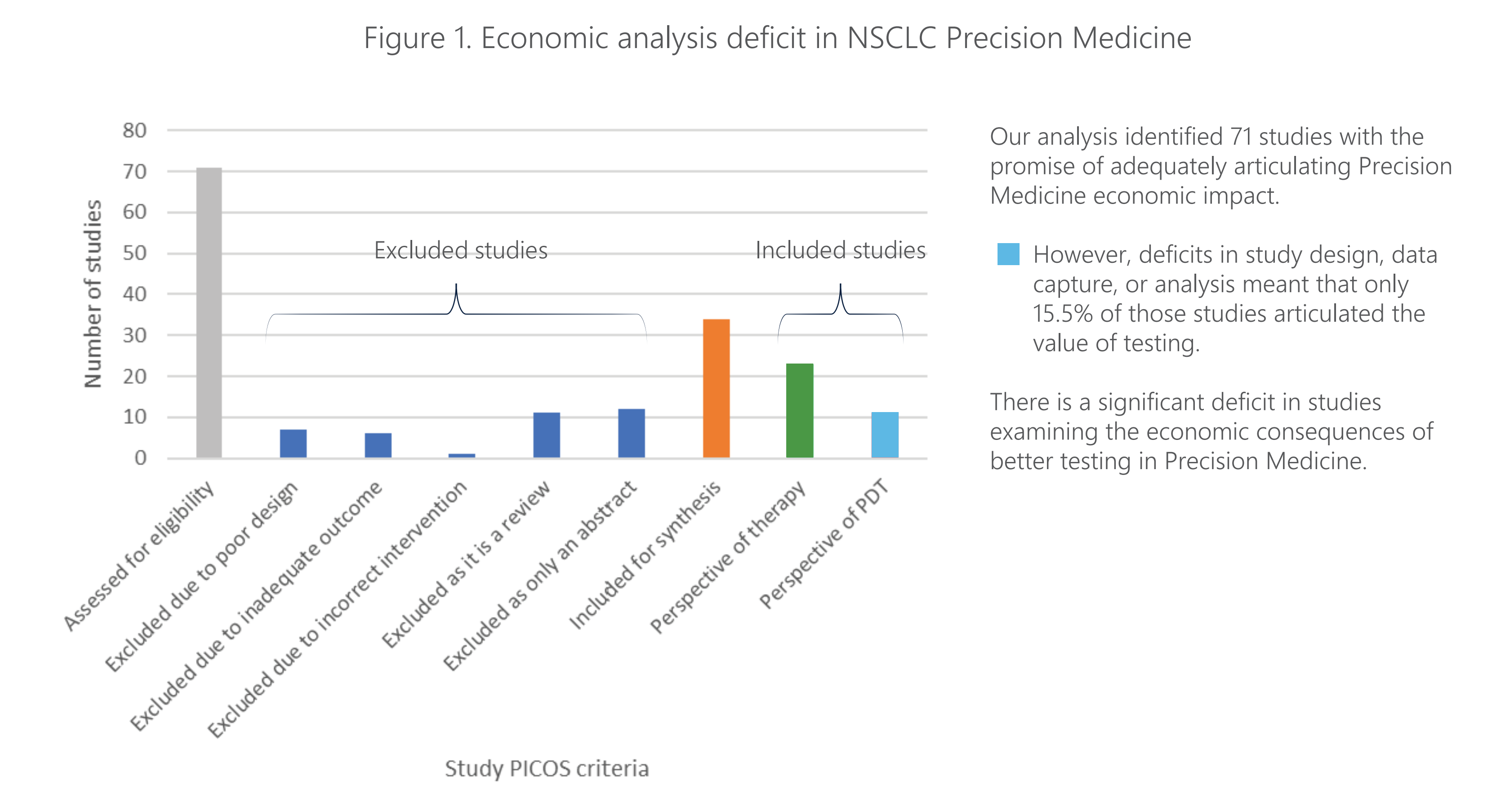
- To determine the cost-effectiveness of PDTs for predicting response to treatments in non-small cell lung cancer (NSCLC).

METHODS

- This systematic review is registered with PROSPERO (registration number: CRD42020171234) and asked the research question "What is the cost-effectiveness of PDTs for predicting response to treatment in NSCLC?"
- A systematic literature search was conducted (1 January 2009-31 December 2019) using the following sources: MEDLINE, EMBASE, Cochrane Library, SCOPUS, Web of Science, NHS EED, Econlit databases, American Society of Clinical Oncology (ASCO), and International Society for Pharmacoeconomics and Outcomes Research (ISPOR) websites.
- Articles were screened for eligibility based on the PICOS (Population, Intervention, Comparator, Outcome, Study Design) criteria.

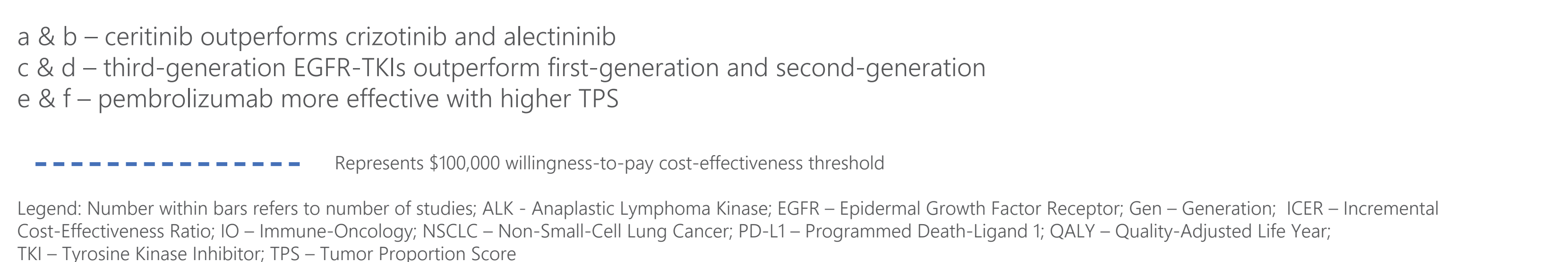
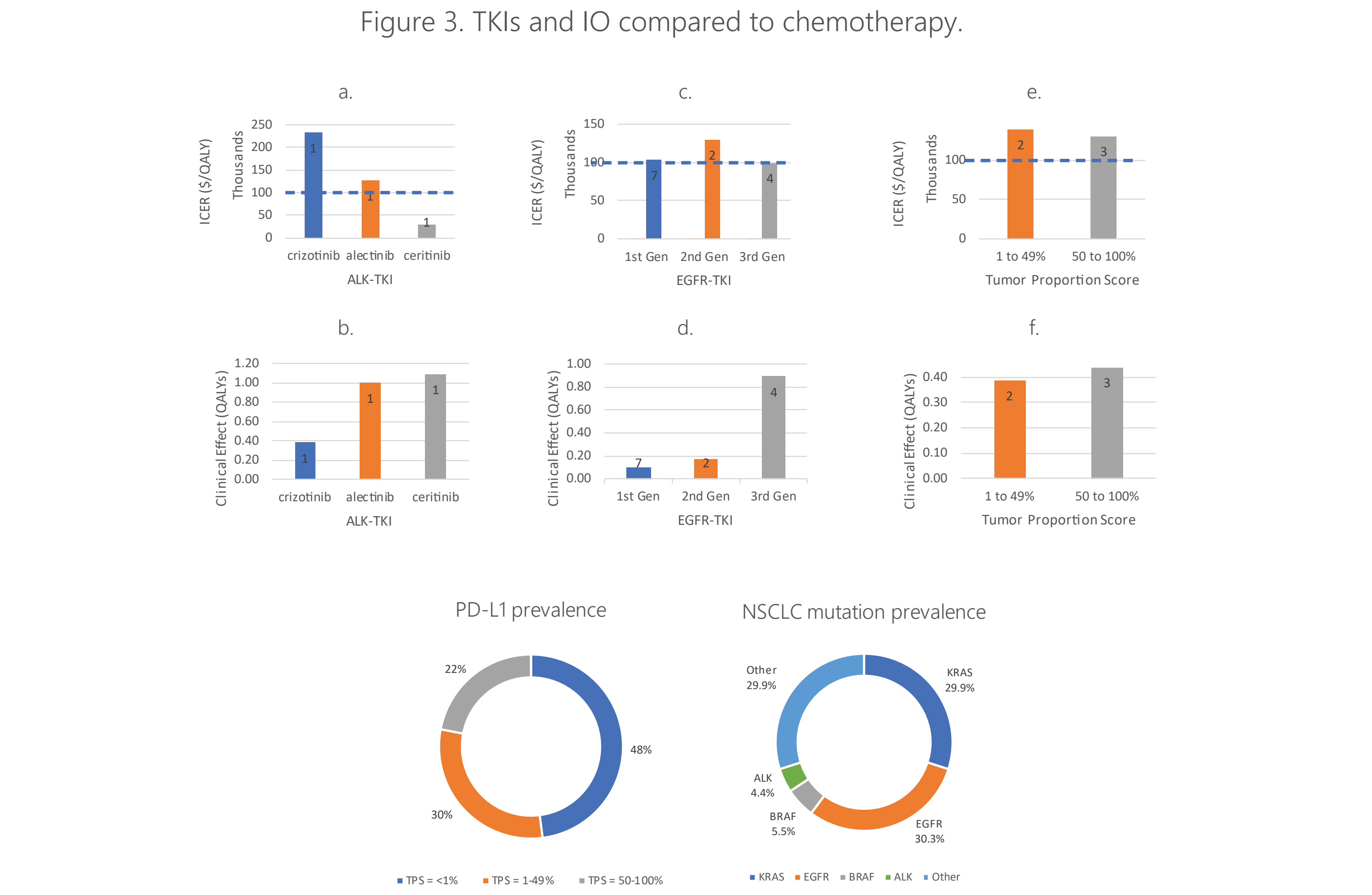
RESULTS

- Study selection was conducted according to Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) guidelines. Thirty-four eligible studies were identified from 18,720 articles: of the 71 studies initially rated as eligible, 37 were excluded and 34 were synthesized (Figure 1).
- Twenty empirical and methodological data points were extracted, and each of the 34 eligible articles were subjected to the Consolidated Health Economic Evaluation Reporting Standards (CHEERS) grading system.
- **For IO drugs:** One study (2 scenarios) demonstrated greater net monetary benefit (NMB) when treating NSCLC tumors with nivolumab guided by a higher PD-L1 protein expression represented by the tumor proportion score (TPS) (Figure 2a).³
- **Five EGFR-TKI studies:** Gain in clinical effect (0.04 - 0.09 quality-adjusted life-years [QALYs]) was equivalent to 15 - 33 quality-adjusted life days (QALDs). Three studies generated incremental cost-effectiveness ratios (ICERs) at just below \$0/QALY,⁴⁻⁶ with one study just below -\$100K⁷ and another study just above \$100K, breaching the \$100K willingness-to-pay—cost-effectiveness threshold (WTP CET).⁸ Taken as an aggregate, the NMB for four erlotinib studies is \$7,233 greater (57% increase) when erlotinib treatment of NSCLC patients is guided by the EGFR PDT than when not guided by PDT (Figure 2b). Guiding gefitinib therapy by EGFR PDT yields an NMB that is \$7,190 greater (29% increase) than when treating all patients with gefitinib without EGFR PDT guidance (Figure 2c).
- **For ALK-TKIs compared to chemotherapy:** Ceritinib produces more QALYs than alectinib, which in turn produces more QALYs than crizotinib (Figure 3b).^{9,10}
- **For EGFR-TKIs compared to chemotherapy:** While the second-generation EGFR-TKI (afatinib) outperforms first-generation EGFR-TKIs (erlotinib, gefitinib), QALY gains are marginal. However, third-generation osimertinib QALY gains are more substantial (Figure 3d).⁹⁻²¹
- **For all TKIs compared to chemotherapy:** Of 13 studies (16 scenarios) comparing TKIs to chemotherapy, only 6 scenarios generate ICERs that would breach the \$100K WTP CET.
- **For IO drugs compared to chemotherapy:** Three studies (6 scenarios) generate greater QALYs as PD-L1 TPS increases (Figure 3f); 5 of 6 scenarios generate ICERs that breach the \$100K WTP CET.²²⁻²⁴
- **For TKIs guided by different testing scenarios:** Of QALYs generated from 11 studies (25 scenarios), 10 of 25 are just at or below 0 QALYs. Twelve of the scenarios generate between 3 and 24 QALDs when compared to the standard PDT or no PDT, while one study produces 29 QALDs—but this is to guide treatment for stage I/II rather than stage IIIb/IV NSCLC.²⁵⁻³⁵ Seven scenarios breach the \$100K WTP CET.



TESTING CAN INCREASE THE ECONOMIC VALUE OF PRECISION MEDICINE BY ALMOST 60%.

Numbers within bars refers to number of studies; ΔNMB – Difference between standard of care and new intervention; EGFR – Epidermal Growth Factor Receptor; N - Nivolumab; NMB – Net Monetary Benefit; PD-L1 – Programmed Death-Ligand 1; % figure refers to tumor proportion score



DISCUSSION

- The economic value of PDT is greater than precision treatment alone.
- While the AURA3 and FLAURA clinical trials established osimertinib as having greater progression-free and overall survival than first-generation and second-generation EGFR-TKIs,^{36,37} the CEAs based on these trials show a much greater clinical effect.
- ALK-TKIs produce a greater clinical effect and are more cost-effective when compared to chemotherapy.
- As PD-L1 protein expression rises, IO use shows both increased clinical effectiveness and increased cost-effectiveness (i.e., increased QALYs/decreased ICERs).
- Better identification of treatment responders through use of PDTs in a treated population increases clinical efficacy and can also be cost-saving.

CONCLUSION

- Increasing the precision by identification of the responder population through the use of PDTs improves the clinical efficacy of Precision Medicines, while also decreasing costs. These results are relevant from clinical trial, VBP agenda, and policy perspectives.

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