NEW DRUG DEVELOPMENT PARADIGMS INITIATIVE

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Learning Ecosystems Accelerator for
Patient-centered, Sustainable innovation

DESIGN LAB BRIEFING

Immuno-oncology case study

June 2022

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Learning Ecosystems Accelerator for
Patient-centered, Sustainable innovation

Launched in January 2018, the LEAPS Project (Learning Ecosystems Accelerator for Patient-centered, Sustainable innovation) is advancing the mission of the NEWDIGS consortium – to deliver more value from biomedical innovation faster to patients, in ways that work for all stakeholders – through a new collaborative systems approach to the planning, production, and use of real-world evidence across R&D and healthcare delivery. Components of a model system prototyped for Rheumatoid Arthritis (RA) will be piloted in Massachusetts (2020 launch), and will inform related efforts in other diseases and geographies. Success in LEAPS targets better patient outcomes while also reducing waste and inefficiency across the system.

NEWDIGS is an international "think and do tank" dedicated to delivering more value faster to patients, in ways that work for all stakeholders. NEWDIGS designs, evaluates, and initiates advancements that are too complex and cross-cutting to be addressed by a single organization or market sector. Its members include global leaders from patient advocacy, payer organizations, biopharmaceutical companies, regulatory agencies, clinical care, academic research, and investment firms.

LEAPS Design Lab Summary Briefing, June 2022
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Introduction to Case Study for Integrated Pilot Concept

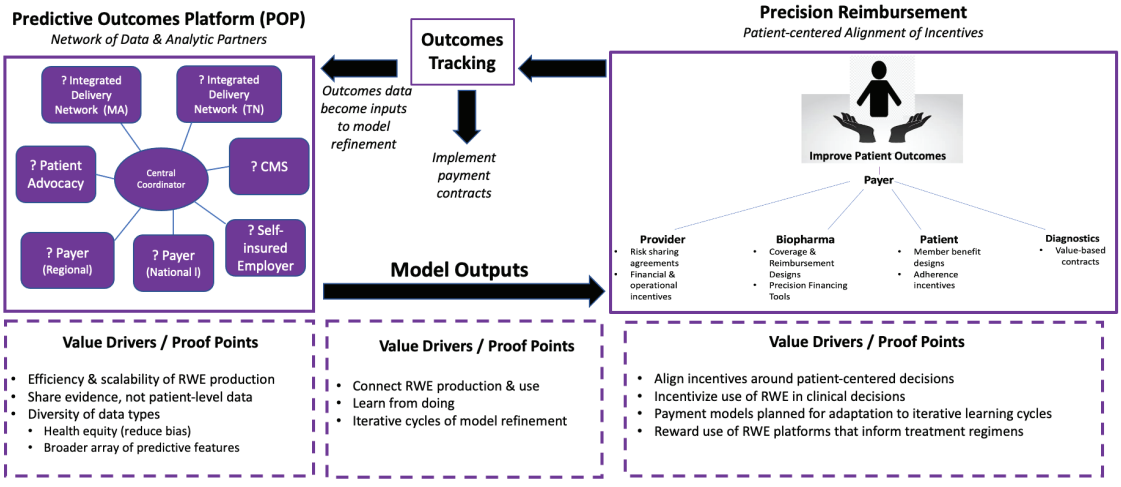
The LEAPS Project of NEWDIGS is focused on modernizing how we plan, produce, and use real-world evidence (RWE) in order to advance the knowledge, practice, and sustainability of precision medicine.

Building on our work to date, this Design Lab will focus on our two current, inter-dependent innovation pillars:

1. **Precision Reimbursement**, to ensure access to evidence-based therapy while reducing uncertainty and rewarding value demonstrated in real world use. Precision (formerly "Adaptive") Reimbursement is a key priority for fueling the use of RWE, and for incentivizing the production of new RWE to improve our understanding of sub-populations and targeted drug therapy regimens
2. **RWE Production**, with a particular focus on improving the targeted use of drug therapies to drive better patient outcomes and incentive alignment. Our evolving concept centers around a Predictive Outcomes Platform (POP), where outcomes data tracked for Precision Reimbursement contracts serves as one key input into predictive modeling. The modeling in turn is designed to improve contract designs as well as clinical outcomes.

Together, these two pillars reinforce a powerful emerging theme from LEAPS—the need for innovative reimbursement models and RWE capabilities to evolve together in order to advance regimen optimization, and more broadly, precision medicine. The LEAPS integrated pilot concept is intended to bridge these pillars. (see Figure 1)

Figure 1: LEAPS Integrated Pilot Concept



Overview of the LEAPS integrated pilot concept to be explored through a portfolio of case studies. The first case study will be focused on improving our ability to predict which patients with advanced non-small cell lung cancer are likely to benefit from treatment with immune checkpoint inhibitors.

We will evaluate a portfolio of diverse case studies to inform our pilot designs. Each case will provide a narrowly focused opportunity for action and learning, while a strategically selected portfolio of cases will support the development of a broader, more generalizable set of design principles.

This Design Lab will focus on the first case study in the portfolio: Improving our ability to predict which patients with advanced non-small-cell lung cancer (NSCLC) are likely to benefit from treatment with immune checkpoint inhibitors (ICIs).

The pilot concept will be explored through the lens of 3 key questions:

- **Treatment selection**: Can we identify sub-populations of patients characterized by shared features, including 'omic, molecular, tumor-specific, as well as clinical, laboratory, and socio-economic characteristics identified from real-world data (RWD), that improve our ability to predict who will/will not benefit from immune checkpoint inhibitors (ICIs)?
- **Value for cost:** Does the improved selection of treatments significantly impact the total cost of care?
- **Distributed network (platform) approach to predictive modeling:** Can we identify and corroborate predictive models using a distributed network of diverse data sources and analytics?

Once the pilot infrastructure and processes are designed for the first Case Study, we will explore potential ways to scale it in a variety of dimensions that may be of interest to stakeholders within the LEAPS community including, for example, earlier stages of NSCLC, other tumor types, and/or other drug therapy classes, among others.

Important Design Considerations

The following are some of the key questions that have emerged in team discussions. This list will evolve through discussions within/between Teams before and during the June Design Lab, and will shape our design activities.

1. **Treatment Selection** *(For the Core Protocol Team)*
   How important is it to have a control arm in this pilot? If you think it is important, what type of control arm(s) should we consider (e.g., standard of care, individual products vs. product classes, etc.)?
2. **Value for Cost** *(For the Precision Reimbursement Team)*
   How does improved ability to predict treatment benefit of ICIs impact (1) total cost of care (financial and non-financial) and (2) payer coverage and reimbursement policies for patients with advanced NSCLC?
3. **Platform Approach** *(For the Methods Team)*
   How do we integrate multiple predictive models targeting the same outcome variable but derived from different data sources/types within a distributed POP?

Case Study #1: Immuno-Oncology

I. Introduction to Immune Checkpoint Inhibitors and advanced NSCLC

Objective: Improve our ability to predict subgroups of patients with advanced NSCLC who will benefit from ICIs.

Immune checkpoint inhibitors: current approvals and biomarkers

Cancer immunotherapy, using a patient's own immune system to attack cancer, has emerged as a promising tool to fight cancer recent years. ICIs are a type of cancer immunotherapy that target immune checkpoints regulating the mechanisms of T-cell activation, thereby enabling T-cell antitumor response.(1) The most well-characterized immune checkpoint targets are cytotoxic T-lymphocyte associated protein 4 (CTLA-4) and programmed cell death receptor-1 (PD-1) and programmed cell death receptor-1 ligand (PD-L1), though investigation of many other immune checkpoints and development of ICIs for additional targets is robust.(2) The first FDA-approved ICI was the anti-CTLA-4 monoclonal antibody ipilimumab, approved for advanced melanoma in 2011.(1) Since 2014, the FDA has approved 7 anti-PD-1 or anti-PD-L1 agents with over 85 oncology indications for this class of drug. (Table 1) Many additional ICIs are in development.(2)

Note: Bolded drugs are approved for the treatment of advanced non-small cell lung cancer (NSCLC) (initial case study).

ICIs are effective across a broad range of malignant tumors, but the response rate varies from <5% (pancreatic) to 40-50% (renal cell carcinoma, melanoma).(3) Additionally, while ICIs are generally well-tolerated compared to chemotherapy (4-7), immunotherapy poses the risk of the immune system mistakenly targeting healthy cells. Such immune-related adverse events (irAEs) are estimated to occur in about 1 in 5 patients receiving immunotherapy.(8)

Key points

- Immune Checkpoint Inhibitors (ICIs) are a promising class of treatment for cancer and an active area of research and development. The first ICI, the anti-CTLA-4 monoclonoal antibody ipilimumab, was appoved by the FDA in 2011for advanced melanomoa. Since 2014, the FDA has approved 7 anti-PD-1 or anti-PD-L1 agents with over 85 oncology indications.
- While 3 tumor-related biomarkers are FDA-approved as companion diagnostics for ICI therapeutics, these existing biomarkers are imperfect, and it remains difficult to identify patients most likely to benefit from ICIs.
- Evidence supporting other markers of response to ICIs exists, but none are systematically studied or implemented clinically.
- The probability of response is likely a function of **collective features** rather than any single biomarker, but most investigation of predictors beyond a single factor are limited to 2 or 3 factors or to a single data type.
- The proposed case study is based on the hypothesis that composite predictive markers comprised of both existing biomarkers and real-world features from diverse data types will improve our ability to predict benefit from ICI therapy.
- Advanced NSCLC was selected as the initial tumor focus due to the size of the patient population, large number of FDA-approvals for ICI therapy, potential impact of improving response prediction (currently estimated to be ~27%), and data availability.
- A subset of patients with advanced NSCLC treated with ICIs experiences durable response and survival of >5 years, representing a paradigm shift from palliative care management for advanced NSCLC and highlighting the potential impact of improving our ability to predict benefit from ICI therapy in patients with advanced NSCLC.

Consequently, predicting patients most likely to benefit from ICIs is an active area of research and is of great importance in this field.

Currently, three tumor-related biomarkers are FDA-approved as companion diagnostics for ICI therapeutics: PD-L1 protein expression (immunohistochemical), tumor mutational burden (TMB) (genomic), and microsatellite instability (MSI)/mismatch repair deficiency (dMMR) (genomic).(9) However, these existing biomarkers have significant deficiencies in positive and negative predictive values.(10) While evidence supporting other markers associated with response to ICIs exists, none are systematically studied or implemented clinically. Additionally, the probability of response is likely a function of collective features rather than any single biomarker, but most investigations of predictors beyond a single factor are limited to 2 or 3 factors or to a single data type.

The proposed case study is based on the hypothesis that composite predictive markers comprised of both existing biomarkers and real-world features from diverse data types will improve our ability to predict benefit from ICI therapy.

Table 1. FDA-Approved ICIs

Drug	Target	Approval
Ipilimumab	**CTLA-4**	**2011**
Nivolumab	**PD-1**	**2014**
Pembrolizumab	**PD-1**	**2014**
Atezolizumab	**PD-L1**	**2016**
Durvalumab	PD-L1	2017
Avelumab	PD-L1	2017
Cemiplimab	**PD-1**	**2019**
Dostarlimab	PD-1	2021

Initial tumor focus: advanced non-small cell lung cancer (NSCLC)

NSCLC was selected as the initial tumor focus for this case study due to the size of the patient population, potential impact of improving response prediction, and data availability. With an estimated 236,740 new cases and 130,180 deaths forecast in the US in 2022, lung cancer is the second most common cancer in both men (2nd to prostate) and women (2nd to breast) and the leading cause of cancer-related deaths.(11) Lung cancer is broadly categorized as NSCLC and small cell lung cancer, with NSCLC comprising 85% of cases.(12) This case study is further focused on advanced NSCLC to simplify possible treatment paradigms for initial pilot activities.

NSCLC has the highest number of FDA-approvals for ICI therapy of any cancer. Lung cancer is forecast to comprise at least 50% of the global cancer immunotherapy market from 2021-2031.(13) The current response rate for ICIs in NSCLC is low, estimated in a recent study to be about 27% (3), indicating a significant area for improvement. However, a subset of advanced NSCLC patients experiences durable response and survival of >5 years. For example, 5-year overall survival rates of 16% and 31.9% were observed in recent clinical trials of 2nd line nivolumanb and 1st line pembrolizumab, respectively.(14) The potential for durable response and long-term survival

represents a paradigm shift from palliative care management for advanced NSCLC and highlights the potential impact of improving our ability to predict benefit from ICI therapy in patients with advanced NSCLC.(12)

This case study will be structured around **3 critical areas of uncertainty** that must be addressed in a coordinated way across the pilot:

1. **Knowledge uncertainties** related to clinical decision-making associated with the use of ICIs in advanced NSCLC. Knowledge uncertainties will be addressed through RWE production.
2. **Behavioral and economic uncertainties** related to the financial and non-financial costs and benefits of care for patients with advanced NSCLC, and associated stakeholder behaviors. Behaviors and economic uncertainties will inform evaluation parameters for the pilot, as well as design of incentives for "Precision Reimbursement."
3. **Methodologic uncertainties** for:
   - **RWE production** related to our approach to generating predictive models and will inform the data/analytics design and implementation plan.
   - **Precision Reimbursement** related to metrics and evidence criteria acceptable to all stakeholders to inform incentive design.

II. Knowledge Uncertainties

This section describes the knowledge uncertainties related to clinical decision-making associated with the use of ICIs in advanced NSCLC that could be addressed through RWE production.

Use of ICIs for advanced NSCLC

Treatment options for patients presenting with advanced NSCLC include chemotherapy, targeted therapy, and immunotherapy. National Comprehensive Cancer Network® (NCCN) guidelines recommend systemic treatment options for advanced NSCLC based upon many factors including histologic subtype, presence of actionable driver mutations, PD-L1 expression levels, patient performance status, and contraindications to particular therapeutic agents.(15) Figure 2 illustrates where ICIs as a class fall within the NCCN guidelines for first-line treatment of advanced NSCLC. Recommendations for specific ICIs are not summarized in this case study.

Depending on the clinical presentation and PD-L1 expression, ICIs are either given alone or with chemotherapy. Patient preferences for a

Key points

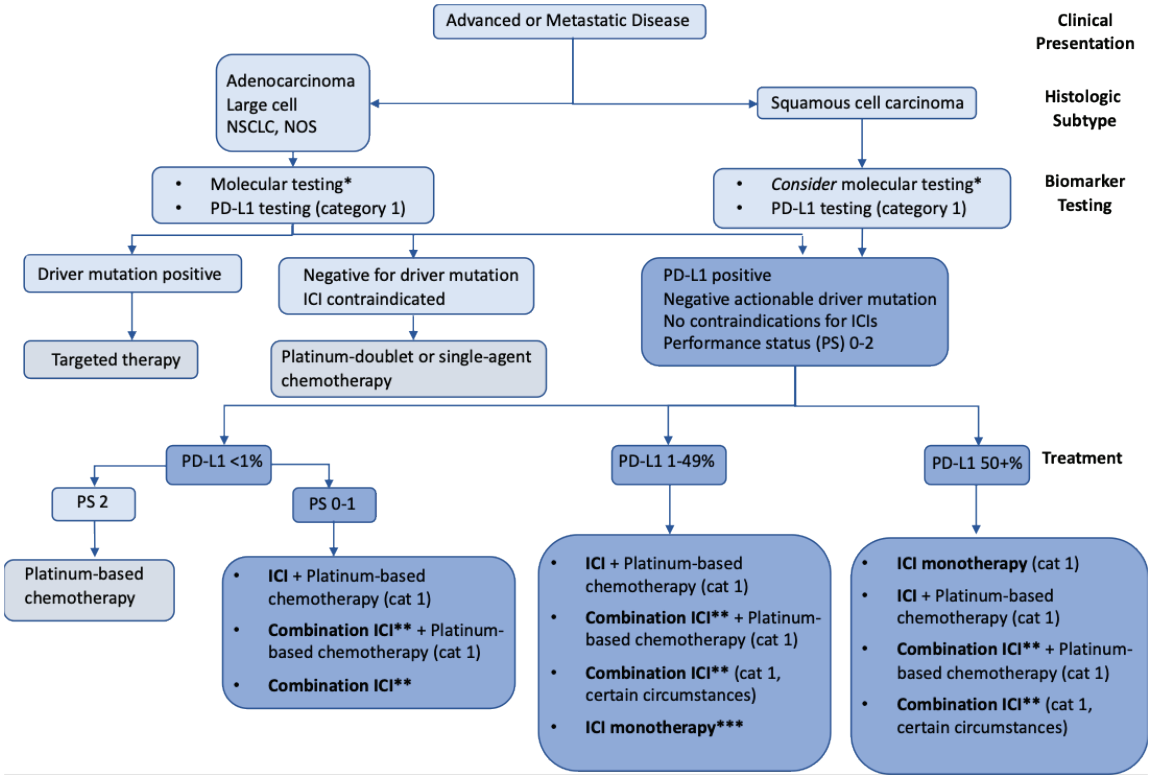
- Absent driver mutations or contraindications to immunotherapy, ICIs are recommended for patients presenting with advanced NSCLC either alone or in combination with chemotherapy based on PD-L1 expression levels.
- PD-L1 expression is the primary biomarker used to guide clinical decision-making, but it is limited in its ability to predict response to ICIs, with a positive predictive value (PPV) and negative predictive value (NPV) for treatment response of approximately 45% and 69%, respectively.(10)
- Evidence supports many potential predictors of ICI response, including additional biomarkers (histological markers, genomic markers, routine laboratory tests) and patient characteristics (demographics, clinical characteristics, prior therapy, and proxies for microbiome diversity), many of which are unlikely to be sufficient as a single factor.
- There is emerging evidence that a multi-factor approach will improve predictive power of biomarkers, but research to date has been limited to composite biomarkers of 2-3 factors from a single data type or features from

particular therapy and side effect profile impact treatment decisions, however there is a reluctance to treat with ICIs alone in case the patient does not respond, and subsequent performance status precludes chemotherapy. This highlights the need to improve our ability to improve prediction of treatment benefit from ICI therapy.

2 different data types.

- The proposed pilot will build on this emerging evidence, combining existing biomarkers with multiple features from several diverse data types (including both 'omics and real-world data) to test whether or not our model can predict benefit from ICIs in patients with advanced NSCLC better than the current practice of predicting response via PD-L1 immunohistochemistry alone.

Figure 2. Treatment guidelines for clinical presentation of advanced NSCLC by drug class



NOS: Not Otherwise Specified; PS: Performance Status
Note: Recommendations for specific therapeutic agents not included in this summary. Bevacizumab (anti-vascular endothelial growth factor (VEGF) antibody) is also recommended in some ICI regimens (not shown).
** Molecular testing includes EGFR mutation (category 1 for non-squamous cell), ALK (category 1 for non-squamous cell), KRAS, ROS1, BRAF, NTRK1/2/3, METex14 skipping, RET.*
*** Combination ICI refers to nivolumab (anti-PD-1 antibody) and ipilimumab (CTLA-4 inhibitor).*
**** Recommended for patients with poor performance status or contraindications to chemotherapy.*

Predictive Biomarkers

Of the three FDA-approved biomarkers for ICI therapeutics, PD-L1 immunohistochemistry is the primary biomarker relevant to advanced NSCLC and is recommended as routine clinical practice prior to treatment initiation.(15) MSI has a very low prevalence of only 1-2% of NSCLC cases (9) and TMB has limited and conflicting data for evidence in predicting ICI response in NSCLC.(15)

While PD-L1 testing is a helpful tool to guide clinical decision-making, it remains limited in its ability to predict response. Not all PD-L1-positive patients exhibit response to ICIs, while response is experienced by some PD-L1-negative patients. In a recent meta-analysis of 22 NSCLC studies, PD-L1 expression had a 45% (95% CI: 38%, 51%) positive predictive value (PPV) and 69% (95% CI: 60%, 77%) negative predictive value (NPV) for treatment response.(10) Additionally, PD-L1 testing is complicated by inter- and intratumor heterogeneity as well as be variation in expression levels over time.(9)

The limitations of PD-L1 expression highlights our hypothesis that the probability of response is likely a function of **collective features** that more fully capture the multi-factorial aspects of tumor immunobiology and ICI response rather than any single biomarker. This case study seeks to test the hypothesis that we can improve the predictive value of the existing biomarkers by combining them with real-world features in a composite predictive marker. **Can our model, comprising multiple features from diverse data types (both 'omics and real-world data), predict benefit from ICIs in patients with advanced NSCLC better than the current practice of predicting response to ICIs via PD-L1 immunohistochemistry alone?**

There is emerging evidence supporting our hypothesis that a multi-factor approach is necessary to predict benefit from ICI therapy. For example, studies of composite biomarkers comprised of 2 or 3 factors (of the same data type) have been more strongly associated with response than the factors individually. Ayers et al. found that among patients with NSCLC treated with ICIs, both high pre-treatment neutrophil-to-lymphocyte ratios (NLR) and anemia were independently associated with poor survival and could be combined to further stratify patients.(16) Kao et al. found the modest predictive power of TMB for clinical outcomes following ICI treatment in patients with NSCLC was improved when combined with PD-L1 and NLR.(17) This is further evidenced by exploration of potential clinically-based prognostic scores such as EPSILoN (Eastern Cooperative Oncology Group performance status (ECOG PS), smoking, liver metastases, lactate dehydrogenase (LDH), NLR) (18, 19), models comprising multiple pre-treatment blood biomarkers (20), and multiomic models (21) and to predict ICI response. In an example of improved predictive power from multiple data types, Chowell et al. combined genomic features with clinical and demographic features to develop a model that outperformed the FDA-approved biomarker TMB for predicting response to ICI among a cohort of patients with cancer (including 37% NSCLC).(3)

The proposed pilot will build on this emerging evidence, combining multiple features from several diverse data types to increase predictive power.

Potential features to pursue

A number of potentially predictive factors of ICI response in NSCLC have been identified with emerging evidence of clinical significance. Table 2 summarizes potential features to pursue in this pilot that are both plausible and practical. Feature selection should include the following considerations:

1. Avoid "fishing" for signals. Begin with a hypothesis based on a possible signal(s) described in the literature.
2. Available data
3. Multi-stakeholder agreement on meaningful real-world endpoints *(Note: a structured process for mapping of the key stakeholders who will be considered within scope will be proposed at the upcoming Design Lab.)*

4. Reasonable cycle time to achieve endpoints and measure impact

Radiographic data is another rich source for potential predictive biomarkers for ICI response. However, given the amount of data cleaning and curation required it is lower priority for the initial feature selection.

Table 2. Potential predictive features to pursue

Histopathology	
Marker	*Findings/Rationale*
PD-L1 Expression	FDA-approved predictive biomarker. Current "gold standard" to select patients most likely to respond to ICI. (9, 22, 23)
Tumor infiltrating lymphocytes (TILs)	High level of TILs in baseline biopsy is associated with better prognosis and response to ICIs. (23, 24)
Genomic	
Marker	*Findings/Rationale*
Tumor Mutational Burden (TMB)	FDA-approval for TMB predictive biomarker was pan-tumor. Data for TMB and ICI response in NSCLC is less consistent, but there is evidence that high TMB is associated with better ICI response. (23, 25)
STK11	STK11 gene mutation associated with poorer survival in ICI-treated NSCLC patients (23)
KEAP1	KEAP1 gene mutation associated with poorer survival in ICI-treated NSCLC patients (23)
Routine Laboratory Data	
Marker	*Findings/Rationale*
Neutrophil-to-Lymphocyte Ratio (NLR)	High NLR is associated with poor prognosis in ICI-treated NSCLC patients. (14, 26)
Platelet-to-Lymphocyte Ratio (PLR)	High PLR is associated with less durable radiographic response in ICI-treated NSCLC patients. (27)
Lactate Dehydrogenase (LDH)	Low pre-treatment LDH levels associated with better prognosis in ICI-treated NSCLC patients. (14, 28)
C-reactive protein (CRP)	Elevated CRP associated with poor prognosis in ICI-treated NSCLC patients. (14, 23)
Albumin	Low pre-treatment albumin associated with poor prognosis in ICI-treated NSCLC patients. (29)
Hemoglobin	Higher pre-treatment hemoglobin associated with better disease control rate in ICI-treated NSCLC patients. (20)
Calculated measures and scores	
Composite measures of inflammation, e.g., ALI	ALI is a measure if system host inflammation. Higher ALI is associated with longer survival, higher ORR, and longer time on treatment for ICI-monotherapy NSCLC patients. (30)
ALI = [body mass index * serum albumin]/NLR	

Patient Demographics and Clinical Characteristics	
Marker	*Findings/Rationale*
Age	While there is the potential for age-related immune dysfunction to impact ICI response, the impact remains unclear. (23) A recent meta-analysis observed comparable efficacy in ICI-based combination therapy vs. non-ICI therapy for <65 vs. 65+ years NSCLC patients. (31) However, the effect of age may depend on treatment type (e.g., ICI alone vs. with chemotherapy) and age groupings.
Sex	Evidence that men may have better response to single agent ICI than women (14) and women derive more benefit from addition of chemotherapy to ICI than men. (32) Additionally, predictors of response may be different for men vs. women. (33)
BMI	Higher BMI (≥25) associated with better prognosis than BMI <25 among ICI-treated NSCLC patients. (14)
Race/Ethnicity	There is limited data on the role of race or ethnicity on ICI response, but the pilot would provide an opportunity for further exploration. (34)
ECOG-PS	Excellent or Good performance status (ECOG-PS≤2) associated with better PFS and OS in ICI-treated NSCLC patients. (14)
Smoking Status	Current or prior smoking status predictor of response to ICIs. (35)
Cancer-related metadata	
Marker	*Findings/Rationale*
Prior cancer therapy	Prior chemotherapy was strong predictor of ICI response in integrated model across several cancer types. (3)
Pharmacy data	
Marker	*Findings/Rationale*
Antibiotic use	Higher diversity of gut microbiome diversity is associated with better efficacy of ICIs in advanced NSCLC patients. Recent antibiotic use is associated with reduced ICI efficacy and poorer prognosis among ICI-treated NSCLC patients. (14, 23, 24)
Steroid use	Baseline systemic corticosteroid use is associated with poorer prognosis among ICI-treated NSCLC patients. (14)
Socioeconomic Data	
Marker	*Findings/Rationale*

Income	Socioeconomic status (SES) is an unexplored area in relation to ICI response. This pilot would provide an opportunity for exploration of potential relationships, bearing in mind health equity considerations.
Employment status	
Zip Code	
Education level	

ALI: advanced lung cancer inflammation index; BMI: body mass index; CRP: C-reactive protein; ECOG-PS: Eastern Cooperative Oncology Group Performance Status; KEAP1: kelch-like ECH-associated protein 1; LDH: lactate dehydrogenase; NLR: neutrophil-to-lymphocyte ratio; OS: overall survival; PD-L1: programmed cell death-ligand 1; PFS: progression free survival; PLR: platelet-to-lymphocyte ratio; SES: socioeconomic status; STK11: serine/threonine kinase 11; TIL: Tumor infiltrating lymphocyte; TMB: tumor mutational burden

Ongoing studies

As we work through the case study and pilot design, it is important to be aware of ongoing studies that may provide additional evidence during this process. A starting list is summarized in Appendix I.

III. Behavioral and Economic Uncertainties

This section describes the closely intertwined behavioral and economic uncertainties related to the financial and non-financial costs and benefits of care for patients with advanced NSCLC, and associated stakeholder behaviors. Behavioral and economic uncertainties will inform evaluation parameters for the pilot, as well as design of incentives for "Precision Reimbursement."

Key Uncertainties

The list below begins to outline key behavioral and economic uncertainties related to the design and implementation of this pilot:

- What percentage of eligible patients with advanced NSCLC receive ICIs?
- What prevents eligible patients from receiving ICIs?
  - Treatment setting?
  - Patient choice?
  - Payer-related barriers?
- What percentage of non-eligible advanced NSCLC patients (patients unlikely to benefit from ICIs) receive ICIs?

Key points

- The economic burden of NSCLC is substantial
  - Estimated US expenditures for lung cancer care totaled $23.8 billion in 2020.
  - Indirect economic burden due to lost productivity, diminished quality of life, pre-mature mortality, and caregiving needs is also significant.
- Financial and non-financial costs associated with inadequate ICI response prediction vary by stakeholder (e.g., opportunity costs of ineffective treatment, side effects, cost-effectiveness, market penetration, etc.) and will guide pilot evaluation parameters and incentive design.
- Current utilization
  - There are deficiencies in testing rates for actionable mutations and PD-L1 expression, resulting in suboptimal treatment for many patients with NSCLC.
  - While there has been rapid update of ICIs, there is continued reliance on chemotherapy and a substantial portion of patients with advanced NSCLC receive chemotherapy alone.

- What is the true cost of advanced NSCLC for stakeholders?
  - How would better prediction of benefit from ICIs impact the cost (financial and non-financial) of advanced NSCLC?

- Economic cost/value drivers
  - Most literature supports economic benefits of ICIs when considering total cost of care as ICIs are associated with less supportive care, fewer AEs, and reduced AE-related costs than chemotherapy.
  - Published cost-effectiveness models suggest ICI treatment is cost-effective for NSCLC in several scenarios.
  - Published cost-effectiveness models suggest PD-L1 testing is cost effective and increases the cost-effectiveness of ICI treatment for NSCLC.
- Quality of Life
  - ICIs demonstrated significantly improved health-related quality of life (HRQoL) compared to chemotherapy in clinical trials of ICIs in NSCLC, especially in patients with PD-L1 expression 50%, but real-world data are limited.
  - Identifying real-world quality of life metrics important to patients with NSCLC receiving ICIs is an area of need.
- Financial and non-financial costs associated with the current patterns of biomarker testing and ICI use highlight the potential impact of improving our ability to predict benefit from ICI therapy in patients with advanced NSCLC.

Potential impact of successful pilot

Economic burden of NSCLC
The economic burden of cancer in general, and lung cancer in particular, is substantial. Estimated annual US expenditures for cancer care in 2020 totaled $208.9 billion, of which $23.8 billion ($21.9 billion medical services, $1.8 billion prescription drugs) were attributed to lung cancer.(36) Average per patient annualized cancer-related costs for NSCLC versus all cancer sites by phase of care are summarized in Table 3.

In addition to the direct economic burden summarized above, the indirect costs of NSCLC due to lost productivity, diminished quality of life, pre-mature mortality, and caregiving needs are significant and not well documented. One recent cross-sectional study in the US estimated a mean annual productivity loss of $123,792 for patients with NSCLC and $90,421 for their caregivers.(37) Analysis of US cancer deaths in 2015 estimated lost earnings of $94.4 billion due to pre-mature mortality, with lung cancer as the leading cause of cancer deaths comprising by far the highest portion at $21.3 billion (versus 2nd colorectal at $9.4 billion).(38)

Table 3. Average (per patient) annualized 2007-2013 cancer-attributable costs in 2020 US dollars by cancer site and phase of care.

Cost	Cancer Site	Initial Care	Continuing Care	Last year of life
Medical Services	All Sites	$43,516.10	$5,517.60	$109,727.30
	NSCLC	$67,148.10	$12,284.50	$109,102.70
Oral Prescription Drugs	All Sites	$1,873.9	$1,041.1	$4,372.4
	NSCLC	$3,747.8	$2,810.9	$4,997.1

Note: Phase of care defined as initial care (first year following diagnosis), last year of life (year prior to death), and continuing care (time in between)
Data from: Cancer Trends Progress Report https://progressreport.cancer.gov/after/economic_burden *(36)*

Costs (financial and non-financial) by stakeholder

Table 4 begins to summarize financial and non-financial costs associated with the current ability to predict ICI response and ICI/biomarker use patterns by stakeholder (i.e., who cares and why?) to guide pilot evaluation parameters and incentive design.

Table 4. Financial and non-financial costs associated with inadequate ICI response prediction by stakeholder

Patients	Providers	Payers	Developers	Diagnostic Companies
Opportunity costs of ineffective treatment Side effects, diminished QoL associated with chemotherapy (if likely to benefit from ICIs) Unnecessary risk of irAEs (if unlikely to benefit from ICIs) Health disparities Financial Toxicity[1]	Prescribing decisions under uncertainty Financial risk depending on incentive structure	Financial costs associated with delayed time to effective treatment Paying for things that don't work; added cost of combinations with chemo that may not be necessary Total cost of care & cost-effectiveness of chemotherapy vs. ICIs when considering costs associated with Hospitalizations, ED visits, Supportive Care/AE management How to define Prior Authorization/step therapy preferences (links to knowledge uncertainties) Challenges of determining target drug price/cost, including rebates, and any innovative payments models (eg, outcomes-based) Self-insured employers: Lost productivity	Suboptimal market penetration Suboptimal product performance: demonstrate better value through more targeted use Timing & value – could product be used earlier in patient journey?	Suboptimal market penetration Timing & value – would diagnostic have more value if used earlier in patient journey?

[1] For example, ICIs have the highest average annual cost-sharing liability (~$10,000) of Medicare Part B drugs for Traditional Medicare and Medicare Advantage Beneficiaries without supplemental insurance. (39)

Current utilization of biomarker testing and ICIs for NSCLC

There are known gaps between recommendations and actual biomarker testing rates and ICI use. This pilot has the potential to generate RWE and align incentives regarding biomarker testing and ICI use, with the goal of increasing timely utilization of effective treatment, reducing the risk of inappropriate treatment, and reducing unnecessary costs.

Biomarker testing patterns
Despite NCCN recommendations and improvements over time, deficiencies in testing rates for actionable mutations and PD-L1 expression remain, resulting in suboptimal treatment for many patients with NSCLC. Payer coverage for select biomarker testing for NSCLC is common, but the range of tests covered as well as the policies for step edits and prior authorization varies and may impact access.(40)

A recent retrospective chart review of 3,474 patients with metastatic NSCLC initiating 1st-line systemic therapy between April 1, 2018 and March 31, 2020 examined testing rates and turn-around times for PD-L1 along with 4 biomarkers of actionable mutations with specific targeted therapy indications (ALK, BRAF, EGFR, and ROS1). While 90% of patients had at least one biomarker test, only 46% had all 5. At 83%, the overall testing rate was highest for PD-L1, followed by ALK, EGFR, ROS1, and BRAF with overall testing rates of 70%, 70%, 68%, and 55%, respectively. Additionally, accounting for turnaround times, 10-13% of patients for each test received results during/after 1st line treatment.(41)

ICI use patterns
Since approval of the 1st ICI for NSCLC in 2015, and subsequent approval of 4 additional ICIs for NSCLC, the treatment landscape has rapidly changed. Retrospective claims studies show rapid uptake of ICIs following this approval.(42, 43) In a cohort of patients diagnosed with advanced NSCLC between January 1, 2010 and June 30, 2019, the proportion of patients receiving ICI-based increased sharply after 2015, with 44% of patients receiving ICIs for any line of therapy and 26% for 1st line therapy in 2018.(42)

Absent contraindications to immunotherapy (e.g., autoimmune comorbidity) or actionable mutation (e.g., EGFR, ALK), ICIs are indicated as 1st-line therapy for advanced NSCLC, either with or without chemotherapy depending on PD-L1 expression status and performance status. As such, the majority (i.e., >50%) of patients presenting with advanced NSCLC are eligible for ICIs.

A critical question to inform this case study is what percentage of eligible patients actually receive ICIs? This is a function of both biomarker and treatment access, and not directly answered from available literature. Data of several retrospective studies of patients with NSCLC show an increasing trend in 1st-line ICI use with time, as well as wide variation depending on the cohort definition.(44-46) The broadest cohort, described by Veluswamy et al., observed an increasing trend of ICI-based therapy from 28% in 2017 to 48% in 2020. However, this trend was driven by a dramatic increase in the proportion patients receiving ICIs + chemotherapy while the proportion of patients receiving ICI alone remained unchanged.(46) While these data suggest an improving trend in proportion of eligible patients receiving ICIs, there is also a continued reliance on chemotherapy and a substantial portion of patients receiving chemotherapy alone.

Additional utilization data is summarized in Appendix II.

Cost/value drivers

The cost and value drivers in this section focus primarily on the payer perspective but will be expanded as new workstreams take shape.

Economic cost/value drivers
Below is a summary of literature of cost-effectiveness of PD-L1 testing, economic benefits of ICIs, and cost-effectiveness of ICIs. More details are in Appendix III.

- While imperfect at predicting response to ICIs, published cost-effectiveness models suggest PD-L1 testing is cost effective and increases the cost-effectiveness of ICI treatment for NSCLC.
- ICIs are high-cost drugs, and combination with chemotherapy significantly increases costs. However, most literature supports economic benefits of ICIs when considering total cost of care as ICIs are associated with less supportive care, fewer AEs, and reduced AE-related costs than chemotherapy.
- Published cost-effectiveness models suggest ICI treatment is cost-effective for NSCLC in several scenarios:
  - ICI was cost-effective compared to platinum-based chemotherapy for patients with PD-L1 expression ≥50% but mixed for patients with PD-L1 expression ≥1%.
  - ICI + chemotherapy was cost-effective compared to chemotherapy for 1st-line treatment regardless of PD-L1 expression status for some models.
  - For 2nd-line treatment, ICI treatment was cost-effective compared to platinum-based chemotherapy in several scenarios and cost-effectiveness was improved when PD-L1 expression was considered.
- These studies highlight the potential for improved biomarkers to impact the cost-effectiveness of ICIs in the treatment of NSCLC.

Improved Quality of Life
Many of the pivotal clinical trials for ICIs in NSCLC demonstrated significantly greater health-related quality of life (HRQoL) improvements in the ICI-based arm versus the comparator chemotherapy group, with some evidence that patients with PD-L1 expression ≥50% experienced greater HRQoL benefit.(47) However, there is limited evidence in real-world populations. A recent observational study of patients treated with ICI or ICI + chemotherapy for metastatic lung cancer in routine clinical practice from 2017-2018 observed improvements in global health that were comparable to clinical trial results, but described higher symptom burden than published trials. The authors also noted the need for patient-reported outcome measures that more fully capture symptoms of immunotherapy (e.g., dermatologic) as well as financial concerns that are more likely to impact patients outside of clinical trial settings.(48) Identifying metrics important to patients will be critical to design of the pilot.

Another study noted the unmet quality of life considerations for long-term survivors of metastatic NSCLC treated with ICIs who describe the experience of outliving the initial prognosis but still living with a terminal illness as a limbo state.(49) This is an important patient journey consideration beyond the initial pilot.

Implementation Challenges

Behavioral and economic uncertainties related to the treatment of advanced NSCLC with ICIs pose some challenges for pilot implementation. A partial list includes:

- Challenges in tracking cancer outcomes due to patient mobility related to fragmentation of care and changes in insurance coverage.
- Challenges associated with biomarker testing:
  - Lack of standardization between tests
  - Undertesting
  - Timing of testing (early vs. late in the patient journey)

IV. Methodologic Uncertainties for RWE Production (Predictive Modeling)

The centerpiece of RWE production in this pilot concept will focus on developing a scalable and continuous capability for predictive modeling that will improve the targeted use ICIs in advanced NSCLC.

A successful solution must have the following characteristics, all critical to the design of our proposed POP:

1. **Preserve privacy:** Minimize need for patient-level data sharing by aggregating evidence (predictive models) produced by a distributed network of data/analysis partners rather than individual participant data.
2. **Leverage diverse data types:** To (a) enhance the **richness of potentially meaningful signals** of predictive markers, and (b) **avoid bias** related to inadequate representation of different patient sub-populations (vital for health equity).
3. **Address potential weaknesses** in data (e.g., incomplete, non-standardized)
4. **Generate actionable models:** That is, be considered fit-for-purpose for key stakeholders.
5. **Designed to scale:** anticipate the use of supporting infrastructure—or platform—for additional studies with similar high-level objectives of predictive modeling for response to a single therapy across multiple diseases or for multiple therapies for one disease.

A key methodologic uncertainty for POP relates to #1: is it feasible to aggregate multiple predictive models derived from different data sets/types? If so, what methods work best under what conditions? Building on discussions to date in LEAPS, we will begin by exploring one potential approach to the aggregation of predictive models—**Federated Learning (FL)**. (50-53)

FL is a distributed artificial intelligence (AI) process that enables the training of high-quality AI models by averaging local updates aggregated from multiple data clients, without the need for direct access to the local data. This approach potentially mitigates privacy leakage risks. Since FL has the potential to attract large computational and dataset resources from a number of data partners to train AI models, the data training quality (and accuracy) would be significantly improved over centralized local AI approaches.

Management of data-related uncertainties within the POP network (items #2-3 above) will be important for ensuring that the predictive models produced are meaningful and valid. A key feature

of the POP network protocol will focus on corroboration of findings from one site with those of another site.

Table 5. Summary of Methodologic uncertainties associated with the POP.

Success Driver	Approach	Uncertainties & Actions
Preserve privacy	Share evidence (models) from POP network partners, not patient-level data	How to integrate different predictive models?
Leverage diverse data types	Strategic selection of data partners to optimize diversity & representativeness Training of accurate AI models Health equity	Case-specific approaches to be incorporated into Core Protocol?
Address data quality issues	Corroboration of findings across sites?? Careful design of test sets??	Case-specific approaches to be incorporated into Core Protocol?
Generate actionable models	Proactively specify modeling parameters that would be fit-for-purpose for decisions/ actions by each stakeholder	Can multi-stakeholder interactive simulations of a range modeling parameters fuel productivity and impact from predictive modeling?
Design to Scale	Define potential scaling dimensions	Can we design Core Protocol to accommodate?

V. Methodologic Uncertainties for Incentive Design (Precision Reimbursement)

Pilot Metrics

What metrics (outcomes and impacts) for evaluating the pilot will be acceptable to all stakeholders and feasible from a data science point of view?
Meaningful outcomes differ among stakeholder groups and addressing the needs of all stakeholders is critical to the success of the pilot. Outcome measures will therefore cover not only clinical outcomes but also economic and quality of life measures, among others. Success metrics will also include system measures to evaluate the broader impact of the pilot. Selection of metrics for the pilot must also consider the feasibility of implementing with available data science tools.

Table 6 is an initial summary of metrics under consideration to lay the groundwork for Design Lab discussion and potential post-Design Lab workstream to fully explore meaningful outcomes for all stakeholders.

Table 6. Pilot Metrics: Partial list to catalyze initial discussion

Category	Measure
Clinical outcomes	Objective Response Rate (ORR): the proportion of patients with a **complete** or **partial response** to treatment according to Response Evaluation Criteria in Solid Tumors (RECIST) criteria (radiographically) • Most common endpoint used in pivotal trials supporting FDA approval of cancer drugs for solid tumors
	Circulating tumor DNA (ctDNA)
	Overall Survival (OS)
	Progression Free Survival (PFS)
	Unplanned hospitalization
	Time to treatment switch
Patient Journey	Time to effective treatment
Quality of Life	What measure best captures what matters to patients with NSCLC? What measures specific to NSCLC (e.g., lung-specific symptoms) are important to patients?
	Example Measures used in KEYNOTE-024 Trial included: • European Organisation for the Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire Core 30 items (QLQ-C30) • EORTC Quality of Life Questionnaire Lung Cancer 13 items (QLQ-LC13) • European Quality of Life 5 Dimensions-3 Level (EQ-5D-3L) questionnaire
Functional	Absenteeism, Presenteeism
Economic	Total cost per life year
	Total cost for the patient population (Gross? Net of all rebates, patient cost-sharing, provider risk sharing?) • For the immediate diagnostic (if any), drug and ancillary costs • For immediate and follow-on treatment until progression • Over some longer period (X years or until death)
	Others
System	Percentage ICI-eligible patients actually receiving ICIs
	Burden of Disease
	Health Equity?

Fit-For-Purpose Predictive Modeling Parameters by Stakeholder

In contrast to the "Upstream"/pre-market space where the FDA sets the standards, evidence standards in the "Downstream"/post-market space are not established and vary by stakeholder. To ensure the evidence generated by the pilot will be considered "fit-for-purpose", it is necessary to understand stakeholder thresholds for actionable evidence and the criteria by which stakeholders will evaluate the credibility of the predictive model. Discussions at Design Lab will investigate this area and the potential for a related post-Design Lab workstream.

VI. Data Sources

Diversity of data sources that serve as inputs into the predictive modeling has been highlighted as a critical success driver for the integrated pilot concept. Examples of data sources and elements to be considered are provided in Table 7 below.

Table 7: Potential data sources and elements for the Predictive Outcomes Platform

Data Source	Data Elements
EMR/Cancer Center Registry	Demographics (age, sex, ethnicity)
	Cancer-related metadata (Tumor type, stage, prior therapy)
	Routine Lab Data (CBC, liver panel)
	irAEs
Genomic	Microsatellite instability
	TMB
	Driver oncogene
Histopathology	Tumor infiltrating lymphocytes
	PD-L1 expression
	Different clones/IVD
Specialty Pharmacy	Drug Regimen
	Dispensing Scheme
	Utilization
Radiographic	Tumor Size, Features (Before and During Treatment)
Patient Generated Health Data	PROs
	Social Media
	Wearables
Socioeconomic	Employment Income Education
Claims	Diagnosis codes
	Procedures
	Utilization
Benefits Management (e.g., Interlink, AIM)	? Clinical use patterns ? Prior authorizations ? Cost of care within different settings

VII. Scaling Strategies

This case study of ICIs to treat advanced NSCLC is the first step for proof of concept for this Methods Innovation. The Predictive Outcomes Platform we develop will be designed to scale through a Core Protocol. Scaling may be possible in multiple dimensions, e.g., to additional data sources/types, ICIs for other cancer types, other stages of NSCLC, or other therapeutic product classes for advanced NSCLC.

Appendix I: Ongoing Studies

Table I. Ongoing studies of combined biomarkers in ICI response (partial list)

Identifier	Study Type	Population	Treatment	Biomarkers	Estimated Completion	Location
ICI-PREDICT (54)	Prospective, Observational	Stage IV or III NSCLC not applicable for definitive chemoradio-therapy	ICI + chemo (1st-line)	Nutritional/ Immunologic Indices	2025	Japan
NCT04918836	Prospective, Observational	Metastatic NSCLC	ICI	(Pre-treatment and during treatment) autoantibod-ies, RF, LDH, complement (C3 C4), anti-tissue antibodies, lymphocyte immunophenotyping	October 2022	France
NCT04589013	Prospective, Observational	Metastatic NSCLC	ICI + chemo	multiparametric test including 6 immunohisto-chemical markers (PD-L1, CD8, FoxP3, PD1, CD163, CD15)	November 2023	France
NCT04629027	Retrospective, Observational	IIIB-IV non-squamous NSCLC	ICI	clinical pathological char-acteristics of patients, and dynamic monitoring of peripheral blood molec-ular biological markers	May 2023	China
NCT04923802	Prospective, Observational	Stage I-IV NSCLC	ICI	NGS-based genomic, transcriptomic, and meth-ylomic profiling	May 2025	China
NCT04858828	Prospective, Observational	Advanced NSCLC	ICI + chemo (1st-line)	Next-generation sequenc-ing (NGS)-based gene expression profiling (GEP) and inflammation-relat-ed T-cell receptor (TCR) repertoire profiling. Molecular assays in-cluding tumor mutation burden (TMB), micro-satellite instability (MSI) status, DNA damage repair (DDR)-related gene mutation status, and pro-grammed death-ligand 1 (PD-L1) expression level	March 2024	China

Identifier	Study Type	Population	Treatment	Biomarkers	Estimated Completion	Location
NCT04636047	Prospective, Observational	NSCLC	ICI	Tumor-reactive T-cell receptors (TCR), bTMB, HKA	August 2023	China
NCT04804137	Prospective, Observational	Metastatic non-squamous NSCLC	ICI +/- chemotherapy	T cell sub populations, B lymphocytes, Cytokine inflammatory profile, gut microbiota, lung microbiota	March 2025	France

NCT trials identified from Pan et al. et al. The key to immunotherapy: how to choose better therapeutic biomarkers for patients with non-small cell lung cancer. Biomark Res. 2022;10(1):9. (23)

Appendix II: Additional ICI Utilization Details

Table II summarizes the distribution of 1st line treatment class (ICI, ICI + chemo, chemo, and other/targeted therapies) for several retrospective studies of patients with NSCLC. These data show an increasing trend in ICI use with time, as well as wide variation, some of which can be explained by exclusions of patients with EGFR or ALK mutations (44, 45) or who received tyrosine kinase inhibitors (45) in some cohorts. The broadest cohort, described by Veluswamy et al., observed an increasing trend of ICI-based therapy from 28% in 2017 to 48% in 2020. However, this trend was driven by a dramatic increase in the proportion patients receiving ICIs + chemotherapy while the proportion of patients receiving ICI alone remained unchanged. (46) While these data suggest an improving trend in proportion of eligible patients receiving ICIs, there is also a continued reliance on chemotherapy and a substantial portion of patients receiving chemotherapy alone.

Table II. 1st Line Treatment patterns for advanced NSCLC

Study	Population	Time Frame	Treatment Categories
Veluswamy (46)	5,431 patients initiating 1st-line treatment for NSCLC (IBM MarketScan® database)	Overall: May 2017—October 2020	40% ICI-based -15% ICI alone 25% ICI + chemo 47% chemotherapy 13% targeted therapy
Veluswamy et al. (46), Distribution by year			
2017	2018	2019	2020
28% ICI-based • 15% ICI alone • 13% ICI + chemo 61% chemotherapy 11% targeted therapy	38% ICI-based • 15% ICI alone • 23% ICI + chemo 49% chemotherapy 13% targeted therapy	46% ICI-based • 14% ICI alone • 32% ICI + chemo 40% chemotherapy 14% targeted therapy	48% ICI-based • 14% ICI alone • 34% ICI + chemo 38% chemotherapy 14% targeted therapy

Nadler et al. (44)	7,746 patients initiating 1st-line treatment for stage IV NSCLC (US Oncology Network) *Patients with documented EGFR or ALK excluded	March 2015 – August 2018	15.9% ICI-based • 11.7% ICI alone • 4.2% ICI + chemo 75.6 % chemotherapy 8.5% targeted therapy
Stenehjem et al. (45)	3,995 patients initiating 1st-line treatment for stage IV NSCLC (Flatiron Health Oncology Database) *Patients with documented EGFR or ALK excluded, Patients receiving tyrosine kinase inhibitor excluded	August 2018 – December 2019	75% ICI-based • 20 % ICI alone • 55% % ICI + chemo 20% chemotherapy 5% other therapy

Appendix III: Additional Cost/Value Driver Details

Cost effectiveness of PD-L1 biomarker testing
While imperfect at predicting response, data indicate that PD-L1 testing is cost effective and increases the cost effectiveness of ICI treatment for NSCLC.

A decision analysis model based on data from 4 phase III RCTs of ICIs compared the cost-effectiveness and economic burden of 2nd-line treatment of NSCLC with ICI versus docetaxel with and without patient selection via PD-L1 expression (≥1%). Compared to treating all patients, selection via PD-L1 expression resulted in 183% improvement in incremental quality-adjusted life-year (QALY) and 65% decrease in incremental cost-effectiveness ratio (ICER). (55) Another cost-effective analysis based on data from a phase III trial of 1st-line treatment of NSCLC with chemo-immunotherapy versus chemotherapy calculated ICER/QALY of $132,392, $77,754, and $44,731 for scenarios of no testing, PD-L1 ≥1%, and PD-L1 ≥50%, respectively. (56)

Cost benefits of ICIs for NSCLC
ICIs are high-cost drugs, and combination with chemotherapy significantly increases the costs. However, most of the literature supports economic benefits of ICIs when total cost of care including costs associated with hospitalizations, emergency department (ED) visits, and supportive care/AE management are considered.

Pre- versus Post-ICI approval
Some studies have compared total cost of care in a "pre" versus "post" ICI period to understand the economic impact of ICIs on cancer care. Korytowsky et al. compared costs and healthcare resource utilization between pre (March 2013 to March 2014) and post (March 2015 to December 2016) propensity score matched cohorts of patients with NSCLC initiating systemic therapy in a multi-payer database. While the cost of systemic therapy was significantly higher post-ICI ($27,928) than pre-ICI ($21,025, $p<0.001$), total cost of care was significantly lower post-ICI ($113,117) than pre-ICI ($129,977, $p<0.001$) due to significantly lower ED and hospitalization

costs. Additionally, the percentage patients with hospitalizations or ED visits as well as the mean number of hospitalizations or ED visits were significantly lower in the post-ICI cohort. (Table III) (57) A more recent study with longer study duration found a trend of increasing mean per patient per year (PPPY) total costs from 2010 to 2018 among patients with advanced NSCLC initiating 1st-line systemic treatment, driven by increases in outpatient costs for systemic therapy. Other costs (inpatient, outpatient costs unrelated to systemic therapy, pharmacy costs) were relatively stable, but still comprised the majority (>60%) of the economic burden. (42) However, the objective of this study was to assess the overall burden and trends by year for advanced NSCLC and did not formally compare pre-/post-ICI periods as the prior study (i.e., with propensity score matched cohorts).

However, there is evidence that the management of AEs associated with chemotherapy has a higher burden than AEs associated with ICIs. In a retrospective administrative claims study (January 2008 – February 2018) of patients with metastatic NSCLC initiating 1st-line treatment with ICIs, ICIs + chemotherapy, or chemotherapy, the ICI cohort experienced significantly fewer AEs than the other 2 cohorts and had the lowest total AE-related costs, with significantly lower costs than the chemotherapy cohort. (Table II). Mean per patient per month (PPPM) AE-related costs for the ICI cohort were significantly lower than both the ICI + chemotherapy and chemotherapy cohorts. Additionally, among patients with AE-related costs, patients in the ICI cohort were significantly less likely to have high costs (defined as 90th percentile of $49,402) than the chemotherapy cohort. (58)

Table III. Summary of cost benefits of ICIs

Pre- versus Post-ICI Time Period				
Reference	**Population**		**Comparison**	
Korytowsky et al. (57)	Patients with metastatic NSCLC initiating systemic therapy Multi-payer database		Pre (March 2013-March 2014) vs. Post (March 2015–December 2016) ICI period Propensity score matched cohorts	
	Results			
	Measure	*Pre*	*Post*	*P-value*
	Any hospitalization (n, %)	946 (61)	713 (46)	<0.001
	Hospitalizations (mean (SD))	2.3 (1.6)	2.1 (1.7)	0.006
	LOS (mean (SD)	1.7 (2.7)	2.1 (8.4)	0.155
	Any ED visit (n, %)	1194 (77)	1016 (66)	<0.001
	ED Visits (mean (SD))	3.3 (3.0)	2.9 (2.6)	0.002
	Total cost of care (mean (SD))	$129,977 ($112,479)	$113,117 ($96,557)	<0.001
	ED Visit cost	$36,639 ($50,541)	$23,331 ($27,065)	<0.001
	Hospitalization Cost	$24,876, ($61,778)	$17,680 ($56,115)	0.013

	Systemic therapy cost	$21,025 ($38,531)	$27,928 ($48,566)	<0.001
	Per patient per month total cost of care (mean (SD))	$12,681 ($10,371)	$10,758 ($7221)	<0.001
Reduced AE-related costs				
Reference	**Population**		**Comparison**	
Engel-Nitz et al. (58)	Patients with metastatic NSCLC initiating 1st-line systemic therapy with ICI, ICI + chemo, chemo Managed care administrative claims database, January 2008-February 2018)		AEs and AE-related costs among treatment cohorts (ICI, ICI + chemo, chemo)	
	Measure		**Result**	
	AE IRR (95% CI)		ICI: Reference Chemotherapy: 1.4 (1.2, 1.7) ICI-Chemotherapy: 1.4 (1.1, 1.7)	
	Total AE-Related Costs Per Patient (Mean (SD))		ICI: $16,319 (31,962) ICI + Chemo: $18,806 (26,708) Chemo: $23,009 (38,415)* *p<0.001 for Chem vs. ICI	
	Per patient per month AE-Related Costs (Mean)		ICI: $4,259 ICI + Chemo: $6,323 (p<0.001) Chemo: $6,269 (p=0.020) p-value for comparison to ICI	
	High AE costs OR (95% CI)		Chemo: Reference ICI: 0.60 (0.38, 0.95) ICI-Chemotherapy: 0.79 (0.51, 1.20)	

ED: emergency department; IRR: incidence rate ratio; LOS: length of stay; OR: odds ratio; SD: standard deviation

Cost-effectiveness of ICIs for NSCLC

Several models have examined the cost-effectiveness of ICI treatment for NSCLC with varying results. A recent systematic literature review of 22 cost-effectiveness studies observed ICIs for the treatment of NSCLC is cost-effective, i.e., meets a willingness to pay (WTP) threshold in the US of $100,000 per QALY gained, in several scenarios. In 1st-line treatment of advanced or metastatic NSCLC, ICI treatment was cost-effective compared to platinum-based chemotherapy for patients with PD-L1 expression ≥50% but were mixed of patients with PD-L1 expression ≥1%. ICI + chemotherapy was cost-effective compared to chemotherapy for 1st-line treatment regardless of PD-L1 expression status for some models. For 2nd-line treatment, ICI treatment was cost-effective compared to platinum-based chemotherapy in several scenarios and cost-effectiveness was improved when PD-L1 expression was considered. (59)

These studies highlight the potential for improved biomarkers to impact the cost-effectiveness of ICIs in the treatment of NSCLC.

References

1. Wei SC, Duffy CR, Allison JP. Fundamental Mechanisms of Immune Checkpoint Blockade Therapy. Cancer Discov. 2018;8(9):1069-86.
2. Marin-Acevedo JA, Kimbrough EO, Lou Y. Next generation of immune checkpoint inhibitors and beyond. J Hematol Oncol. 2021;14(1):45.
3. Chowell D, Yoo SK, Valero C, Pastore A, Krishna C, Lee M, et al. Improved prediction of immune checkpoint blockade efficacy across multiple cancer types. Nat Biotechnol. 2022;40(4):499-506.
4. Brahmer JR, Rodríguez-Abreu D, Robinson AG, Hui R, Csőszi T, Fülöp A, et al. Health-related quality-of-life results for pembrolizumab versus chemotherapy in advanced, PD-L1-positive NSCLC (KEYNOTE-024): a multicentre, international, randomised, open-label phase 3 trial. Lancet Oncol. 2017;18(12):1600-9.
5. Reck M, Rodríguez-Abreu D, Robinson AG, Hui R, Csőszi T, Fülöp A, et al. Pembrolizumab versus Chemotherapy for PD-L1-Positive Non-Small-Cell Lung Cancer. N Engl J Med. 2016;375(19):1823-33.
6. Horn L, Spigel DR, Vokes EE, Holgado E, Ready N, Steins M, et al. Nivolumab Versus Docetaxel in Previously Treated Patients With Advanced Non-Small-Cell Lung Cancer: Two-Year Outcomes From Two Randomized, Open-Label, Phase III Trials (CheckMate 017 and CheckMate 057). J Clin Oncol. 2017;35(35):3924-33.
7. Rittmeyer A, Barlesi F, Waterkamp D, Park K, Ciardiello F, von Pawel J, et al. Atezolizumab versus docetaxel in patients with previously treated non-small-cell lung cancer (OAK): a phase 3, open-label, multicentre randomised controlled trial. Lancet. 2017;389(10066):255-65.
8. Brown TJ, Mamtani R, Bange EM. Immunotherapy Adverse Effects. JAMA Oncol. 2021;7(12):1908.
9. Wang Y, Tong Z, Zhang W, Buzdin A, Mu X, Yan Q, et al. FDA-Approved and Emerging Next Generation Predictive Biomarkers for Immune Checkpoint Inhibitors in Cancer Patients. Front Oncol. 2021;11:683419.
10. Mariam A, Kamath S, Schveder K, McLeod HL, Rotroff DM. Large-Scale Meta-Analysis of Potential Biomarkers for Treatment Response to Anti-PD-1/PD-L1 Immune Checkpoint Inhibitors. medRxiv. 2020:2020.11.25.20238865.
11. Siegel RL, Miller KD, Fuchs HE, Jemal A. Cancer statistics, 2022. CA Cancer J Clin. 2022;72(1):7-33.
12. Duma N, Santana-Davila R, Molina JR. Non-Small Cell Lung Cancer: Epidemiology, Screening, Diagnosis, and Treatment. Mayo Clin Proc. 2019;94(8):1623-40.
13. Lung Cancer is Expected to Acquire 50% of the Global Cancer Immunotherapy Market, Finds Fact.MRMay 31, 2022. Available from: https://www.biospace.com/article/lung-cancer-is-expected-to-acquire-50-percent-of-the-global-cancer-immunotherapy-market-finds-fact-mr/.
14. Brueckl WM, Ficker JH, Zeitler G. Clinically relevant prognostic and predictive markers for immune-checkpoint-inhibitor (ICI) therapy in non-small cell lung cancer (NSCLC). BMC Cancer. 2020;20(1):1185.
15. National Comprehensive Cancer Network. NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for Non-Small Cell Lung Cancer V.3.2022. March 16, 2022April 29, 2022. Available from: https://www.nccn.org/professionals/physician_gls/pdf/nscl.pdf.
16. Ayers KL, Ma M, Debussche G, Corrigan D, McCafferty J, Lee K, et al. A composite biomarker of neutrophil-lymphocyte ratio and hemoglobin level correlates with clinical response to PD-1 and PD-L1 inhibitors in advanced non-small cell lung cancers. BMC Cancer. 2021;21(1):441.

17. Kao C, Powers E, Wu Y, Datto MB, Green MF, Strickler JH, et al. Predictive Value of Combining Biomarkers for Clinical Outcomes in Advanced Non-Small Cell Lung Cancer Patients Receiving Immune Checkpoint Inhibitors. Clin Lung Cancer. 2021;22(6):500-9.
18. Rhone R, Dumais K, Powery HW, Gentile F, Raez LE. Clinical predictive markers of response to immune checkpoint inhibitor therapy in advanced non-small cell lung cancer. Journal of Clinical Oncology. 2021;39(15_suppl):e21044-e.
19. Prelaj A, Ferrara R, Rebuzzi SE, Proto C, Signorelli D, Galli G, et al. EPSILoN: A Prognostic Score for Immunotherapy in Advanced Non-Small-Cell Lung Cancer: A Validation Cohort. Cancers (Basel). 2019;11(12).
20. Benzekry S, Grangeon M, Karlsen M, Alexa M, Bicalho-Frazeto I, Chaleat S, et al. Machine Learning for Prediction of Immunotherapy Efficacy in Non-Small Cell Lung Cancer from Simple Clinical and Biological Data. Cancers (Basel). 2021;13(24).
21. Lee JS, Ruppin E. Multiomics Prediction of Response Rates to Therapies to Inhibit Programmed Cell Death 1 and Programmed Cell Death 1 Ligand 1. JAMA Oncol. 2019;5(11):1614-8.
22. Bai R, Lv Z, Xu D, Cui J. Predictive biomarkers for cancer immunotherapy with immune checkpoint inhibitors. Biomark Res. 2020;8:34.
23. Pan Y, Fu Y, Zeng Y, Liu X, Peng Y, Hu C, et al. The key to immunotherapy: how to choose better therapeutic biomarkers for patients with non-small cell lung cancer. Biomark Res. 2022;10(1):9.
24. Yang W, Lei C, Song S, Jing W, Jin C, Gong S, et al. Immune checkpoint blockade in the treatment of malignant tumor: current statue and future strategies. Cancer Cell Int. 2021;21(1):589.
25. Ikeda T, Oi H, Yoh K, Matsumoto S, Kato T, Nishino K, et al. Optimal next-generation sequencing (NGS) panel for estimating tumor mutation burden (TMB) and its clinical implication for non-small cell lung cancer (NSCLC). Journal of Clinical Oncology. 2021;39(15_suppl):9097-.
26. Ren F, Zhao T, Liu B, Pan L. Neutrophil-lymphocyte ratio (NLR) predicted prognosis for advanced non-small-cell lung cancer (NSCLC) patients who received immune checkpoint blockade (ICB). Onco Targets Ther. 2019;12:4235-44.
27. Cao Y, Palmer JP, Ibrahim S, Dhawan N, Afzal MZ, Shirai K. Association of baseline higher platelet-to-lymphocyte and neutrophil-to-lymphocyte ratios with less durable radiographic response to immune checkpoint inhibitors in non-small cell lung cancer. Journal of Clinical Oncology. 2021;39(15_suppl):e21137-e.
28. Zhang Z, Li Y, Yan X, Song Q, Wang G, Hu Y, et al. Pretreatment lactate dehydrogenase may predict outcome of advanced non small-cell lung cancer patients treated with immune checkpoint inhibitors: A meta-analysis. Cancer Med. 2019;8(4):1467-73.
29. Guo Y, Wei L, Patel SH, Lopez G, Grogan M, Li M, et al. Serum Albumin: Early Prognostic Marker of Benefit for Immune Checkpoint Inhibitor Monotherapy But Not Chemoimmunotherapy. Clin Lung Cancer. 2022.
30. Mountzios G, Samantas E, Senghas K, Zervas E, Krisam J, Samitas K, et al. Association of the advanced lung cancer inflammation index (ALI) with immune checkpoint inhibitor efficacy in patients with advanced non-small-cell lung cancer. ESMO Open. 2021;6(5):100254.
31. Yan X, Tian X, Wu Z, Han W. Impact of Age on the Efficacy of Immune Checkpoint Inhibitor-Based Combination Therapy for Non-small-Cell Lung Cancer: A Systematic Review and Meta-Analysis. Front Oncol. 2020;10:1671.
32. Conforti F, Pala L, Bagnardi V, Viale G, De Pas T, Pagan E, et al. Sex-Based Heterogeneity in Response to Lung Cancer Immunotherapy: A Systematic Review and Meta-Analysis. J Natl Cancer Inst. 2019;111(8):772-81.

33. Lang D, Brauner A, Huemer F, Rinnerthaler G, Horner A, Wass R, et al. Sex-Based Clinical Outcome in Advanced NSCLC Patients Undergoing PD-1/PD-L1 Inhibitor Therapy-A Retrospective Bi-Centric Cohort Study. Cancers (Basel). 2021;14(1).
34. Nazha B, Chen Z, Goyal S, Engelhart A, Carlisle JW, Beardslee T, et al. Evaluating the role of race in outcome of advanced non-small cell lung cancer (NSCLC) patients treated with immune checkpoint inhibitor (ICI): Our institutional experience. Journal of Clinical Oncology. 2019;37(15_suppl):9042-.
35. Xu Y, Wang Q, Xie J, Chen M, Liu H, Zhan P, et al. The Predictive Value of Clinical and Molecular Characteristics or Immunotherapy in Non-Small Cell Lung Cancer: A Meta-Analysis of Randomized Controlled Trials. Front Oncol. 2021;11:732214.
36. Cancer Trends Progress Report. Available from: https://progressreport.cancer.gov.
37. Chiu K, MacEwan JP, Bognar K, Peneva D, May SG, Zhao L, et al. Estimating productivity losses for cancer patients and caregivers of cancer patients. Journal of Clinical Oncology. 2020;38(15_suppl):e19381-e.
38. Islami F, Miller KD, Siegel RL, Zheng Z, Zhao J, Han X, et al. National and State Estimates of Lost Earnings From Cancer Deaths in the United States. JAMA Oncol. 2019;5(9):e191460.
39. Cubanski J, Sroczynski N, Neuman T. Medicare Part B Drugs: Cost Implications for Beneficiaries in Traditional Medicare and Medicare AdvantageMay 2, 2022. Available from: https://www.kff.org/medicare/issue-brief/medicare-part-b-drugs-cost-implications-for-beneficiaries-in-traditional-medicare-and-medicare-advantage/.
40. ADVI. Payer Coverage Policies of Tumor Biomarker Testing, September 2020. Commissioned By: American Cancer Society Cancer Action Network and LUNGevity Foundation. Available from: https://www.lungevity.org/sites/default/files/biomarker/ACS-CAN-LUNGevity_PayerCoveragePoliciesofTumorBiomarkerTesting_092020.pdf.
41. Robert NJ, Nwokeji ED, Espirito JL, Chen L, Karhade M, Evangelist MC, et al. Biomarker tissue journey among patients (pts) with untreated metastatic non-small cell lung cancer (mNSCLC) in the U.S. Oncology Network community practices. Journal of Clinical Oncology. 2021;39(15_suppl):9004-.
42. Zhang X, Beachler DC, Masters E, Liu F, Yang M, Dinh J, et al. Health care resource utilization and costs associated with advanced or metastatic nonsmall cell lung cancer in the United States. J Manag Care Spec Pharm. 2022;28(2):255-65.
43. Khozin S, Miksad RA, Adami J, Boyd M, Brown NR, Gossai A, et al. Real-world progression, treatment, and survival outcomes during rapid adoption of immunotherapy for advanced non-small cell lung cancer. Cancer. 2019;125(22):4019-32.
44. Nadler E, Arondekar B, Aguilar KM, Zhou J, Chang J, Zhang X, et al. Treatment patterns and clinical outcomes in patients with advanced non-small cell lung cancer initiating first-line treatment in the US community oncology setting: a real-world retrospective observational study. J Cancer Res Clin Oncol. 2021;147(3):671-90.
45. Stenehjem D, Lubinga S, Betts KA, Tang W, Jenkins M, Yuan Y, et al. Treatment patterns in patients with metastatic non-small-cell lung cancer in the era of immunotherapy. Future Oncol. 2021;17(22):2940-9.
46. Veluswamy R, Hirsch FR, Taioli E, Wisnivesky J, Strauss R, Harrough D, et al. Real-World longitudinal practice patterns in the use of PD-1 and PD-L1 inhibitors as First-Line therapy in patients with Non-Small cell lung cancer in the United States. Cancer Med. 2022.
47. Procailo K. The impact of immune checkpoint inhibitors on cost and quality of life in the initial treatment of patients with advanced or metastatic NSCLC. Am J Manag Care. 2021;27(18 Suppl):S333-S9.
48. Steffen McLouth LE, Lycan TW, Levine BJ, Gabbard J, Ruiz J, Farris M, et al. Patient-Reported

Outcomes From Patients Receiving Immunotherapy or Chemoimmunotherapy for Metastatic Non-Small-Cell Lung Cancer in Clinical Practice. Clin Lung Cancer. 2020;21(3):255-63.e4.
49. Park R, Shaw JW, Korn A, McAuliffe J. The value of immunotherapy for survivors of stage IV non-small cell lung cancer: patient perspectives on quality of life. J Cancer Surviv. 2020;14(3):363-76.
50. Warnat-Herresthal S, Schultze H, Shastry KL, Manamohan S, Mukherjee S, Garg V, et al. Swarm Learning for decentralized and confidential clinical machine learning. Nature. 2021;594(7862):265-70.
51. Sheller MJ, Edwards B, Reina GA, Martin J, Pati S, Kotrotsou A, et al. Federated learning in medicine: facilitating multi-institutional collaborations without sharing patient data. Sci Rep. 2020;10(1):12598.
52. Kaissis GA, Makowski MR, Rückert D, Braren RF. Secure, privacy-preserving and federated machine learning in medical imaging. Nature Machine Intelligence. 2020;2(6):305-11.
53. Kaissis G, Ziller A, Passerat-Palmbach J, Ryffel T, Usynin D, Trask A, et al. End-to-end privacy preserving deep learning on multi-institutional medical imaging. Nature Machine Intelligence. 2021;3(6):473-84.
54. Takamori S, Ohba T, Shimokawa M, Matsubara T, Haratake N, Miura N, et al. Prospective observational study of nutritional/immunologic indices as predictive biomarkers for the response to anti-PD-1 drugs in non-small cell lung cancer (ICI-PREDICT study). PLoS One. 2021;16(10):e0258616.
55. Aguiar PN, Perry LA, Penny-Dimri J, Babiker H, Tadokoro H, de Mello RA, et al. The effect of PD-L1 testing on the cost-effectiveness and economic impact of immune checkpoint inhibitors for the second-line treatment of NSCLC. Ann Oncol. 2017;28(9):2256-63.
56. Wan N, Zhang TT, Hua SH, Lu ZL, Ji B, Li LX, et al. Cost-effectiveness analysis of pembrolizumab plus chemotherapy with PD-L1 test for the first-line treatment of NSCLC. Cancer Med. 2020;9(5):1683-93.
57. Korytowsky B, Radtchenko J, Nwokeji ED, Tuell KW, Kish JK, Feinberg BA. Understanding total cost of care in advanced non-small cell lung cancer pre- and postapproval of immuno-oncology therapies. Am J Manag Care. 2018;24(20 Suppl):S439-S47.
58. Engel-Nitz NM, Johnson MP, Bunner SH, Ryan KJ. Real-World Costs of Adverse Events in First-Line Treatment of Metastatic Non-Small Cell Lung Cancer. J Manag Care Spec Pharm. 2020;26(6):729-40.
59. Ding H, Xin W, Tong Y, Sun J, Xu G, Ye Z, et al. Cost effectiveness of immune checkpoint inhibitors for treatment of non-small cell lung cancer: A systematic review. PLoS One. 2020;15(9):e0238536.