

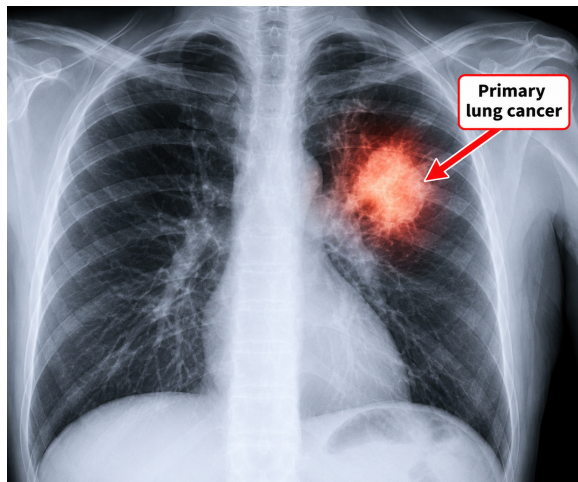
Lung Cancer in the Era of Precision Oncology: Epidemiology, Molecular Biology, and Therapeutic Challenges (Part 1).

Paul Marik · Cancer & Metabolic Healing · October 3, 2026

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Cancer Playbook: Smarter Strategies for Treatment

Lung cancer remains one of the greatest challenges in modern oncology. Despite remarkable advances in early detection, molecular diagnostics, surgery, radiotherapy, targeted therapy, and immunotherapy, it continues to be the **leading cause of cancer-related mortality worldwide**, accounting for approximately **2.5 million new cases and 1.8 million deaths annually**. More people die from lung cancer each year than from breast, colorectal, prostate, pancreatic, and liver cancers combined. Although mortality rates have declined modestly in many high-income countries because of reductions in tobacco use and improvements in treatment, the global burden of disease remains substantial owing to population aging, continued smoking in many regions, environmental pollution, and increasing recognition of lung cancer in never-smokers.



Approximately **85%** of lung cancers are classified as **non-small cell lung cancer (NSCLC)**, with the remaining **15%** comprising **small cell lung cancer (SCLC)**. NSCLC includes three principal histological subtypes: adenocarcinoma, squamous cell carcinoma, and large-cell carcinoma. Over recent decades, adenocarcinoma has become the predominant subtype worldwide, largely replacing squamous cell carcinoma. This epidemiological shift is thought to reflect changes in cigarette design and smoking behavior, increasing exposure of peripheral airways to tobacco carcinogens, and the growing incidence of lung cancer among never-smokers. Adenocarcinoma is also the histological subtype most strongly associated with actionable oncogenic driver mutations, making it the principal focus of modern precision oncology.

Cigarette smoking remains the dominant risk factor, responsible for approximately **80–90%** of lung cancers. However, lung cancer is increasingly recognized as a heterogeneous disease with multiple environmental and genetic contributors. Radon exposure represents the second leading cause of lung cancer overall and the leading cause among never-smokers in many countries. Additional established risk factors include asbestos, silica, diesel exhaust, arsenic, chromium, nickel, ambient air pollution, chronic obstructive pulmonary disease (COPD), pulmonary fibrosis,

prior thoracic irradiation, and inherited genetic susceptibility. Importantly, lung cancer arising in never-smokers has emerged as a distinct biological entity with unique molecular characteristics, epidemiology, and therapeutic responsiveness. If considered separately, lung cancer in never-smokers would rank among the most common causes of cancer-related death worldwide.

The prognosis of lung cancer is determined principally by disease stage at diagnosis, molecular subtype, and response to therapy. Patients diagnosed with Stage I NSCLC who undergo complete surgical resection may achieve five-year survival rates exceeding **80–90%**, emphasizing the importance of early detection through low-dose computed tomography (LDCT) screening. Unfortunately, most patients continue to present with locally advanced or metastatic disease, for which long-term survival remains poor. Although targeted therapies and immune checkpoint inhibitors have substantially improved outcomes for selected patients, advanced lung cancer remains an incurable disease in the vast majority of cases because of the inevitable emergence of therapeutic resistance.

Over the past two decades, the treatment of lung cancer has undergone a profound transformation driven by advances in molecular biology. Comprehensive genomic profiling is now standard practice for patients with advanced NSCLC, allowing treatment to be tailored according to specific oncogenic alterations. This shift from histology-based to molecularly guided therapy represents one of the greatest successes of precision oncology. Numerous actionable driver mutations have been identified, including alterations involving **EGFR, ALK, ROS1, RET, MET, BRAF, HER2, and NTRK**, each associated with highly effective targeted therapies. More recently, selective inhibitors of **KRAS G12C** have extended precision medicine to the most common oncogenic driver in Western lung adenocarcinoma.

Despite these remarkable advances, three biological subtypes dominate contemporary clinical practice because of their prevalence, distinct biology, and therapeutic implications: **KRAS-mutant NSCLC, EGFR-mutant NSCLC, and small cell lung cancer (SCLC)**.

KRAS-mutant NSCLC accounts for approximately **25–35%** of lung adenocarcinomas in Western populations and approximately **10–15%** in East Asian populations. The most common alterations occur at codon 12, particularly **G12C, G12D, and G12V**. Activated KRAS drives constitutive signaling through the RAF–MEK–ERK and PI3K–AKT–mTOR pathways, promoting proliferation, survival, metabolic reprogramming, angiogenesis, and invasion. KRAS-mutant tumors are strongly associated with cigarette smoking and frequently harbor co-mutations involving **STK11, KEAP1, and TP53**, which profoundly influence prognosis and responsiveness to immunotherapy. Although the development of selective KRAS G12C inhibitors represents a major therapeutic milestone, resistance develops almost universally through secondary mutations, bypass signaling, and metabolic adaptation.

EGFR-mutant NSCLC represents the second major molecular subtype and occurs in approximately **10–15%** of lung adenocarcinomas in Western populations and **40–60%** of East Asian patients. These tumors occur predominantly in women, never-smokers, and patients with adenocarcinoma histology. Most clinically relevant mutations consist of exon 19 deletions and the exon 21 L858R substitution, both of which confer sensitivity to epidermal growth factor receptor (EGFR) tyrosine kinase inhibitors (TKIs). Third-generation inhibitors such as osimertinib have transformed the natural history of EGFR-mutant lung cancer, producing prolonged progression-free survival and improved control of central nervous system metastases. Nevertheless, acquired resistance remains nearly universal and develops through secondary EGFR mutations, MET

amplification, activation of bypass pathways, epithelial-to-mesenchymal transition, histologic transformation to SCLC, and metabolic remodeling.

In contrast, **small cell lung cancer (SCLC)** is a biologically distinct neuroendocrine malignancy characterized by rapid proliferation, early metastatic dissemination, and one of the highest mortality rates among solid tumors. Nearly all SCLC tumors demonstrate inactivation of the tumor suppressor genes **TP53** and **RB1**, resulting in profound genomic instability. Unlike NSCLC, SCLC lacks routinely actionable driver mutations and remains largely dependent upon platinum-based chemotherapy and immune checkpoint inhibitors. Although initial response rates are high, relapse is almost inevitable, and median survival for extensive-stage disease remains poor. Recent molecular profiling has identified several transcriptionally distinct SCLC subtypes, suggesting opportunities for future therapeutic stratification, but effective targeted therapies remain limited. Although these three biological subtypes differ substantially in their genomic landscapes and therapeutic management, they ultimately converge upon many of the same downstream adaptive mechanisms. Regardless of the initiating oncogenic mutation, lung cancers exhibit enhanced glycolysis, mitochondrial plasticity, activation of the PI3K–AKT–mTOR pathway, chronic inflammation, angiogenesis, persistence of cancer stem cells, remodeling of the tumor microenvironment, and progressive immune suppression. These conserved biological processes enable tumors to survive therapeutic pressure, evolve resistance, and ultimately recur despite initially effective treatment.

This observation has important implications for the future of lung cancer therapy. Precision oncology has demonstrated that targeting individual driver mutations can produce remarkable clinical responses, yet durable disease control remains uncommon because tumors continuously adapt through redundant biological networks that extend well beyond the initiating mutation. Increasing evidence therefore supports a complementary systems biology approach that targets the shared metabolic and microenvironmental processes sustaining malignant progression. Rather than viewing lung cancer solely as a collection of genomic alterations, this perspective recognizes cancer as a **complex adaptive biological system** in which genetic, metabolic, stromal, and immunological networks interact dynamically throughout disease evolution.

Precision Oncology

The introduction of molecular profiling has fundamentally transformed the management of advanced non-small cell lung cancer (NSCLC). Unlike traditional chemotherapy, which was administered largely according to histological subtype, contemporary treatment is increasingly guided by the identification of specific oncogenic driver mutations. Current international guidelines recommend comprehensive molecular testing for all patients with advanced non-squamous NSCLC and for selected patients with squamous cell carcinoma, particularly never-smokers and younger individuals. This precision medicine approach has dramatically improved response rates, progression-free survival, quality of life, and, in many cases, overall survival.

Although numerous molecular alterations have now been identified, only a subset are currently considered actionable. Importantly, the success of targeted therapy depends on the continued dependence of the tumor on its initiating oncogenic driver. Unfortunately, almost all patients eventually develop acquired resistance through secondary mutations, activation of bypass signaling pathways, histologic transformation, or metabolic adaptation. Consequently, while targeted therapy has revolutionized lung cancer treatment, durable disease control remains uncommon.

COMMON ACTIONABLE MUTATIONS IN NON-SMALL CELL LUNG CANCER (NSCLC) and Their Specific Targeted Treatments

DRIVER ALTERATION	APPROX. FREQUENCY IN NSCLC	TYPICAL PATIENT PROFILE	APPROVED / PREFERRED TARGETED THERAPY (FIRST LINE UNLESS NOTED)	KEY RESISTANCE MECHANISMS (MOST COMMON)	KEY POINTS
 EGFR Mutations (exon 19 del, L858R)	10–15% (West) 30–50% (East)	 More common in women, never-smokers, Asian ethnicity, adenocarcinoma	Osimertinib (3rd generation TKI) ± Platinum-based chemotherapy (selected patients with extensive disease)	- Secondary EGFR mutations (e.g., T790M, C797S) - MET amplification - HER2 amplification - Bypass signaling (KRAS, BRAF, PI3K) - Histologic transformation to SCLC	  - Comprehensive molecular testing is essential for all patients with advanced NSCLC. - Targeted therapies yield high response rates and better quality of life. - Acquired resistance develops in almost all patients. - Combination strategies are critical to improve durability.
 KRAS Mutations (G12C, G12D, G12V, etc.)	25–35% (West) 10–15% (East)	 More common in smokers, adenocarcinoma	KRAS G12C: Sotorasib or Adagrasib (after prior therapy) Clinical trials: combinations with SHP2 inhibitors, MEK inhibitors, immunotherapy or chemotherapy	- Secondary KRAS mutations - Activation of alternative RAS isoforms - EGFR/MET amplification - Bypass signaling (PI3K, MAPK) - Metabolic reprogramming	
 ALK Rearrangements	3–7%	 Younger patients, never-smokers or light smokers, adenocarcinoma	Alectinib (preferred) Lorlatinib, Brigatinib (CNS activity with all agents)	- Secondary ALK mutations - Activation of bypass pathways - Histologic transformation	
 ROS1 Rearrangements	1–2%	 Younger patients, never-smokers or light smokers, adenocarcinoma	Entrectinib (preferred) Crizotinib, Repotrectinib (Active in CNS)	- Secondary ROS1 mutations - Activation of bypass pathways	
 RET Rearrangements	1–2%	 Younger patients, never-smokers, adenocarcinoma	Selpercatinib (preferred) Pralsetinib (Strong CNS activity)	- Secondary RET mutations - Activation of bypass pathways	
 MET Alterations (exon 14 skipping or amplification)	2–4% (exon 14 skip) 2–5% (amplification)	 Older patients, smokers or never-smokers, adenocarcinoma	Capmatinib or Tepotinib (for exon 14 skipping) Crizotinib or Capmatinib (for amplification)	- MET amplification (on prior EGFR TKI) - Secondary MET mutations - Activation of bypass pathways	
 BRAF Mutations (V600E, others)	2–4%	 Smokers or never-smokers, adenocarcinoma	Dabrafenib + Trametinib (Preferred combination) Encorafenib + Binimetinib (alternative)	- BRAF amplification - MEK mutations - Activation of bypass pathways	
 HER2 Mutations (ERBB2)	2–4%	 More common in never-smokers, adenocarcinoma	Trastuzumab Deruxtecan (T-DXd) (after progression on prior therapy)	- HER2 secondary mutations - Activation of bypass pathways	
 NTRK Fusions	<1%	 Younger patients, never-smokers or light smokers, adenocarcinoma	Larotrectinib or Entrectinib (Tumor-agnostic approval)	- Secondary NTRK mutations - Activation of bypass pathways	
 SMALL CELL LUNG CANCER (SCLC)	~15% of all lung cancers	 Typically heavy smokers, older age	Platinum (Cisplatin/Carboplatin) + Etoposide + Atezolizumab or Durvalumab followed by maintenance immunotherapy	Very limited actionable mutations Resistance mechanisms: - TP53 & RB1 loss (universal) - Genomic instability - Neuroendocrine plasticity	 NOTE Frequencies vary by ethnicity, smoking history, and geographic region. All therapies are subject to change with emerging evidence and regulatory updates.

CNS = Central Nervous System | TKI = Tyrosine Kinase Inhibitor | SCLC = Small Cell Lung Cancer | Data as of May 2026

Limitations of Precision Oncology

The success of targeted therapy represents one of the greatest achievements in modern oncology. Nevertheless, it also illustrates the principal limitation of mutation-centered treatment. Regardless of whether the initiating alteration involves EGFR, KRAS, ALK, RET, MET, or another oncogenic driver, resistance almost invariably develops through activation of common downstream adaptive mechanisms, including metabolic reprogramming, mitochondrial plasticity, epithelial-to-mesenchymal transition, remodeling of the tumor microenvironment, and immune escape.

These shared biological adaptations provide the rationale for the **Five-Axis Metabolic Trap** proposed in this review (see part 2). Rather than competing with precision oncology, this systems biology framework seeks to complement molecularly targeted therapy by simultaneously targeting the conserved metabolic and microenvironmental processes that enable tumors to survive despite successful inhibition of their initiating driver mutation. By integrating mutation-specific therapy with interventions directed at these shared adaptive pathways, it may ultimately be possible to achieve more durable disease control than either strategy alone. The Five-Axis Metabolic Trap is a systems-based therapeutic framework designed to apply continuous multi-target pressure to the interconnected metabolic networks that sustain malignant growth. Rather than replacing evidence-based surgery, radiotherapy, chemotherapy, targeted therapy, or immunotherapy, this approach seeks to complement conventional treatment through the rational integration of dietary intervention, repurposed pharmaceuticals, nutraceuticals, and immune restoration.