VALUE OF MEDICINES—LUNG CANCER

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UNDERSTANDING LUNG CANCER

Lung cancer, like all cancers, occurs when the body's own cells—specifically those that control cell growth and division or the repair of damaged DNA—mutate and multiply out of control. In more than 90 percent of lung cancer cases these genetic changes are acquired, not inherited.[1] Lung cancer is first defined by the appearance of cells affected, and presents as either small cell lung cancer (SCLC) or non-small cell lung cancer (NSCLC):

SMALL CELL LUNG CANCER (SCLC)[1,4,5]

- 15 percent of cases
- Grows quickly and is likely to metastasize; meaning the cancer has spread beyond the lung, most commonly to the liver, brain, bones, and adrenal glands
- 5-year survival rate for localized stage cancer is 27 percent, for distant stage the survival rate is three percent

NON-SMALL CELL LUNG CANCER (NSCLC)

- 85 percent of cases
- Further categorized by mutated cell type:
  - Adenocarcinoma is the most common form
  - Squamous cell carcinoma accounts for approximately 25 percent of lung cancers
  - Large cell carcinoma accounts for about 10 percent of NSCLC tumors
- 5-year relative survival rate for localized cancers is 61 percent while for distant stage the survival rate is six percent.

LUNG CANCER SUBTYPES

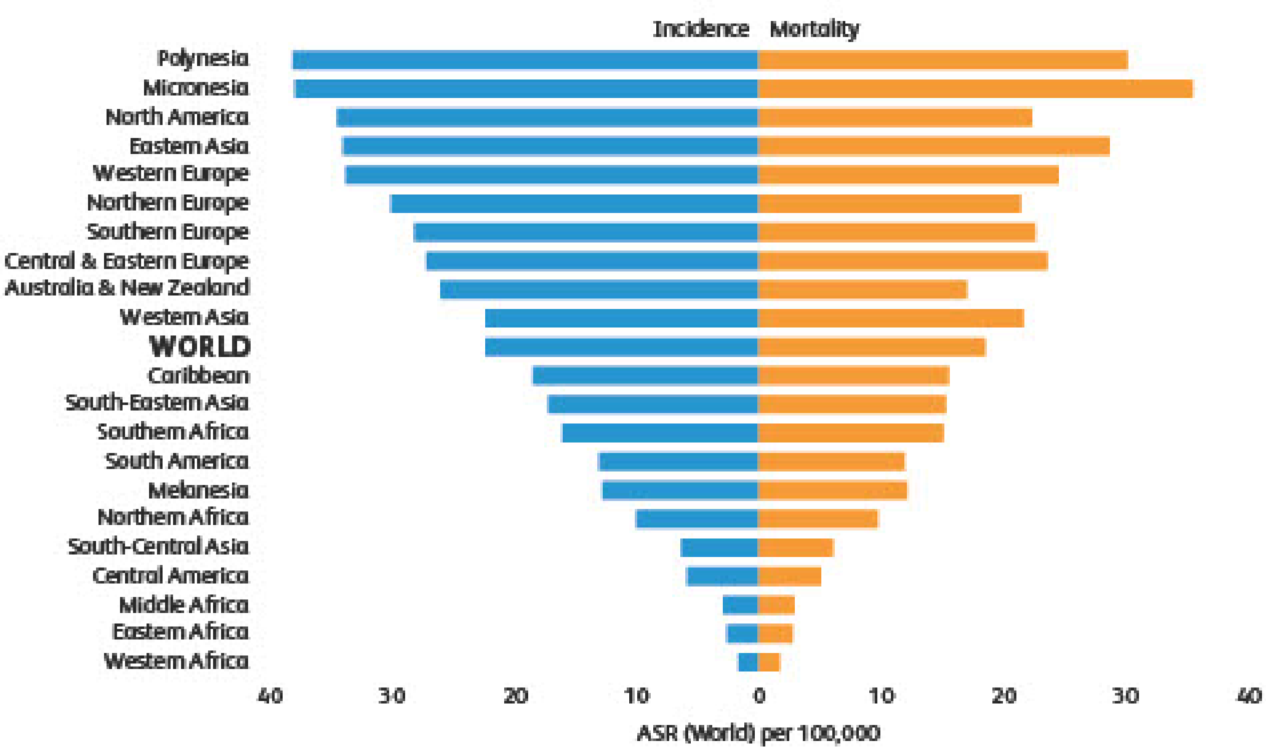
Recent research has further divided lung cancer by the specific genetic mutation driving tumor growth (also known as a biomarker).[6] Some of these (e.g., ROS, BRAF) are described further in **Prevention, Screening, and Treatment.**

GLOBAL INCIDENCE

Lung cancer is the second-most commonly diagnosed cancer in the world with 2.1 million new cases in 2018.[2,7] In that same year 1.8 million people died from lung cancer—more than twice as many as any other cancer type.[2] The global five-year survival rate (17.8 percent) is much lower than other leading cancers.[8]

The rates of lung cancer vary significantly among regions of the globe and even within them.

LUNG CANCER INCIDENCE AND MORTALITY RATES, 2018[9]



KEY TAKEAWAYS

Lung cancer is the most prevalent and lethal cancer globally, afflicting more than 2 million people annually. In the U.S., someone is diagnosed with lung cancer every 2.3 minutes.[1]

Lung cancer healthcare costs exceed $10 billion per year in the U.S., the E.U., and China each.[2]

Cancers occur when mutations build up in genes that control cell growth and repair. While inherited genetics can be a factor, most mutations that drive lung cancer are acquired during a person's lifetime.[3]

For a large portion of patients, risk factors for lung cancer can be genetic or acquired. Acquired risk factors include cigarette smoking, environmental carcinogens, such as exposure to radon, and other respiratory diseases. For others, lung cancers can develop with no known risk factors for the disease.

Research advances are leading to the development of biomarker-driven therapies aimed at genetic drivers of tumor growth and several immunotherapies aimed at a patient's own immune system. Advances in research and development will continue to create new options for treatment.

COSTS OF LUNG CANCER

Lung cancer imposes significant costs on patients, caregivers, and societies everywhere. These include direct costs such as provider office visits, hospitalization, surgery, radiation, and medications including chemotherapy; and indirect costs including lost worker productivity from illness and early mortality.

BRAZIL

A 2018 study found, for 251 public hospital patients, the average cost of NSCLC was $5647 USD, with 71% of costs being associated to outpatient care. The main components of cost were hospital stays (22.6%), radiotherapy (15.5%) and chemotherapy (38.5%).[15]

CANADA

In 2011, direct medical costs for asbestos-related lung cancer were nearly $C 34,000 per person diagnosed. Lost productivity and other indirect costs exceeded $C 261,000 per person.[14]

CHINA

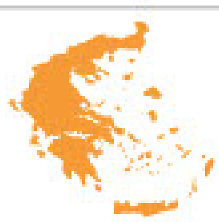
2015 estimated direct medical costs of lung cancer exceeded 64.2 billion RMB ($10.3 billion USD), or about 2 percent of China's entire medical costs that year. Indirect lung cancer costs were more than 424.3 billion RMB ($68.1 billion USD).[17]

EUROPEAN UNION

A review of 2015-2016 financial and medical data found direct costs of caring for patients with lung cancer (including primary care, hospital inpatient/outpatient care, and drugs/oxygen) amounts to more than €3 billion per year.[10]

GERMANY, FRANCE, AND THE UNITED KINGDOM

A 26-month study of the surgical removal of cancerous tissue in stage IB-IIIA NSCLC estimated direct annual costs of €575 million in Germany, €478 million in France, and €326 million in the UK.[11]



GREECE

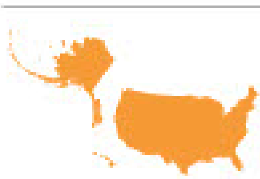
A 32-month study of 113 lung cancer patients counted €1.85 million in direct costs and more than 27,000 days of lost productivity.[12]

JAPAN

A 2009 study of 20,567 lung cancer patients found average total charges of $6015 USD in SCLC and $6993 in NSCLC.[16]

MOROCCO

Approximately 3,500 new cases of lung cancer occur each year, with 96 percent diagnosed at locally advanced or metastatic stages III and IV. Total medical costs were estimated in 2012 at $12 million USD.[18]



UNITED STATES

Direct spending on lung cancer care in 2018 exceeded $14.1 billion, a more than $1 billion increase over 2014.[13]

LUNG CANCER CAUSES AND RISK FACTORS

Research has found that environmental and lifestyle factors can expose people to carcinogens and increase the risk of developing lung cancer; the greatest risk factor being long-term tobacco smoking. For the approximately 20 percent of lung cancer patients that have never smoked or used tobacco the causes can range from genetic mutations to air pollution to lung diseases like tuberculosis.[19]

TOBACCO

Cigarette smokers face five to ten times the risk of lung cancer as non-smokers, while second-hand smoke exposes non-smokers to a 20 percent increased risk.[3,20] Smoking contributes to 80 percent of lung cancer deaths in women and 90 percent in men.[21] The causal link between smoking and cancer was established more than 50 years ago, and numerous public health campaigns have drawn attention to it since.[22] While these have helped bring the rates of cigarette smoking down, they may have contributed to lung cancer stigma—the belief that a person caused their own cancer.[23] Studies and surveys have associated lung cancer stigma with delays in medical help-seeking behavior.[24] Considering lung cancer's high mortality and costs, delaying diagnosis and treatment can be detrimental.

ENVIRONMENTAL FACTORS

Ten to fifteen percent of people who get lung cancer have never smoked tobacco.[25] The leading environmental cause of lung cancer is radon, an odorless, colorless gas that can contaminate indoor air.[26] Estimates suggest that radon causes between 3 to 14 percent of all lung cancers in a country, depending on the national average radon level and smoking prevalence.[26]

ENVIRONMENTAL FACTORS LINKED TO LUNG CANCER[3]

GENETIC AND OTHER FACTORS

Studies show that people with a family history of lung cancer have two to four times the risk of lung cancer versus those without, even after controlling for smoking and other factors.[3] Research is ongoing into the specific chromosomes that may make someone more susceptible to lung cancer. People with other lung diseases including COPD, asthma, and tuberculosis also face a significantly increased risk.[19]

EXPOSURE TO MULTIPLE CARCINOGENS CREATES COMBINED EFFECTS

Exposure to multiple risk factors can increase lung cancer risk even further:

- Cigarette smokers who also have significant exposure to radon face 25 times the risk of those who are not exposed to either.[3]
- Asbestos fiber inhalation found in the working environment, ambient air in the vicinity of point sources such as factories handling asbestos, or indoor air in housing and buildings containing friable (crumbly) asbestos materials is estimated to cause 10,000 lung cancer and mesothelioma deaths annually in the U.S.[3]
- Studies also show a combined effect relationship between cigarette smoking and asbestos exposure.[3]
- There is an established combined effect between family history and smoking, with smoking relatives of lung cancer patients having a higher risk of lung cancer than either nonsmoking relatives of lung cancer patients or smokers with a lack of lung cancer in their family.[3]

PREVENTION, SCREENING, AND TREATMENT

PREVENTION

There's no sure way to prevent lung cancer, but environmental and lifestyle choices reduce risks.[27]

- DON'T SMOKE
- AVOID SECONDHAND SMOKE
- TEST YOUR ENVIRONMENT FOR RADON AND OTHER CARCINOGENS

The cancer death rate rose during most of the 20th century: however, declines in smoking, as well as improvements in early detection and treatment, have resulted in a continuous decline in the cancer death rate since its peak in the U.S. of 215.1 deaths per 100,000 population in 1991. The overall drop of 29 percent as of 2017 (152.4 per 100,000) translates into an estimated 2.9 million fewer cancer deaths than if rates had remained at their peak.[28]

29% reduction in cancer death rate from 1991–2017*

2.9 million lives saved

*this decline is primarily the result of reductions in smoking and advances in early detection and treatment

SCREENING

Yearly screening for individuals at high-risk can reduce overall lung cancer death by 20 percent. Recommendations include conducting a low-dose CT scan for persons between the ages of 55 and 74 years, with some guidelines extending the criteria for patients up to the age of 80 years or starting from the age of 50 years if other risk factors for lung cancer exist.[29]

Those not considered at high risk but who have other lung cancer risk factors may still want to discuss with their health provider options for screening and monitoring their lung health.[30]

HIGH RISK IS DEFINED AS:

- age 55 to 80
- with a 30 pack-year smoking history, and
- currently smoke or have quit within the past 15 years

TREATMENT

Each lung cancer case is as unique as the patient afflicted, and treatment journeys will vary. Some pathways include the following:

TREATMENT PATHWAY[31]

NON-METASTATIC	METASTATIC	METASTATIC BIOMARKER DRIVEN
Surgery	Chemotherapy & Immunotherapy	Biomarker-driven therapy, alone or with chemotherapy
Radiation	Second-line agent on tumor progression	Second-line agent on tumor progression
Chemotherapy	Radiation (palliative)	Radiation (palliative)
	Best supportive care	Best supportive care

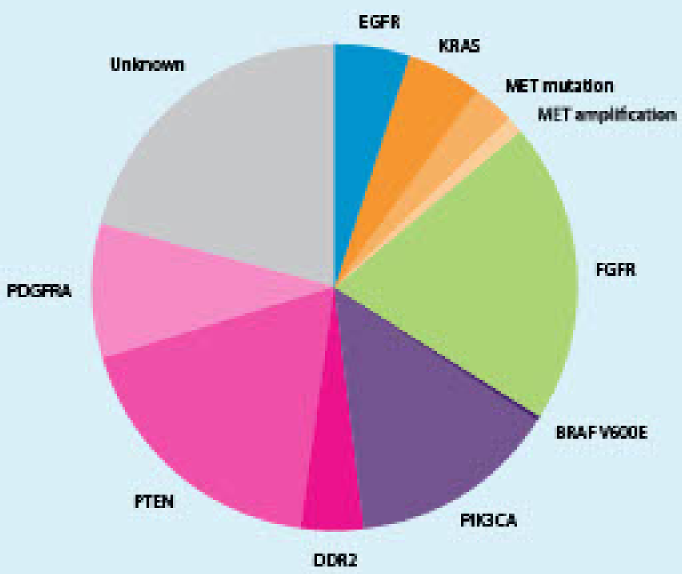
These pathways are changing fast. Until recently, the standard of care for metastatic NSCLC was four to six cycles of chemotherapy, and to offer second-line therapy upon tumor progression.[32] While platinum chemotherapy remains an important agent for treating advanced lung cancer, there are new options that can be explored for front-line treatment.

PRECISION MEDICINE

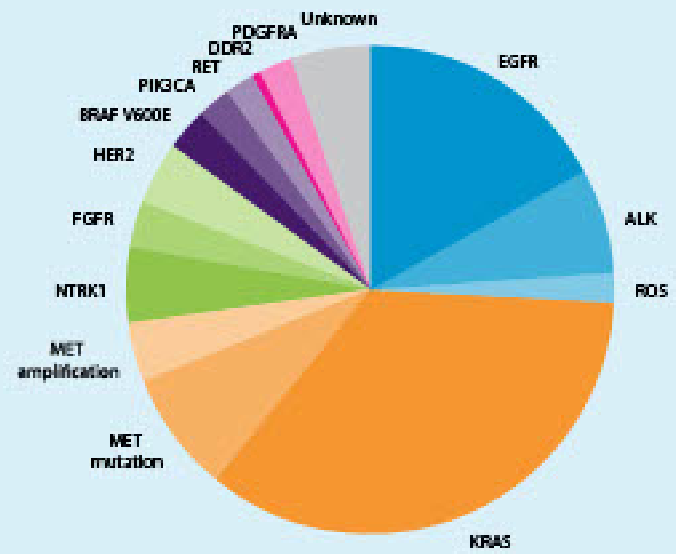
Precision medicine focuses on disease mechanisms and developing treatments to target them.[33] Currently in NSCLC there are at least ten known and testable biomarkers. Biomarkers are identified through additional screening of biopsy tissue with specialized tests, known as companion diagnostics. Additionally, more than half of lung adenocarcinoma cases (the most common subtype of NSCLC) have an identifiable molecular driver. While biomarkers continue to be researched, five have approved drug therapies: epidermal growth factor receptor (EGFR), anaplastic lymphoma kinase (ALK), ROS, BRAF, and neurotrophic tyrosine receptor kinase (NTRK).[6,34]

BIOMARKERS AND THEIR FREQUENCY IN NSCLC TYPES[35,36,37,38]

SQUAMOUS CELL CARCINOMA



ADENOCARCINOMA



BIOMARKER*

- **EGFR**
- **ALK**
- **ROS**
- KRAS
- MET mutation
- MET amplification
- **NTRK1**
- FGFR
- HER2
- **BRAF V600E**
- PIK3CA
- RET
- DDR2
- PTEN
- PDGFRA

*bolded biomarkers are FDA-approved biomarker-driven therapy in adenocarcinoma

For patients with lung cancer where the tumor's genetic driver can be attacked, these drugs can slow cancer's progression and potentially extend lives—providing invaluable benefits for patients and families.

IMMUNOTHERAPY

The immune system is a complex network of organs, cells and molecules that protects the body from:[39]

- **INFECTIOUS AGENTS, SUCH AS BACTERIA AND VIRUSES**
- **ABNORMAL CELLS PRODUCED BY THE BODY**

THE IMMUNE SYSTEM INCLUDES:[39]

Adaptive immunity:
Learned defense system in response to a specific foreign substance. This includes:

- B-cells that produce antibodies to destroy threats, and
- T-cells that identify and directly destroy abnormal cells, including cancer

Innate Immunity:
Always-on defense system that provides immediate protection itself against foreign organisms and toxins

IMMUNOTHERAPIES ENHANCE THE IMMUNE SYSTEM'S ABILITY TO FIGHT AGAINST THREATS. THESE INCLUDE:[39]

General therapies that enhance the immune system overall, such as interferons and colony stimulating factors[39]

Cancer-targeting therapies that modify the immune system to recognize that the cancer is foreign to the body and needs to be attacked[39]

Currently approved cancer-targeting immunotherapies target cellular checkpoints[39]:

PD-1/PD-L1, a molecular "brake" that prevents the immune system from attacking cancer cells

CTLA-4, a protein that normally keeps the immune system in check

Recent studies in patients with advanced NSCLC show prolonged survival with immunotherapy versus chemotherapy.[40] One study found a fivefold advantage in 5-year survival rates while a second study showed a benefit in overall and progression-free survival with immunotherapy at five years. The 5-year overall survival was 13.4 percent compared to 2.6 percent. While current immunotherapies do not work for every patient, the science is advancing with greater numbers of lung cancer patients eligible for checkpoint inhibitor therapy.[41]

VALUE OF TREATMENT

The American Cancer Society found that lung cancer mortality rate in the U.S. declined 4.3 percent *annually* from 2013 to 2017.[28,42] "We found increases in survival for lung cancer at every stage in diagnosis," said Rebecca Siegel, the study's lead author and scientific director of surveillance research at ACS. In addition to reduced rates of smoking, she credited much of the decline to improvements in treatments and tumor scanning/assessment.[43]

There's potential for more progress as newer treatments gain awareness: this is vital, as lung cancer still caused more deaths in 2017 in the U.S. than breast, prostate, colorectal, and brain cancers combined.

FUTURE

Early Detection through improved CT scanning, marker detection via blood sample, and computer machine learning and deep learning.[44,45]

Precision Medicine and Immunotherapy will remain key areas of research in lung cancer, with hundreds of clinical trials ongoing exploring the deeper drivers of tumor growth. Drug combinations that target multiple mutations and cancer pathways benefit some patients who do not respond to a single therapy alone and may overcome or delay the development of treatment resistance; researchers expect more of this approach going forward.

Because tumor mutations vary between patients, future therapies that target them may need to be customized and patient-specific to be most effective.[46]

Companion diagnostics are essential to matching patients with biomarker-driven therapies, but challenges remain in test variability and access.

More options mean more complexity, and providers will need to evaluate a greater number of data points than ever to effectively deliver personalized medicine treatments.

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