

REVIEW ARTICLE

Personalized treatment of the non-responder population: The biggest unmet clinical demand in precision medicine

Shu-Ti Lin, Sharon S. Yeh, and Chen Yeh*

OncoDxRx, Los Angeles, California, United States of America

Abstract

Current approaches to therapy design and treatment strategies fall short in addressing a critical challenge of precision medicine: only a small fraction of treated patients respond to precision-targeted drugs. An even more concerning limitation is our present inability to predict drug responses for non-responders—especially in life-threatening conditions such as aggressive cancers, where negative biomarker results may leave insufficient time to pursue alternative treatments. Consequently, accurately predicting therapeutic responses in these high-risk patients or identifying optimal candidates for specific therapies remains a pressing and unresolved clinical need. For years, clinicians have grappled with a fundamental question: Why do some patients experience dramatic—sometimes complete—clinical responses, while most see little to no benefit? The challenge lies in identifying non-responders early and determining what interventions could convert them into responders. Emerging research is now shedding light on why certain cancer patients fail to respond to precision therapies, offering hope for guiding patients and physicians toward more effective treatments. One particularly promising frontier is the use of gene–drug mapping technologies, which could revolutionize care by transforming non-responders into responders. Additionally, understanding the interplay between cancer cells and the immune system may unlock the full potential of precision medicine, bringing us closer to effective therapies for every cancer patient.

*Corresponding author:

Chen Yeh
(cyeh.oncodrx@gmail.com)

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1. Introduction

Cancer is one of the most significant global health challenges and a major cause of mortality worldwide. Encouragingly, advancements in early detection technologies, precision genetic therapies, and immunotherapies have contributed to declining death rates for several cancer types. Despite this progress, the battle against cancer continues, with the World Health Organization projecting a staggering 35 million new cases by 2050—a 77% surge compared to the 20 million cases reported in 2022.¹ Over the past decade, groundbreaking scientific discoveries have transformed our understanding of cancer development, paving the way for precision medicine. These advances have improved overall survival (OS) rates, yet significant challenges persist. Certain cancers remain notoriously difficult to treat, particularly once they metastasize. Researchers now

recognize that cancer's complexity—driven by its genetic diversity and ability to adapt—makes it exceptionally hard to eliminate.² Even when treatments initially succeed, the disease often returns, more aggressive and resistant than before.

Previously, tumors were viewed as uniform masses of rapidly dividing cells. However, we now know they are highly heterogeneous ecosystems composed of distinct subpopulations, or subclones, each with unique genetic mutations.³ These subclones vary in growth rates, treatment responses, and metastatic potential, contributing to the dynamic and unpredictable nature of cancer. This intra-tumor heterogeneity helps explain why some patients fail to respond to therapy or experience relapse.⁴ Under treatment pressure, resistant subclones may emerge through pre-existing mutations, cellular plasticity, or evolutionary adaptation. Cutting-edge computational and experimental tools now allow scientists to analyze individual tumor cells and track their evolution with unprecedented precision.⁵ These insights are revealing why certain therapies fail—and offering new strategies to outmaneuver resistance and improve patient outcomes. Collectively, a critical gap remains in improving outcomes for non-responder populations, who have long been excluded from the benefits of precision medicine. Addressing this unmet need requires intensified research efforts to develop more inclusive and effective treatment strategies.

2. A complex ecosystem

Cancer treatment has undergone a transformative shift in recent decades, moving from generalized therapies to precision medicine tailored to the unique molecular drivers of each patient's disease.⁶ Scientists worldwide are now working to decode the complex genetic diversity within and between tumors—known as intra- and inter-tumor heterogeneity—to expand the reach of personalized treatments.

Historically, molecular diagnostics relied on sequencing a small tissue sample from a single tumor biopsy. However, in highly heterogeneous cancers, this approach may miss critical genetic variations, leading to two key risks: overlooking a potentially effective therapy if the target mutation goes undetected, or selecting an inappropriate treatment based on a molecular feature that is not dominant across the tumor. Compounding this challenge, a tumor's molecular profile can evolve over time, requiring dynamic adjustments to treatment strategies.⁷

Although genomic mutations in cancer cells contribute to functional differences among subclones, they do not tell the whole story. Tumors thrive within a dynamic ecosystem—composed of immune cells, stromal cells,

blood vessels, extracellular matrix, and other factors—that actively shapes the behavior of malignant cells, even those with identical genetics.⁸ This intricate microenvironment introduces another layer of complexity to tumor heterogeneity. For instance, tumors can exhibit vastly different immune profiles, which critically influence their response to treatments like immunotherapy.

Recent research into tumor heterogeneity, evolution, and drug resistance has revealed that genetic diversity exists even in early-stage cancers—and progressively increases over time. Understanding these evolving landscapes is essential for developing more effective, personalized therapies. A central priority for precision medicine is developing methods to accurately map tumor heterogeneity and monitor its changes—ensuring therapies stay one step ahead of the disease's evolution.

3. Non-small cell lung cancer: Predominance of non-responders to precision medicine

In current clinical practice, lung cancer treatment is individualized according to stage, histology, and molecular profile, with surgery, radiotherapy, chemotherapy, targeted therapy, and immunotherapy used in different combinations⁹ (Table 1). For early-stage non-small cell lung cancer (NSCLC), surgery remains the cornerstone, often followed by adjuvant chemotherapy or immunotherapy if there is a high risk of recurrence. In patients who are not surgical candidates, stereotactic body radiotherapy provides excellent local control. For locally advanced disease, particularly stage III, concurrent chemoradiation is standard, and consolidation immunotherapy with durvalumab has become routine for unresectable cases. In metastatic disease, molecular testing is essential. Patients with actionable driver alterations, such as *EGFR*, *ALK*, *ROS1*, *RET*, *MET*, or *KRAS* G12C, are treated with targeted tyrosine kinase inhibitors (TKIs), while those without such mutations are considered for immunotherapy, either alone or in combination with chemotherapy, depending on programmed death-ligand 1 (PD-L1) expression levels. Small cell lung cancer, which is biologically distinct, is generally treated with platinum-based chemotherapy combined with immunotherapy, though relapse is common.

Patients with primary resistance lack an initial response due to innate genomic alterations or immune evasion, whereas those with acquired resistance relapse after prior benefit, driven by clonal evolution or bypass pathway activation. Despite these advances, primary non-response, or primary resistance, is a major challenge across all therapies.¹⁰ In chemotherapy, about 70% to 80%

Table 1. Rates of primary non-response and acquired resistance by therapy class in patients with non-small cell lung cancer

Therapy class	Primary non-response/ resistance rate	Acquired resistance rate (in responders)	Key determining factors
Targeted therapy (e.g., for <i>EGFR</i> , <i>ALK</i>)	~10–20%	~100% (eventually)	Presence of specific oncogenic driver; mechanisms of resistance (e.g., T790M, C797S in <i>EGFR</i>)
Immunotherapy (as a single agent)	~40–60% (highly variable)	~25–50%	PD-L1 tumor proportion score, tumor mutational burden
Chemotherapy (platinum doublet)	~70–80%	~100% (eventually)	Tumor histology, patient performance status
Immunotherapy plus chemotherapy	~50–55% (for PD-L1 low/negative)	Data evolving	Combination therapy improves response rates compared with chemotherapy alone, reducing non-response

of patients fail to achieve a meaningful response, with objective response rates typically in the 20–30% range. Immunotherapy has transformed outcomes for some patients, but the majority do not respond: approximately 40–60% of patients treated with programmed cell death 1 (PD-1) or PD-L1 inhibitors as monotherapy show no objective benefit, and even when combined with chemotherapy, a significant fraction—around 50–55%—still demonstrate primary resistance. Targeted therapies have higher initial efficacy, with response rates of 60–80% in patients with sensitizing mutations, but a small subset of patients exhibit intrinsic resistance due to co-mutations or tumor heterogeneity that prevent effective drug activity from the outset.

Acquired resistance is nearly universal in responders, though the timing and mechanisms differ by therapy.¹¹ For chemotherapy, resistance typically develops within a few months, as tumor cells adapt through enhanced DNA repair, drug efflux, or clonal selection. For targeted therapies, resistance emerges after a median of 9 to 18 months. In *EGFR*-mutant NSCLC, for example, secondary *EGFR* mutations such as T790M or C797S, *MET* amplification, and histologic transformation to small-cell carcinoma are common mechanisms. Similarly, tumors with *ALK* rearrangements treated with anaplastic lymphoma kinase (ALK) inhibitors can develop acquired resistance through secondary *ALK* mutations or activation of bypass pathways. Immunotherapy resistance is more complex: while some patients achieve durable responses lasting years, more than half of initial responders eventually relapse. Studies suggest that about 25–50% of patients who initially benefit from checkpoint inhibitors will develop acquired resistance, often within two years, though a subset may relapse later with oligoprogression rather than widespread disease.

Management of non-responders and those with acquired resistance requires careful sequencing of therapies and often enrollment in clinical trials.¹² For chemotherapy

failures, second-line options include docetaxel, with or without ramucirumab, or other single-agent regimens. For targeted therapy resistance, next-generation inhibitors such as osimertinib for *EGFR* T790M or lorlatinib for resistant *ALK* disease are used. For immunotherapy resistance, options are more limited, but strategies include rechallenge with immunotherapy in combination with chemotherapy, switching to alternative checkpoint inhibitors, or participation in trials testing antibody–drug conjugates, bispecific antibodies, or cell-based therapies. Re-biopsy or liquid biopsy at progression is increasingly important because it can reveal new mutations or mechanisms of resistance that guide subsequent therapy. Thus, while modern therapies have significantly improved survival and quality of life for lung cancer patients, resistance—both primary and acquired—remains the central barrier to long-term disease control, and overcoming it is the focus of ongoing research and innovation.

Primary resistance to targeted therapies often stems from pre-existing subclonal driver mutations, inefficient drug target binding, or concurrent pathway activation; acquired resistance emerges through on-target secondary mutations (e.g., *EGFR* T790M), bypass signaling (e.g., *MET* or *HER2* amplification), histologic transformation, or non-genetic adaptive mechanisms, including epithelial-mesenchymal transition and drug-tolerant persister cell states. Taken together, chemotherapy has high primary non-response rates and rapid acquired resistance, targeted therapies achieve high initial responses but nearly universal resistance within 1–2 years, and immunotherapy shows durable benefit in a minority of patients but faces both primary resistance in about half and acquired resistance in most responders over time. This dynamic landscape underscores the urgent and unmet need for predictive drug efficacy/response testing, biomarker-driven personalized therapies at progression, and new clinical trials to extend lung cancer patient survival and improve outcomes.

4. Predominance of non-responders across all stages of non-small cell lung cancer

Lung cancer treatment is highly dependent on the stage of disease at diagnosis, as well as the molecular and immunologic profile of the tumor¹³ (Figure 1). In the earliest stages, such as stage 0 and stage I, surgery is the cornerstone of therapy. Patients who are medically fit usually undergo lobectomy or segmentectomy, and in many cases, this can be curative. Depending on risk factors such as tumor size, lymph node involvement, or molecular features, adjuvant chemotherapy, immunotherapy, or targeted therapy may be added to reduce the risk of recurrence. For patients who cannot undergo surgery, stereotactic body radiotherapy is often used as an alternative with excellent local control rates.

In stage II disease, surgery remains the primary treatment, but adjuvant chemotherapy is more strongly recommended because the risk of microscopic spread is higher. Increasingly, immunotherapy or targeted therapy is incorporated after surgery and chemotherapy if the tumor harbors specific biomarkers such as *EGFR* mutations or PD-L1 expression. Stage III disease is more complex, as tumors are often locally advanced and may involve mediastinal lymph nodes. In these cases, a multimodal approach is required. Patients may receive concurrent chemoradiation, sometimes followed by surgery if the disease becomes operable. For those with unresectable stage III disease, consolidation immunotherapy with durvalumab after chemoradiation has become standard, as it significantly improves survival.

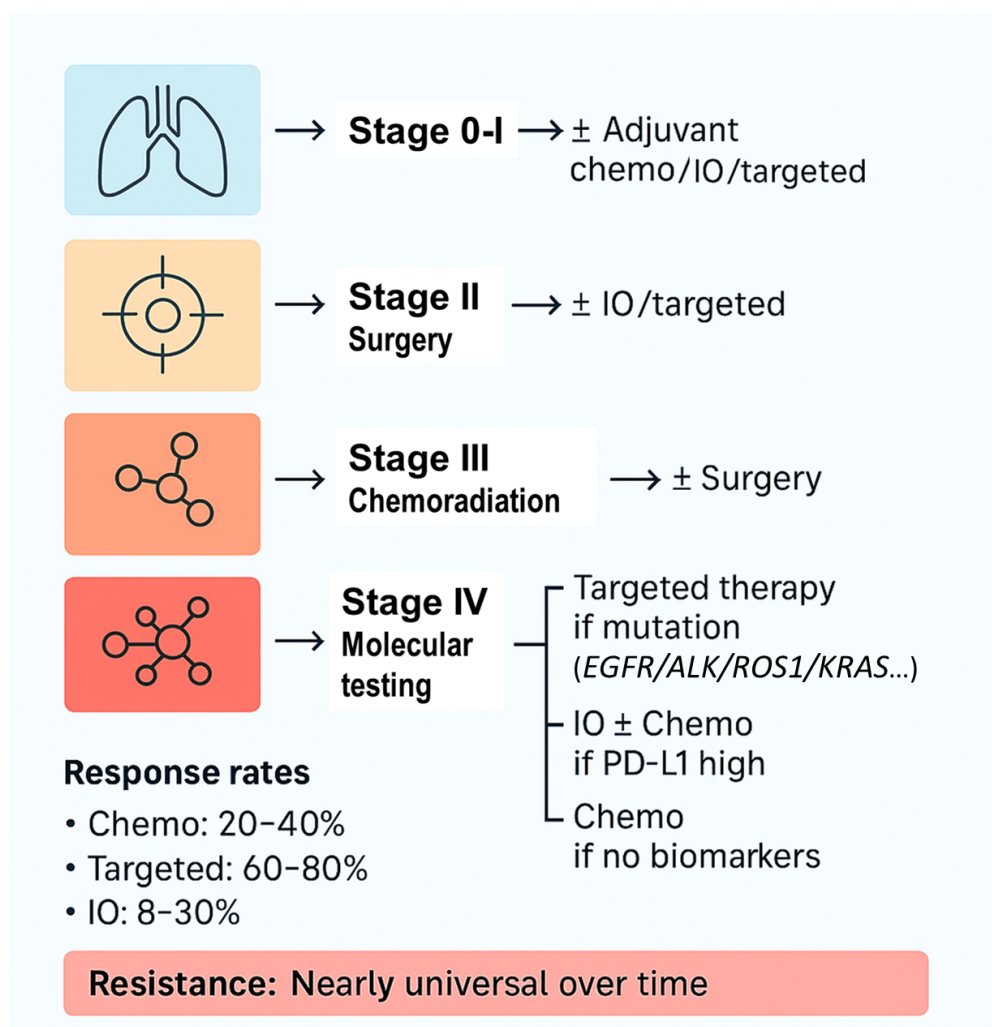


Figure 1. The treatment response rates in different stages of non-small cell lung cancer
Abbreviation: IO: Immunotherapy

Stage IV disease represents metastatic cancer, and here the treatment strategy is guided by molecular testing. If the tumor carries a driver mutation such as *EGFR*, *ALK*, *ROS1*, or *KRAS* G12C, targeted therapy with TKIs is the preferred first-line option, as these drugs achieve high response rates and can control disease for many months. If no actionable mutation is found, immunotherapy alone or in combination with chemotherapy is considered, depending on PD-L1 expression levels. For patients without actionable driver alterations or favorable immunotherapy biomarkers, chemotherapy remains a key component of treatment, often in combination with immunotherapy to improve outcomes.

Primary resistance to NSCLC precision medicine arises from tumor heterogeneity, co-occurring driver mutations, inefficient drug penetration, or bypass pathway activation; additionally, lack of actionable targets in certain histologies, low tumor mutational burden, poor antigen presentation, and suppressive immune microenvironments collectively limit initial response to targeted therapies or immunotherapies. Response rates vary substantially between treatment modalities.¹⁴ Traditional chemotherapy achieves objective response rates of about 20–40%, with median progression-free survival of only a few months. Targeted therapies, by contrast, can induce responses in 60–80% of patients, with median progression-free survival ranging from 9 to 18 months depending on the mutation and drug used. Immunotherapy has lower response rates overall, typically 8–30%, but in those who respond, the benefit can be long-lasting, sometimes extending survival for years. Unfortunately, resistance is nearly universal across all modalities. With chemotherapy, resistance develops quickly, often within months. With targeted therapy, secondary mutations or bypass signaling pathways eventually lead to disease progression. Even immunotherapy, despite its durability in some patients, faces both primary resistance (patients who never respond) and acquired resistance (patients who relapse after an initial response).

In the absence of biomarkers, clinicians rely on tumor histology, disease stage, performance status, organ function, prior therapy history, treatment toxicities, patient preferences, and empirical evidence from large clinical trials to guide sequential or combination regimen choices. When patients do not respond to initial therapy or develop resistance, treatment strategies shift to second-line or salvage approaches^{15,16} For chemotherapy-pretreated patients, docetaxel is a standard option, and combining it with ramucirumab, an anti-angiogenic antibody, has shown improved outcomes. In targeted therapy, next-generation inhibitors are used to overcome specific

resistance mutations, such as osimertinib for *EGFR* T790M or lorlatinib for resistant *ALK* disease. For immunotherapy non-responders, options are more limited, but rechallenge with immunotherapy in combination with chemotherapy or novel agents is sometimes attempted. Clinical trials play a crucial role for these patients, offering access to antibody–drug conjugates, bispecific antibodies, or cell-based therapies that may overcome resistance. Re-biopsy or liquid biopsy at progression is increasingly important, as it can reveal new mutations or mechanisms of resistance that guide the choice of subsequent therapy.

In essence, lung cancer treatment is a dynamic process that evolves with the stage of the disease and the biology of the tumor. While modern therapies have dramatically improved outcomes, resistance remains the central challenge, and the management of non-responders relies on a combination of second-line drugs, biomarker-driven strategies, and clinical trial enrollment.

5. A broken promise of precision medicine to the non-responders

Precision medicine uses genomic or molecular profiling to stratify patients into subgroups for targeted therapies, whereas personalized medicine tailors broader care aspects—including lifestyle, preferences, and values—beyond just biomarker-driven treatment selection. In current precision medicine approaches for NSCLC, a significant challenge lies in overcoming treatment resistance in non-responders, despite the use of targeted therapies and immunotherapies. One major clinical hurdle is tumor heterogeneity, where genetic and epigenetic variations within a single tumor or between primary and metastatic sites lead to divergent therapeutic responses. Even when a driver mutation (e.g., *EGFR*, *ALK*, or *KRAS*) is identified, subclonal populations with secondary resistance mutations (e.g., *EGFR* T790M, *ALK* G1202R) can evade targeted inhibition. Studies have shown that spatial and temporal heterogeneity complicates biomarker-based treatment selection, as liquid biopsies or single-site biopsies may not capture the full genomic landscape of the tumor.^{5,17}

Another critical issue is the lack of druggable targets for certain molecular subsets. While therapies exist for *EGFR*, *ALK*, *ROS1*, and *BRAF* V600E-mutant NSCLC, many other alterations (e.g., *KRAS* G12C until recently, *NF1*, or *STK11* mutations) lacked effective inhibitors, leaving these patients reliant on chemotherapy or immunotherapy with variable responses. Even with newer Kirsten rat sarcoma viral oncogene homolog (*KRAS*) inhibitors (e.g., sotorasib), acquired resistance mechanisms (e.g., *KRAS* G12D or Y96D mutations) limit long-term efficacy.¹⁸ Additionally,

tumors with co-mutations (e.g., *STK11* + *KRAS*) exhibit primary resistance to immunotherapy, further narrowing therapeutic options.¹⁹

The immune microenvironment also plays a pivotal role in non-response. “Cold” tumors with low tumor mutational burden, poor neoantigen presentation, or immunosuppressive features (e.g., high regulatory T cells, myeloid-derived suppressor cells) often fail to respond to checkpoint inhibitors (PD-1/PD-L1 blockers). For example, *KEAP1*- or *STK11*-mutant NSCLC shows reduced T-cell infiltration and interferon- γ signaling, rendering immunotherapy ineffective.²⁰ Even when PD-L1 expression is high, intrinsic resistance mechanisms (e.g., JAK1/2 mutations) can disrupt interferon signaling, a key pathway for immune activation.²¹

Finally, pharmacodynamic limitations and drug delivery barriers contribute to non-response. Blood–brain barrier penetration is poor for many TKIs, allowing central nervous system metastases to progress despite systemic control.²² Additionally, tumor stroma and fibrosis can impede drug distribution, particularly for larger molecules like antibody–drug conjugates. Metabolic adaptations (e.g., autophagy induced by epidermal growth factor receptor [EGFR] inhibition) further enable cancer cell survival.²³

Current biomarker strategies often measure static DNA alterations or protein expression levels, failing to capture dynamic tumor evolution, post-transcriptional regulation, and tumor microenvironment (TME) influences; in aggressive cancers, rapid clonal shifts, non-genetic drug tolerance, and pathway crosstalk render single-timepoint or single-marker approaches insufficient for reliable therapeutic response prediction. Addressing these challenges requires longitudinal molecular profiling, combination therapies (e.g., TKIs with chemotherapy or anti-angiogenics), and novel strategies like bispecific antibodies or adoptive cell therapy. However, the rapid evolution of resistance underscores the need for dynamic treatment adaptation, highlighting the gap between precision medicine’s promise and its real-world limitations.

6. What makes someone a non-responder?

Patients with NSCLC may fail to respond to precision medicine due to a complex interplay of tumor-intrinsic and extrinsic factors. At the genomic level, primary resistance often stems from tumor heterogeneity, where subclonal populations lacking the targetable mutation or harboring co-occurring genetic alterations evade therapy.¹⁷ For instance, while *EGFR*-mutant NSCLC typically responds to TKIs, the presence of concurrent *TP53* mutations or *PTEN* loss can confer intrinsic resistance.²⁴ Additionally, some patients exhibit “on-target” resistance mechanisms in

which secondary mutations (e.g., *EGFR* T790M or C797S) emerge during treatment, restoring oncogenic signaling despite targeted inhibition.²⁵ Beyond genetic factors, epigenetic modifications and phenotypic plasticity enable tumor cells to transition into drug-tolerant persister states through mechanisms such as epithelial–mesenchymal transition or lineage switching.²⁶ The TME further contributes to non-response through immune evasion, stromal interactions, and metabolic adaptations that create protective niches for resistant cells.²⁷ For example, tumor-associated macrophages and cancer-associated fibroblasts can secrete growth factors that activate bypass signaling pathways (e.g., MET or AXL upregulation), rendering targeted therapies ineffective.²⁸ Tumor cells evade the immune response by downregulating antigen presentation, upregulating checkpoint ligands such as PD-L1, secreting immunosuppressive cytokines, and recruiting regulatory T cells or myeloid-derived suppressor cells, collectively blunting cytotoxic T-cell activity and driving primary or acquired resistance to immunotherapies.²⁰ Pharmacokinetic limitations, including poor drug penetration into tumor sites or rapid drug metabolism, may also prevent adequate target inhibition.²⁹ Importantly, technical challenges in biomarker testing—such as inadequate tumor sampling, spatial heterogeneity, or limitations in detecting low-frequency resistance mutations—can lead to false-negative results and inappropriate treatment selection.³⁰ Emerging evidence suggests that non-genetic adaptive resistance, mediated by transcriptional rewiring or chromatin remodeling, plays a crucial role in early treatment failure.¹¹ Furthermore, the dynamic evolution of resistance mechanisms under therapeutic pressure creates a moving target that often outpaces the development of sequential targeted therapies.³¹ These multifaceted resistance pathways underscore the need for comprehensive molecular profiling at progression, functional drug sensitivity testing, and combinatorial approaches that simultaneously target primary drivers and resistance pathways to overcome non-response in NSCLC precision medicine.

Early identification of non-responders can be improved by combining baseline molecular profiling with early on-treatment functional pharmacodynamic assays—such as rapid ex vivo drug sensitivity testing on fresh biopsies or liquid biopsies (i.e., patient-derived gene expression-informed anticancer drug efficacy [PGA] drug-mapping technology, see Section 8)—and serial monitoring of circulating tumor DNA and/or cell-free mRNA gene overexpression within the first 7–14 days of therapy; this multi-parametric approach detects primary resistance before radiographic progression, allowing clinicians to discontinue ineffective agents promptly, switch to alternative regimens, and avoid cumulative toxicity,

unnecessary costs, and the irreversible loss of critical time in aggressive cancers.

7. Converting non-responders into responders in non-small cell lung cancer: Emerging strategies

Tumor heterogeneity—both within a single patient's lesions and across different patients—drives divergent drug responses, with distinct subclones exhibiting variable sensitivity or innate resistance to the same therapy. Overcoming treatment resistance in NSCLC requires a multifaceted approach that addresses both tumor-intrinsic and extrinsic mechanisms of resistance (Figure 2). One promising strategy involves the use of next-generation TKIs designed to target resistant mutations, such as osimertinib for *EGFR* T790M-positive NSCLC or repotrectinib for *ROS1* fusion-positive cancers with acquired resistance mutations.³² Additionally, combination therapies that simultaneously inhibit primary oncogenic drivers and bypass signaling pathways (e.g., MET inhibitors or human epidermal growth factor receptor 2 inhibitors paired with EGFR TKIs) have shown potential in overcoming resistance.³³ Liquid biopsy-based monitoring of circulating tumor DNA can help identify emerging resistance mutations early, enabling timely therapeutic adjustments.³⁴ Furthermore, targeting epigenetic modifiers, such as histone deacetylase inhibitors or EZH2 inhibitors, may reverse non-genetic resistance mechanisms by restoring drug sensitivity in persister cell populations.³⁵

Another critical approach involves modulating the TME to enhance therapeutic response. Immune checkpoint inhibitors combined with targeted therapies have demonstrated efficacy in converting some non-responders, particularly in tumors with low PD-L1 expression or immunologically “cold” microenvironments.³⁶ Strategies to reprogram the TME—such as stimulator of interferon genes agonists, transforming growth factor beta (TGF- β) blockade, or C-X-C chemokine receptor 4 inhibitors—are being explored to enhance immune infiltration and overcome immune checkpoint inhibitor resistance.³⁷ Additionally, targeting metabolic vulnerabilities, such as glutamine addiction or altered glycolysis in resistant clones, may synergize with existing therapies.³⁸ Advances in single-cell RNA sequencing and spatial transcriptomics are uncovering novel stromal-immune interactions that could be therapeutically exploited to convert non-responders.³⁹

Innovative clinical trial designs are also essential to identify effective salvage therapies for refractory NSCLC. Adaptive platform trials, such as the ongoing LUNG-MAP study, allow for rapid evaluation of multiple targeted and immunotherapeutic combinations in biomarker-selected

populations.⁴⁰ Patient-derived organoids and xenografts are also being utilized to functionally test drug sensitivity and identify personalized rescue therapies.⁴¹ Artificial intelligence-driven predictive models that integrate multi-omics data may further optimize treatment selection by forecasting resistance patterns and identifying latent vulnerabilities.⁴² As these strategies evolve, a precision medicine paradigm that dynamically adapts to tumor evolution—rather than static biomarker testing—will be crucial for converting non-responders into responders in NSCLC.

Collectively, strategies to convert non-responders into responders include combining targeted agents with chemotherapy, radiotherapy, or anti-angiogenic drugs to overcome bypass resistance; adding checkpoint inhibitors to activate dormant T-cells; modulating the TME with TGF- β or indoleamine 2,3-dioxygenase inhibitors; and leveraging PGA drug mapping technology to re-sensitize tumors to prior therapies (or via off-label drug use and drug repurposing), thereby improving clinical outcomes in previously refractory patients.

8. PGA: A drug finder and a response classifier

The revolutionary technology known as PGA operates as a powerful and novel drug finder in the era of precision oncology, moving beyond the structural limitations of mutation-centric genomics⁴³ (Figure 3). At its core, PGA leverages a proprietary liquid biopsy methodology to capture the functional genomic state of a patient's cancer, primarily through the transcriptomic profiling of cell-free messenger RNA (cfmRNA) circulating in the blood.⁴⁴ While next-generation sequencing (NGS) primarily detects static DNA mutations, missing dynamic post-transcriptional regulation, non-genomic drug resistance, and functional drug efficacy, PGA overcomes these limitations by directly measuring tumor-active gene expression signatures to guide real-time treatment decisions. This approach is superior to traditional tumor-only sequencing in that it generates a comprehensive, patient-unique gene expression “fingerprint,” which inherently encompasses complex biological signals from both the tumor cells and the surrounding TME. Crucially, the TME, including immune cell infiltration and stromal components, plays a pivotal role in drug response and resistance, elements often missed by NGS focused solely on mutational hotspots. Once the patient's unique functional signature is established, typically within a rapid turnaround time, it serves as the input for a sophisticated *in silico* biological-twin model. This analytic platform facilitates the search, matching, and ranking of predicted

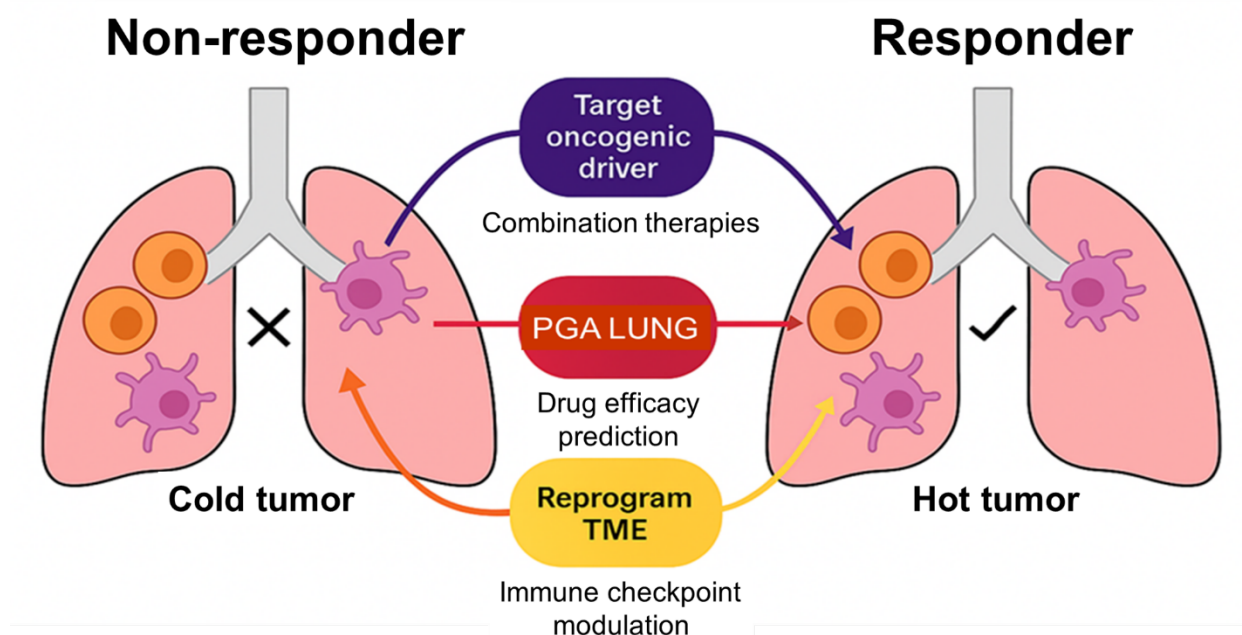


Figure 2. Emerging strategies for converting non-responders into responders in non-small cell lung cancer. The key interventions highlighted are targeting oncogenic drivers, employing drug efficacy prediction technology PGA LUNG, and reprogramming the tumor microenvironment (TME).

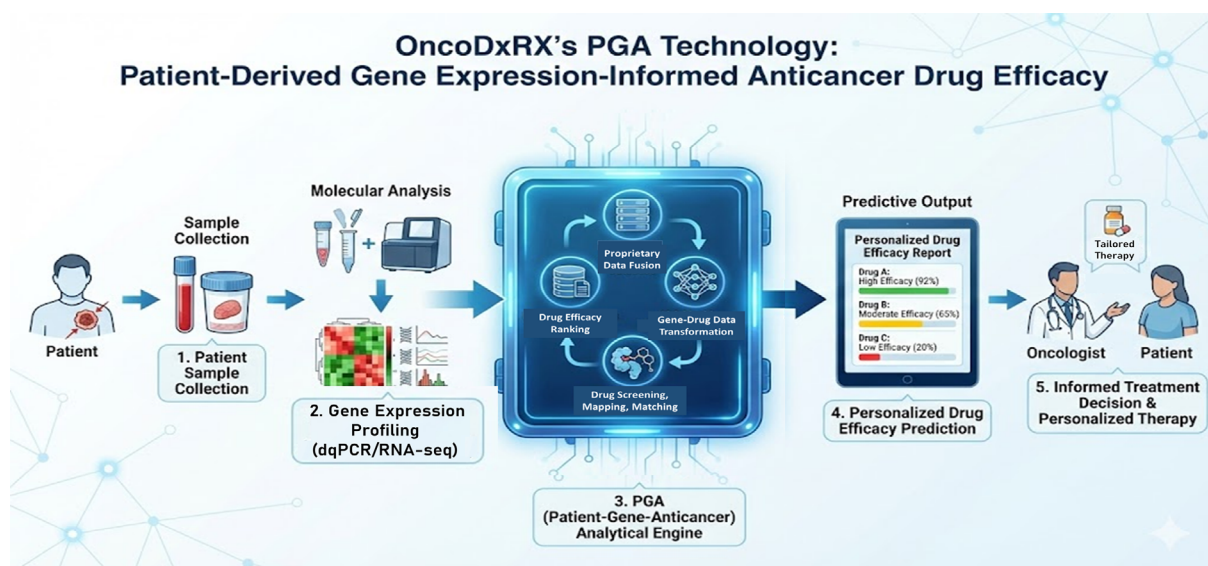


Figure 3. Schematic workflow of the patient-derived gene expression-informed anticancer drug efficacy (PGA) test. (1) Liquid biopsy collection: peripheral blood is drawn from the patient to isolate plasma containing circulating cell-free mRNA (cfmRNA), enabling a non-invasive assessment of the tumor's dynamic gene expression profile. (2) Transcriptomic profiling: the cfmRNA is extracted and profiled to generate a patient-specific gene expression signature, capturing the unique biological activity of the tumor and its microenvironment. (3) *In silico* drug screening & matching: the patient's unique gene signature is digitally mapped against a comprehensive library of approximately 700 United States Food and Drug Administration-approved and investigational anticancer drugs. Proprietary algorithms utilize semi-supervised learning to predict drug sensitivity, calculating Z-scores based on IC_{50} data to rank potential efficacy. (4–5) Personalized treatment report: a comprehensive, actionable report is generated, listing the top-ranked drugs predicted to be most effective for the individual patient, guiding treatment selection for refractory or relapsed cases.

drug efficacy from a vast library of existing compounds—including United States Food and Drug Administration-approved, investigational, and clinical-trial agents (over 700 drugs). This gene-drug mapping capability enables oncologists to identify therapeutic options that align with the overexpression of critical, pathway-driving genes, rather than just the presence of a targetable mutation.⁴⁵ Thus, PGA acts as a comprehensive drug discovery engine, capable of uncovering effective treatments for patients who have exhausted standard-of-care therapies or whose cancers “elude” classical targeted or immune checkpoint blockade approaches based on simple genetic markers.

Further, PGA functions with equal proficiency as a sophisticated response classifier and therapeutic stratification tool. The output of the *in silico* analysis provides precise, personalized predictions of a drug's efficacy, classifying the patient's likely sensitivity or resistance to numerous agents by mapping their unique gene activation patterns to known drug mechanisms of action. This predictive capability is critical for optimizing treatment selection at the single-patient level, minimizing the use of ineffective and potentially toxic drugs, and significantly improving the probability of a positive outcome, a finding that has been supported by clinical outcomes data in patients with refractory or relapsed disease, notably within heterogeneous tumor types such as NSCLC.⁴³ Furthermore, the platform's ability to analyze multiple drug efficacies simultaneously positions it as an invaluable tool for designing rational, tailored combination therapies. By identifying complementary drugs that target different, yet synergistic, aberrant signaling pathways within the patient's functional genomic landscape, PGA overcomes common challenges such as intrinsic or acquired drug resistance. This is achieved by predicting sensitivity across multiple agents, thereby allowing clinicians to construct complex, multimodal treatment regimens—for example, combining immunotherapy with targeted agents or anti-angiogenics—that convert non-responders into clinical responders. By providing actionable, functional-genomic insights, PGA translates the full biological complexity of an individual tumor into a clear therapeutic roadmap, truly realizing the promise of personalized medicine.

PGA gene-drug mapping can be integrated into clinical workflows by collecting a peripheral blood sample at diagnosis or progression, extracting cfRNA for expression profiling, applying the PGA algorithm to rank predicted drug efficacy, and reporting actionable results to oncologists within 3–5 days, enabling selection of the most

effective therapy while avoiding ineffective agents and reducing trial-and-error prescribing.

9. Treating the “un-targetable”

The PGA approach has shown remarkable potential in NSCLC, where tumor heterogeneity and dynamic resistance mechanisms often render targeted and immune therapies ineffective.^{43,45} By matching individual gene signatures with the best anticancer drugs, the PGA platform can identify hidden vulnerabilities that genomic analysis alone might miss, thereby increasing the likelihood of therapeutic success, especially for non-responders. The PGA platform's ability to overcome resistance mechanisms in NSCLC stems from its comprehensive evaluation of both genetic and functional drug responses, capturing complex resistance patterns. While NGS detects actionable mutations, it cannot account for epigenetic modifications, TME interactions, or adaptive signaling pathways that contribute to treatment failure.⁴⁶

Looking ahead, the integration of PGA tests into clinical practice could revolutionize the management of treatment-resistant NSCLC. Moreover, ongoing clinical trials are evaluating PGA-guided therapy in larger NSCLC cohorts.⁴⁷ As the technology evolves, its application could extend beyond late-stage NSCLC to earlier treatment lines, potentially preventing resistance before it develops. By bridging the gap between genomic insights and real-world tumor behavior, PGA technology represents a paradigm shift in precision oncology—one that moves beyond static mutations to dynamic, patient-specific drug response profiling. For NSCLC patients with limited options, this innovation offers a path to more effective, personalized treatment and improved survival outcomes.

The goal for the future is to use data from the PGA drug response prediction assay to aid in determining which of the available therapies are likely to be the best for an individual non-responder in clinical practice. Clinical trials may also be able to eventually incorporate PGA testing in inclusion and exclusion criteria to improve the likelihood of clinically meaningful therapeutic responses. Artificial intelligence integrates multi-omics data—genomics, transcriptomics, proteomics, and metabolomics—to uncover nonlinear, high-dimensional patterns associated with drug sensitivity; machine learning models trained on large-scale pharmacogenomic databases can predict patient-specific responses, identify novel resistance signatures, and prioritize combination therapies with greater accuracy than single-marker or rule-based approaches alone.

10. Beyond responders: Scaling the promise of precision medicine

Non-small cell lung cancer remains a leading cause of cancer-related deaths, with a significant proportion of patients not receiving treatment beyond first-line therapy. Despite advancements in targeted therapies and immunotherapies, ~30–80% of advanced NSCLC patients do not survive long enough to receive second-line treatment (Table 2), often due to rapid disease progression, poor response to initial therapy, or severe treatment-related toxicities. Studies indicate that the median OS of patients with metastatic NSCLC remains around 12–18 months and is even shorter among patients without actionable driver alterations, such as *EGFR* mutations or *ALK* rearrangements, or without favorable immunotherapy biomarkers, such as PD-L1 positivity.^{48–53} Additionally, real-world data reveal that only 30–40% of patients are eligible for second-line options, as many experience clinical deterioration or comorbidities that preclude further treatment. In under-resourced or rural regions, limited access to specialized oncology care, high out-of-pocket costs for molecular testing and targeted agents, delayed diagnosis, and poor performance status collectively prevent many advanced NSCLC patients from receiving second-line therapy. Early identification of resistance mechanisms, improved biomarker-driven strategies, and timely transition to second-line therapies are critical to extending survival. Clinical trials exploring

combination immunotherapies, antibody–drug conjugates, and circulating tumor DNA-guided interventions offer hope, but broader implementation is needed to improve outcomes for this high-risk population. Addressing these challenges requires a multidisciplinary approach, including better patient stratification, rapid genomic profiling, and expanded access to emerging drug response prediction technologies.

Precision medicine has revolutionized cancer care by tailoring treatments to individual genetic profiles, yet its full potential remains unrealized due to disparities in access, biomarker testing delays, and the challenge of extending benefits beyond the initial “responder” population. While therapies targeting *EGFR*, *ALK*, *ROS1*, and PD-L1 have dramatically improved outcomes for some NSCLC patients, only 20–30% of individuals benefit from these breakthroughs, leaving the majority without effective options. Current barriers to translating genomic insights include lengthy turnaround times for comprehensive sequencing, lack of standardized interpretation pipelines for complex variants, poor correlation between DNA mutations and actual drug sensitivity, limited reimbursement for broad panel testing, insufficient tissue samples for both diagnosis and molecular profiling, fragmented data integration between laboratories and electronic health records, and a scarcity of prospective trials validating biomarker-driven decisions. To scale precision

Table 2. Real-world NSCLC patient attrition rates (failure to reach second-line therapy)

Study/reference	Study population	Receiving second-line therapy (%)	Not receiving second-line therapy, %	Key findings/context
US real-world analysis ⁴⁸	Advanced <i>EGFR</i> ⁺ NSCLC	52%	48%	28% of patients died directly after or during first-line therapy without ever initiating a second line.
Global review ⁴⁹	General advanced NSCLC population	40–60%	40–60%	Attrition rates vary by country; US/Italy attrition was reported as high as 40–62%, while Spain/Germany was ~55%.
BC Cancer real-world study ⁵⁰	PD-L1 tumor proportion score > 50% (immunotherapy-treated)	21%	79%	Only 21% received second-line therapy in real-world practice, compared to 53% in the KEYNOTE-024 clinical trial.
Central and Eastern Europe study ⁵¹	<i>EGFR</i> -mutated NSCLC	70%	30%	Even in targeted therapy populations, nearly 1/3 of patients are lost to follow-up or death before second-line treatment.
US community oncology study ⁵²	Post-IO & chemotherapy progression	~32–39%	~61–68%	In patients progressing after chemo-immunotherapy, a majority did not proceed to effective subsequent lines or had very short survival (median overall survival ~8.8 months).
Historical benchmark ⁵³	General NSCLC (chemotherapy era)	60%	40%	Historically, about 40% of patients never received second-line therapy due to rapid clinical deterioration.

Abbreviations: BC: British Columbia; *EGFR*: Epidermal growth factor receptor; IO: Immunotherapy; NSCLC: Non-small cell lung cancer; PD-L1: Programmed death-ligand 1; US: United States.

medicine, healthcare systems must prioritize universal biomarker testing at diagnosis, leveraging liquid biopsies to overcome tissue limitations and artificial intelligence-driven decision support tools to guide oncologists in real time. Beyond diagnostics, expanding treatment options for non-responders—through combination therapies and drug efficacy prediction tools such as PGA—is critical. Furthermore, real-world data and adaptive clinical trials can accelerate the identification of resistance mechanisms and new therapeutic vulnerabilities. Collaboration among payers, regulators, and biopharma is essential to ensure equitable access, reduce costs, and integrate precision medicine into standard care. Novel therapeutic frameworks must integrate dynamic biomarker monitoring, adaptive clinical trial designs, functional drug sensitivity testing, and real-time response prediction algorithms to enable rapid regimen switching; these systems should address tumor heterogeneity, evolution, and non-genetic resistance, while prioritizing combination strategies targeting multiple escape pathways and recalcitrant cancer cell states. By addressing these challenges, the oncology community can move beyond the “lucky few” responders and deliver on the promise of precision medicine for all patients, transforming more cancers from rapidly progressive diseases into manageable chronic conditions.

Future perspectives for non-responders may also rely on nanoparticle-based drug delivery systems that enhance tumor penetration, bypass efflux pumps, and co-deliver synergistic agents to combat resistance; stimuli-responsive formulations enable spatiotemporally controlled release, while biomimetic nanocarriers and exosome-engineered vesicles improve bioavailability and reduce off-target toxicity, together transforming refractory cancers into treatable chronic diseases through precision nanoformulation strategies.⁵⁴⁻⁵⁶

11. Conclusion: Living with cancer—A new treatment paradigm

Cancer is not just a collection of rogue cells—it thrives within a dynamic, interconnected ecosystem where cells constantly adapt and evolve. Decoding this complexity—particularly the mechanisms behind tumor heterogeneity and evolution—could transform cancer care, offering patients more durable and effective treatments.

Yet some cases remain stubbornly difficult to manage, especially in non-responders who experience relentless disease progression or frequent relapses. For these patients, we may need to shift our approach: rather than aiming for eradication, we could treat cancer as a chronic condition to be controlled. This strategy requires viewing tumors as evolving ecosystems, where we can exploit

competition between subclones to suppress the most aggressive variants. However, shifting to a chronic cancer management paradigm faces practical hurdles: fragmented healthcare systems struggle to coordinate continuous, multi-line therapies; patients experience treatment fatigue, cumulative toxicities, and financial toxicity from prolonged drug costs; real-time monitoring requires frequent imaging and biopsies, straining logistics; uneven access to second-line and later treatments exacerbates disparities; and clinical workflows lack standardized algorithms for adaptive, long-term sequencing of molecularly guided interventions.

Since cancer inevitably adapts to every treatment, the key lies in anticipating its next move. By staying ahead of the disease’s evolution, we can strategically select therapies that keep it in check—potentially allowing patients to live with cancer, rather than succumb to it.

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Conflict of interest

All authors are employees of OncoDxRx, which has a commercial and/or proprietary interest in PGA technology discussed in this article. The authors declare this relationship as a potential competing interest.

Author contributions

Conceptualization: Chen Yeh

Writing—original draft: Chen Yeh

Writing—review & editing: All authors

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