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Research Institute℠

IMPROVING CARE SERIES

REAL-WORLD DATA IN CANCER CARE

Breakthrough immune therapies and their effect on health and health care value

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HEALTH SERVICES

OVERVIEW

Cancer today

34% increase in U.S. medical and pharmacy costs for cancer projected from 2015 to 2030[2]

In 2023, an estimated 600,000 people in the United States will lose their lives to cancer and nearly two million nationwide will be newly diagnosed. Cancer is the second leading cause of death in the U.S. behind only cardiovascular disease. Five cancer types account for half of all cancer deaths, led by lung cancer.[1]

While these statistics are grim, treatment has improved significantly over the years, with better understanding of the molecular drivers of many cancers as well as advances in the development of targeted and immune therapies. However, improved outcomes have been accompanied by significantly higher financial costs.

The National Cancer Institute estimates the cancer-attributable cost of medical services and prescription drugs in the U.S. will increase from $183 billion in 2015 to $246 billion by 2030—a relative increase of 34%.[2]

Our report focuses on patients with cancer who are treated with oncology drugs billed under the medical benefit. In this report you will understand:

+ Why the infusion setting for ICI treatment is a major cost driver
+ How health disparities and genomic testing prior to initiation greatly impact therapy
+ How applying evidence-based guidelines for ICI therapy can help prevent wasteful spending

The rise of immune checkpoint inhibitors (ICIs)

After decades of incremental improvement, cancer care has taken a significant step forward with the introduction of a new class of medications known as immune checkpoint inhibitors. These ICIs work by blocking certain proteins called checkpoints, enabling the patient's immune cells to destroy the cancer.

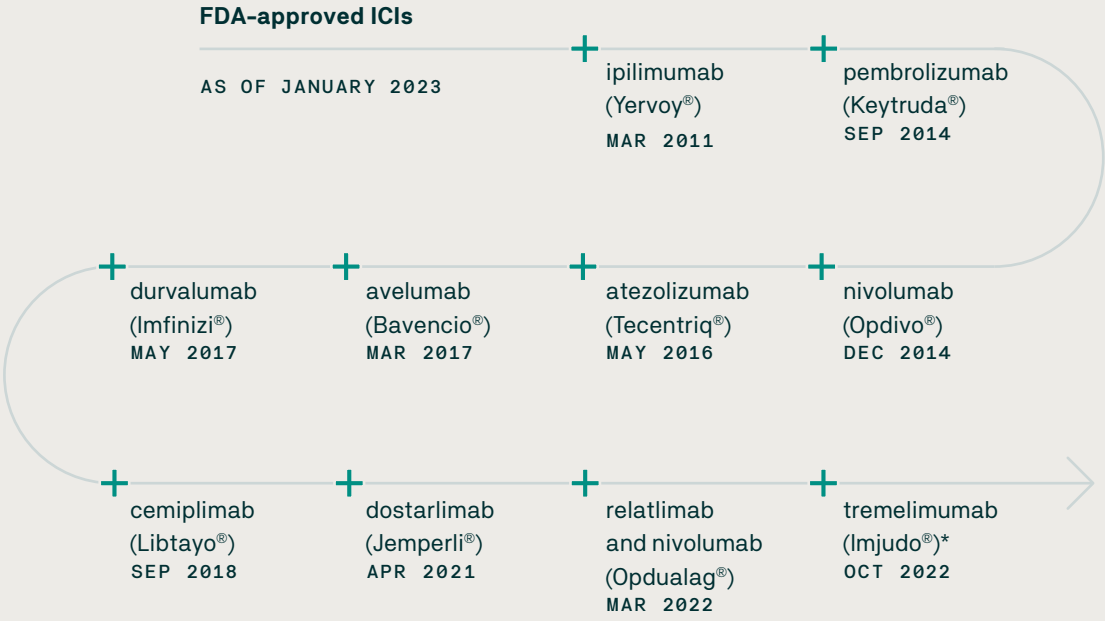
19% annual growth projected for ICI market value from 2022 to 2030[5]

The ICIs have been shown to improve survival in select patient populations and in different types of cancer. Since the introduction of ICIs, survival rates have improved greatly over the last decade for melanoma, lung and kidney cancers.[1]

The global market for ICI sales has increased exponentially, from $360 million in 2011 when they first launched, to an estimated $37.3 billion in 2022.[3,4] Sales are projected to grow by almost 19% annually through 2030—or nearly 400% over eight years.[4]

ICI approvals and pipeline

ICIs first arrived in 2011 when the FDA approved the drug ipilimumab (Yervoy®) for treatment of metastatic melanoma.[5] As of January 2023 the FDA has approved ten ICI drugs, each with one or more indications across a dozen cancer types.[5,6,7,8]



**Given with durvalumab*

5,683 clinical trials involving ICIs initiated since 2021[9]

We expect growth in ICI spending to continue as drug manufacturers seek to expand clinical indications for their existing FDA-approved drugs. Also, new formulations that can be administered as an injection without an infusion, are in the process of approval for 2024.

ICI pipeline

AS OF JANUARY 2023

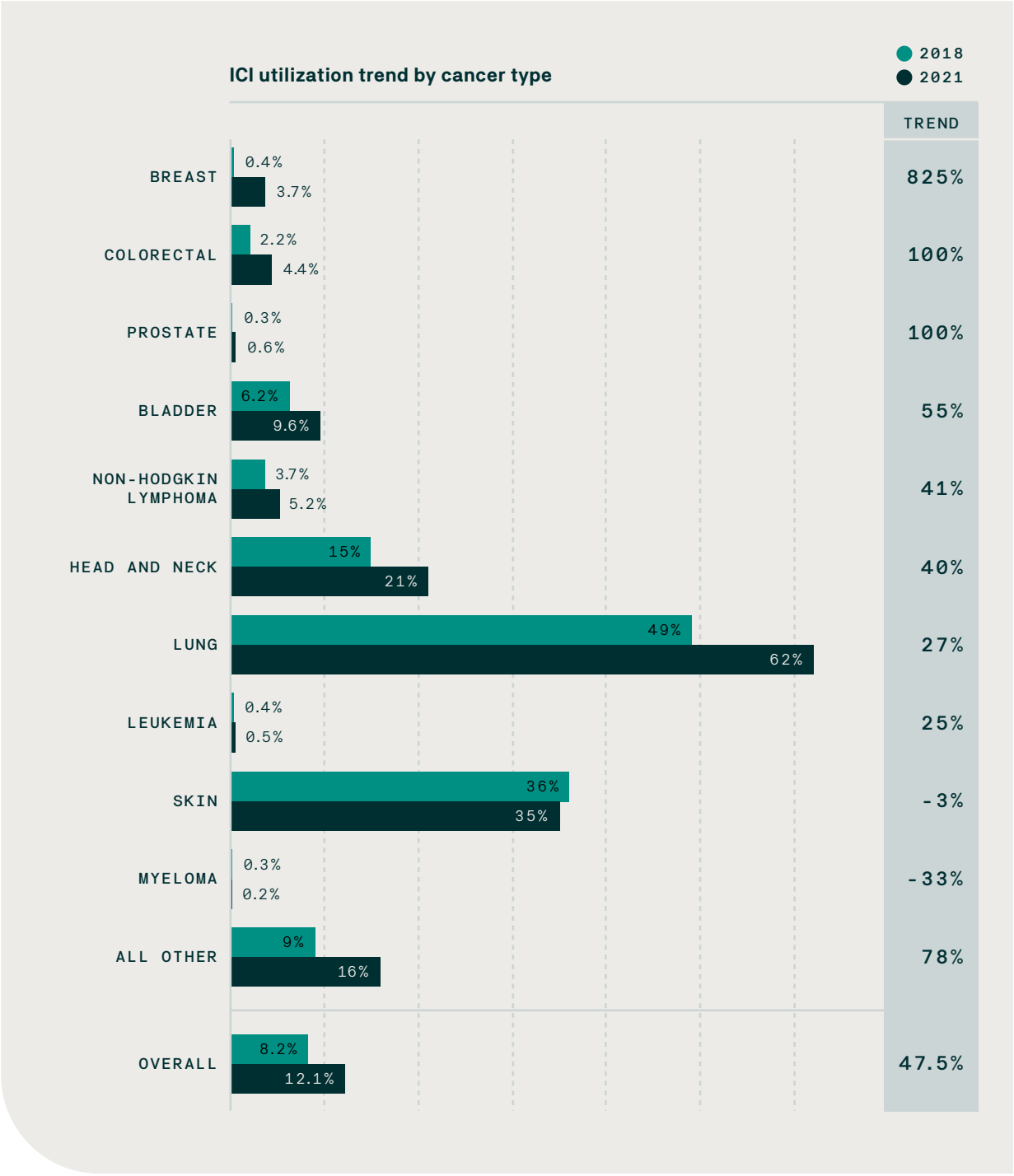
INFUSION · INJECTION · ORPHAN/BREAKTHROUGH · NEW INDICATION

PIPELINE DRUG	MANUFACTURER	INDICATION	PROJECTED LAUNCH
penpulimab	Akeso Sino Biopharmaceutic	Nasopharyngeal carcinoma	Q1–Q2 2023
toripalimab	Coherus Biosciences	Nasopharyngeal carcinoma	Q2 2023
atezolizumab (Tecentriq®)	Genentech	Non-small cell lung cancer	Q3 2023
dostarlimab (Jemperli®)	GlaxoSmithKline	Endometrial cancer	Q3–Q4 2023
cosibelimab	Checkpoint Therapeutics	Squamous cell carcinoma	Q1 2024
batiraxcept	Aravive	Renal cell carcinoma	2024
magrolimab 5F9	Gilead Sciences	Myelodysplastic syndrome (MDS)	2024
nivolumab (Opdivo®)	Bristol Myers Squibb	Renal cell carcinoma	2024
nivolumab and relatlimab-rmbw (Opdualag™)	Bristol Myers Squibb	Colorectal cancer	2024
pembrolizumab (Keytruda®)	Merck	Biliary tract cancer	2024
pembrolizumab (Keytruda® SC)	Merck	Non-small cell lung cancer	2024
sasanlimab	Pfizer	Bladder cancer	2024
evorpacept	ALX Oncology Zymeworks	Gastric cancer	2025
favezelimab	Merck	Colorectal cancer	2025
tebotelimab	MacroGenics	Gastric cancer	2025
fianlimab	Regeneron Pharmaceuticals Sanofi	Melanoma	2026
cetrelimab	Janssen	Bladder cancer	2026
vobramitamab duocarmazine	MacroGenics	Prostate cancer	2026
zimberelimab	Arcus Biosciences	Non-small cell lung cancer	2026

Expanding indications and greater utilization

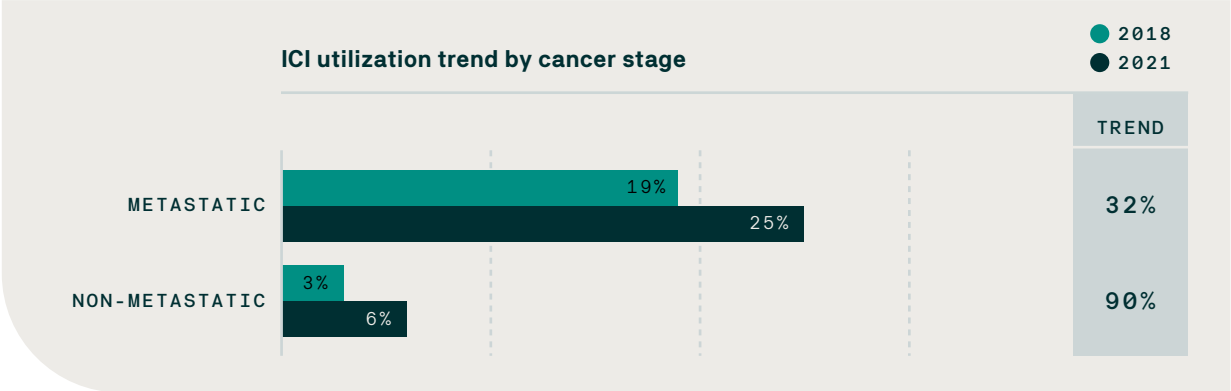
Our data shows ICI use **increased 47.5%** overall from 2018 to 2021

According to Evernorth Research Institute proprietary data, from 2018 to 2021, ICI use among patients receiving oncology drugs increased by 47.5% from 8.2% to 12.1%. This increase is primarily due to expanded indications for ICI use and specifically for use in treating breast cancer (825% increase), colorectal (100% increase) and prostate (100%) cancer.



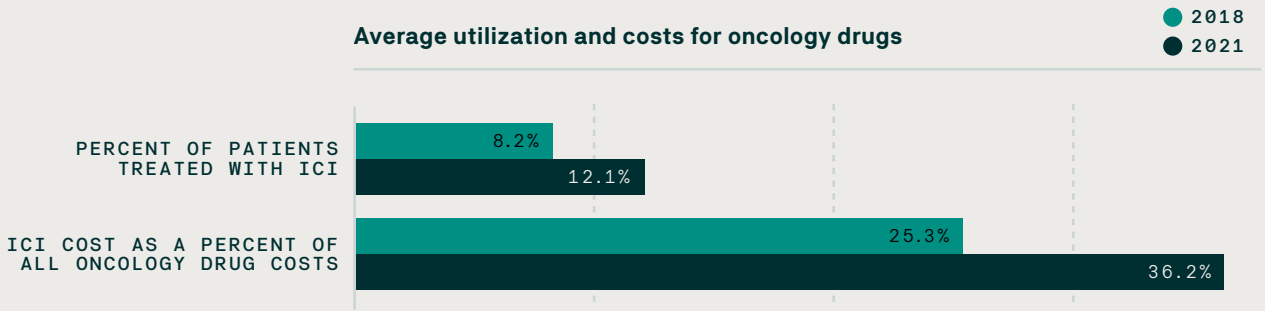
Increasingly, ICIs are being indicated for **earlier stage** cancers[11]

While only 3.7% of patients with breast cancer were treated with an ICI in 2021, this number is significant as breast cancer is the most prevalent cancer in the nation, with 266,000 new cases driving almost 50,000 deaths per year.[10] Historically, ICI use has been limited to treating advanced stage cancers. However, increasingly ICIs are being indicated for earlier stage cancers.[11] In fact, ICI utilization for non-metastatic cancers increased 90% from 2018 to 2021 compared to a 32% increase in usage for metastatic cancers.



More than 1/3 of total oncology drug spend is driven by ICI use

As ICI use has increased, so has ICI drug spend, from 25.3% to 36.2%, or over one third of total spend on oncology medication treatments. In 2021, the average drug cost for a patient treated with an ICI was $132,582, versus $26,095 for a patient not treated with an ICI.



5.1x higher costs for ICI treatment versus other oncology drug treatment

	2018	2021
Number of patients treated with any oncology drug, including ICI	138,591	172,159
Number of patients treated with ICI	11,364	20,831
A: Average cost per patient treated with ICI	$124,722	$132,582
B: Average cost per patient treated with other oncology drugs	$27,249	$26,095
Ratio (A/B)	4.6	5.1

ICIs: A real-world perspective

In this report, the Evernorth Research Institute analyzed ICI and other cancer medication utilization and cost data from a commercially insured population of approximately 50 million lives, sourced from a nationally representative health insurance claims database.

We also analyzed data from a more narrow cohort of patients with metastatic lung cancer who were treated with one or more infusions of pembrolizumab, the ICI most commonly used for this indication.

Three key insights emerged, offering actionable intelligence to help plans optimize cancer care:

INSIGHT 01

The infusion setting for ICI treatment is a major cost driver

INSIGHT 02

Health disparities and genomic testing prior to initiation greatly impact therapy

INSIGHT 03

Applying evidence-based guidelines for ICI therapy can help prevent wasteful spending

INSIGHT

01

The infusion setting for ICI treatment is a major cost driver

Nearly 2/3 of ICI treatment occurred in an outpatient hospital setting in 2021, resulting in an incremental **increase of almost $70,000** per patient

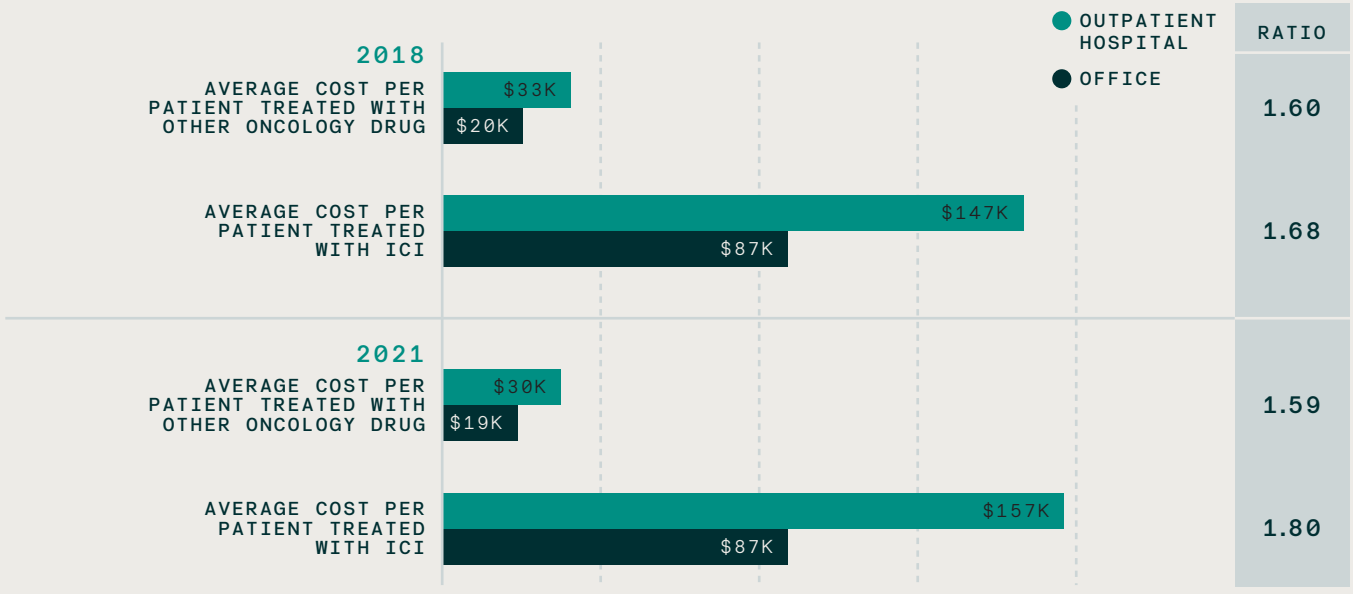
The rise in overall cancer drug spend is driven by the higher cost of ICIs relative to other oncology drugs and is exacerbated by a shift to more expensive treatment facilities. Outpatient hospital infusions are associated with an 80% higher oncology drug cost for ICI patients, without any difference in number of infusions, dosing or quality.

Yet, the percent of ICI treatments taking place in an outpatient hospital setting increased from 63% in 2018 to 66% in 2021. This is in part due to the acquisition of community oncology practices by hospitals and venture capital firms.

Between 2019 and 2021, accelerated by the COVID-19 pandemic, there was an 8% increase in the number of hospital-owned practices, with 4,800 physician practices acquired. By January 2022, hospitals owned more than one-quarter of physician practices.[12]

Average utilization and costs for oncology drugs in outpatient hospital setting vs. office setting, 2018–2021

	2018 OUTPATIENT HOSPITAL	2018 OFFICE	2021 OUTPATIENT HOSPITAL	2021 OFFICE
Percent of patients treated with any oncology drug	59%	40%	65%	34%
Percent of patients treated with ICI	8.8%	7.4%	12.2%	12.1%



INSIGHT

02

Health disparities and genomic testing prior to initiation greatly impact therapy

After a cancer diagnosis, genomic testing for key biomarkers is mandatory for all patients with advanced non-small cell lung cancer to determine the most appropriate treatment.[13] These tests can identify patients who would benefit from ICI therapy versus those who would benefit from alternative targeted therapies. Most cancers present with no targetable mutations and immunotherapy becomes the mainstay of treatment. To improve outcomes, it is critical to ensure ICIs are available to those who would benefit from treatment.[14]

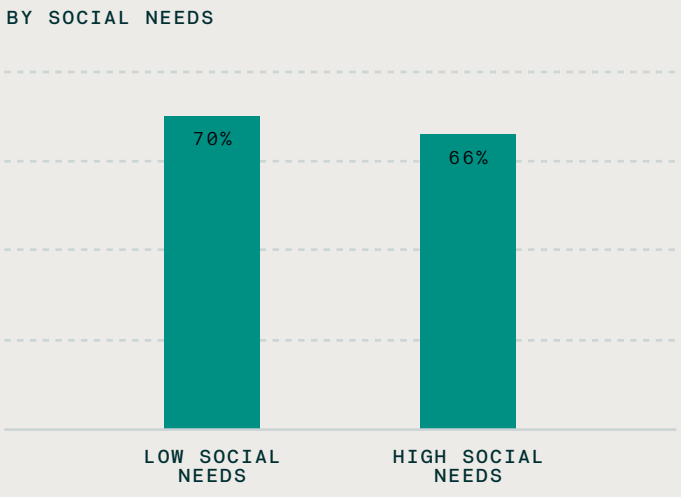
Nearly 1/3 of patients initiating ICI treatment show no evidence of prior biomarker testing

Despite the recommendations, when initiating treatment with pembrolizumab, approximately one third of patients show no evidence of prior biomarker testing.

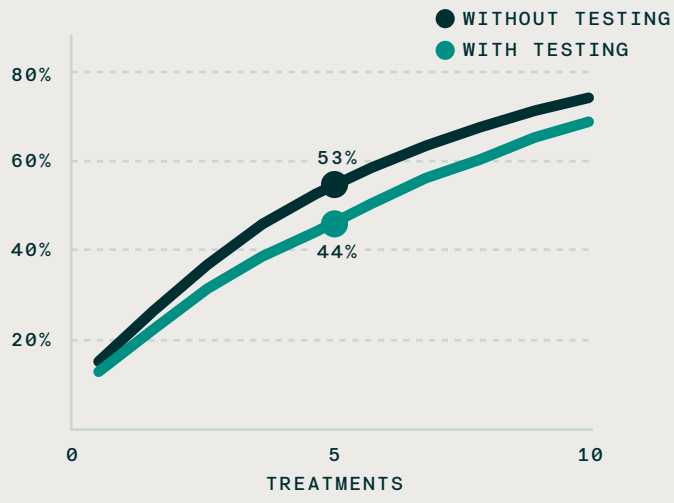
This effect is magnified in patients living in communities with higher social needs, (i.e., lower income, educational attainment, limited transportation options, etc). Compared to people living in communities with lower social needs, people with higher social needs were less likely to receive the required genomic testing.

Those patients with no evidence of testing prior to beginning ICI use were more likely to discontinue ICI therapy, particularly in the early stages of treatment, suggesting a lack of response to pembrolizumab treatment for many of these patients. For example, at the fifth treatment, 53% of patients without testing discontinued ICI therapy compared to 44% of tested patients. By identifying the most appropriate targeted treatment upon diagnosis, providers can avoid prescribing ICI treatment when tests indicate it isn't right for the patient.

Genomic testing in patients before starting ICI use



ICI discontinuation rate is higher in patients without genomic testing



INSIGHT

03

Applying evidence-based guidelines for ICI therapy can help prevent wasteful spending

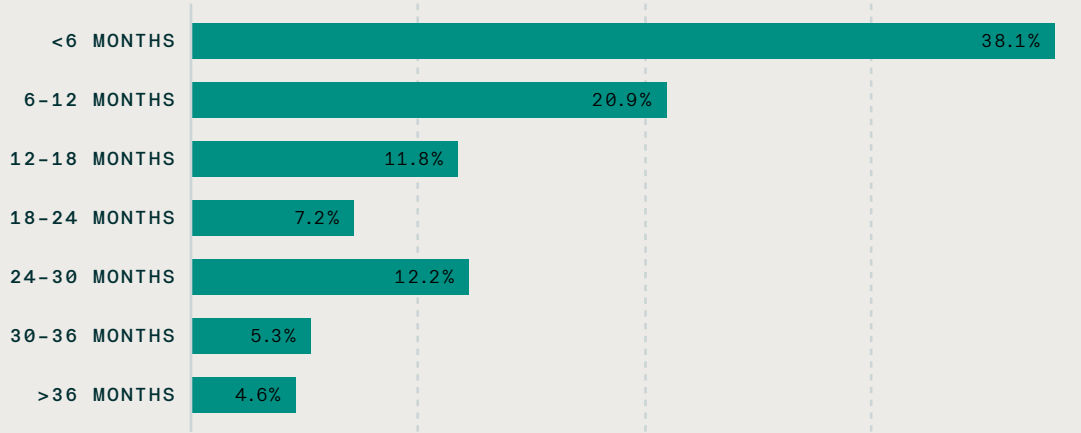
The FDA label and National Comprehensive Cancer Network recommend a maximum ICI treatment duration of 24 months for advanced stage non-small cell lung cancer.[15] A recent study comparing progression-free advanced lung cancer patients who discontinued ICI treatment at two years to those who continue treatment found no evidence to suggest that indefinite immunotherapy improves survival.[16]

Reduce waste by stopping ICI infusions after two years when their use is no longer recommended

To determine how well this guidance is followed in a real-world setting, we identified patients with evidence of continued benefit coverage and regular infusions without a treatment gap of eight weeks or more. Within this patient population, 22% received at least one infusion after the two-year threshold and 5% continued to receive infusions for more than three years.

This data identifies a strong opportunity to reduce waste by stopping ICI infusions after two years when their use is no longer recommended.

Pembrolizumab episode length in metastatic lung cancer patients



Where end-of-life scenarios can be identified, supportive care therapy options may be initiated **in place of more aggressive treatment**

Similarly, aggressive end-of-life care can be harmful to patients and their families, reducing quality of life while increasing both financial hardship and wasteful spending.[17] Making treatment decisions for patients with more advanced cancer is further challenged by a lack of reliable evidence. Patients with poor performance status are typically excluded from clinical trials in favor of higher-functioning patients.[18] A recent study found that ICI therapy did not improve survival outcomes for trial-ineligible patients.[19]

Yet, there is evidence to suggest that ICIs continue to be used for patients who are entering end-of-life scenarios. Within our population, 24% of patients discontinued ICI therapy after one or two infusions. Of those, 35% entered hospice within 90 days of their initial ICI infusion. In cases where end-of-life scenarios can be identified, supportive care therapy options may be initiated in place of more aggressive treatment.

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Final thoughts

The introduction of immune checkpoint inhibitor drugs has proven to be a game changer for cancer care, reflected in their rising utilization since 2018. When used appropriately, ICI therapy can provide significant benefits over alternative therapy options. However, the site of infusion may drive greater costs, while suboptimal conditions may result in waste and can even worsen clinical outcomes.[19]

As the use of ICIs continues, so will their impact on total spend, with higher costs per infusion being compounded by a rapidly expanding patient base, a trend toward outpatient hospital care, and a longer average time in treatment.

The intelligence in this report is designed to help plans address these current trends in oncology. By identifying suboptimal ICI usage and providing actionable insights, our hope is more appropriate use of ICIs will improve patient outcomes and reduce waste.

Taking the next step

Contact us today for more details on our report. Let us help you leverage these insights to optimize cancer care for your population.

Methodology

Data

Data came from the Komodo Healthcare Map—a nationally representative, open-source, longitudinal, and de-identified claims database of more than 320 million insured individuals from all demographic and socioeconomic groups throughout the United States in 2017 through 2021. Drawing open and complete data from both providers and payers, the Komodo Healthcare Map provides a near real-time view of the entire patient journey—including medical and pharmacy services delivered in-network, out-of-network, through a specialist, hospital, or retail clinic, among others.

Population

For the analysis on trends in utilization and cost of ICIs, 689,030 unique medical oncology patients with complete data and commercial insurance coverage were identified in the Komodo database from January 2018 to December 2021. Medical oncology patients were defined as those with any cancer diagnosis and any CPT code for medical oncology drugs on the same medical claim in a calendar year. Only the primary diagnosis and the first two secondary diagnoses on each medical claims were used to identify medical oncology patients. Patients were defined as having commercial insurance coverage if they had at least one day of commercial insurance coverage in a calendar year. Open-source patients were excluded in this present study due to their incomplete data. Patients who were only on a supportive medical oncology drug during the calendar year (n = 223,220) or those with missing allowed amounts for medical oncology drugs (n = 6,654), even after imputation (discussed in more detail shortly), were excluded from the study. The data were then organized as annual files. Each patient could be included in multiple calendar years if they met all the inclusion/exclusion criteria during that year. The final sample included 459,156 eligible medical oncology patients who used any medical oncology drug during the 2018–2021 period (138,591 patients in 2018, 163,500 patients in 2019, 172,269 patients in 2020, and 172,159 patients in 2021).

For the analysis on patient journey, the methodology from the trends populations was applied to identify medical oncology patients and cancer type within the Komodo commercial closed population. 17,089 patients with one or more pembrolizumab infusions between January 2017 and June 2022 were identified among medical oncology patients classified as lung cancer. To isolate the patients further to ensure metastatic disease, we excluded patients if either of the following were true within 90 days of their index pembrolizumab infusion: fewer than two dates of service with an ICD diagnosis code for secondary malignancy or a recent history of radiation therapy longer than 14 treatment fractions. This left a final sample population of 5,588. Patients were indexed on the date of their first pembrolizumab infusion and tracked for the remainder of the study period (i.e., one episode per patient). For the sub-analysis that investigated patients with excessive length of therapy, we selected 1,172 patients with episodes of pembrolizumab initiating between January 2017 and June 2020 who survived for at least two years.

Measurements

Treatment type: In each calendar year, patients were categorized into two mutually exclusive groups based on their recorded use of ICIs—those who used any ICI in a year and those who used any other medical oncology drug.

Primary cancer type: In each calendar year, patients were assigned a primary cancer type that had the highest number of visits. In the presence of ties between multiple cancer types, the cancer type with the highest number of medical oncology claims was selected.

Metastatic status: For the section on ICI utilization and trends, a patient was classified as being metastatic in a calendar year if they had any diagnosis for secondary cancer (of any cancer type) at three or more visits in that year. Only the primary diagnosis and the first two secondary diagnoses on each medical claims were used to identify metastatic patients. For the patient journey section, the same secondary metastatic codes were used but the requirement was two or more service dates in a lookback period of 90 days.

Primary place of service: In each calendar year, patients were assigned a primary place of service that had the highest number of visits for medical oncology. In the presence of ties, the place of services with the highest number of medical oncology claims was selected. Place of service was categorized in this study as outpatient hospital and others (in which office accounts for 95% of visits).

Age: Categorized in this study as 0–17, 18–34, 35–44, 45–54, 55–64, 65–74, and 75+. Age was calculated at the end of each calendar year.

Sex: Male or female.

Social determinants of health (SDOH) index: The SDOH was derived from open source data (e.g., U.S. Census and American Community Survey) and advanced analytical techniques such as unsupervised machine learning (UML), variable clustering, and contribution-based weight allocation. In short, a series of characteristics were derived for each census block and mapped into six domains: economy, education, infrastructure, health, culture, and food access. Using machine learning and advanced analytic methods, each domain was assigned a contribution weight, and was then aggregated to compute an overall SDOH score for each census block. The SDOH score was further aggregated to the first three digits of a zip code level—the lowest geographic identifier available in the Komodo data—by calculating a population-weighted average of the SDOH score across all census blocks in an area. A higher SDOH score represented a higher level of social needs. The EGSDI score was then categorized into low, medium, high, and very high based on its quantile distribution.

Region: Patient's region of residence in each calendar year, categorized as Northeast, South, Midwest, West, and others (e.g., U.S. territories).

Allowed amount: The allowed amount associated with each medical oncology drug. Approximately 70% of drugs had missing allowed amounts. We imputed missing allowed amounts using the average allowed amount from drugs with complete data, matched by drug name, place of service, cancer type, region, and calendar month and year in which the treatment took place.

Early discontinuation of therapy: For the patient journey section, patients were identified as discontinuing early if there were two infusions of pembrolizumab or less within 90 days of index infusion.

Emergency Department (ED): Patients were identified as entering an ED with one or more occurrence of ANY of the below in medical claims:

+ **Revenue code list:** 0450, 0451, 0452, 0456, 0459, 0981
+ **Place of service:** 23
+ **CPT/HCPCS code list:** 99281, 99282, 99283, 99284, 99285

Inpatient: Patients were identified as entering an inpatient facility with one or more occurrence of the below in medical claims:

+ **Revenue code list:** 0100, 0101, 0110, 0111, 0112, 0113, 0114, 0116, 0117, 0118, 0119, 0120, 0121, 0122, 0123, 0124, 0125, 0126, 0127, 0128, 0129, 0130, 0131, 0132, 0133, 0134, 0136, 0137, 0138, 0139, 0140, 0141, 0142, 0143, 0144, 0146, 0147, 0148, 0149, 0150, 0151, 0152, 0153, 0154, 0156, 0157, 0158, 0159, 0160, 0164, 0167, 0169, 0170, 0171, 0172, 0173, 0174, 0179, 0190, 0191, 0192, 0193, 0194, 0199, 0200, 0201, 0202, 0203, 0204, 0206, 0207, 0208, 0209, 0210, 0211, 0212, 0213, 0214, 0219, 1000, 1001, 1002

End of life/hospice: Patients were identified as entering hospice with one or more occurrence of ANY of the below in medical claims:

+ **Revenue code list:** (0115, 0125, 0135, 0145, 0155, 0235, 0650, 0651, 0652, 0655, 0656, 0657, 0658, 0659)
+ **Discharge status code list:** (50, 51)
+ **CPT/HCPCS code list:** (99377, 99378, G1082, Q5001, Q5002, Q5003, Q5004, Q5005, Q5006, Q5007, Q5008, Q5009, Q5010, S0271, S9126, T2042, T2043, T2044, T2045, T2046)

Genomic testing prior to therapy initiation within the patient journey population: Defined as one or more occurrences of any of the below CPT codes within 90 days of index pembrolizumab infusion. We restricted the population to those patients (N = 2,735) initiating therapy on or after January 1, 2020, as this is approximately when genomic testing became recommended prior to ICI initiation.

+ **CPT code list:** (81210, 81235, 81275, 81276, 81445, 81450, 81455, 88360, 0037U)

Excessive therapy: Defined in the patient journey population for those patients who have continuous ICI therapy for more than 24 months.

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