

ORIGINAL RESEARCH ARTICLE

The one-of-a-kind PGA technology harnesses patient's gene signature to predict drug efficacy: A reality check with the real-world treatment trend

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Abstract

In 1937, President Roosevelt launched the National Cancer Act. Eighty-nine years later, challenges remain despite progress, with 50–80% of patients being unresponsive to treatment and over 600,000 cases of mortality annually in the United States (U.S.) Biomarker tests enable precision medicine but exclude most patients. A disruptive technology is needed to expand precision treatments and benefit every cancer patient. The revolutionary drug-finding technology, PGA (patient-derived gene expression-informed anticancer drug efficacy), has been developed and validated previously, which integrates a patient's own gene signature to identify the top-ranking drugs that individual patients are most likely to respond to. In this study, we further conducted a benchmarking reality check to evaluate the clinical utility of PGA in real-world settings. To validate PGA LUNG testing results, the framework incorporates three publicly accessible drug utilization datasets for NSCLC: TCGA, MEDLINE, and NCCN guidelines. To enable a comprehensive assessment of PGA LUNG clinical utility, we defined evaluation metrics by capturing drug usage trends in the best clinical practice. Aligned with TCGA treatment landscapes and real-world NSCLC treatment trends in the U.S., the PGA LUNG test could significantly help oncologists by providing them with reliable predictions to choose the most suitable drugs for their patients. PGA LUNG also highlights the potential for off-label cancer drugs to overcome the challenges of ongoing therapy exhaustion and drug resistance. PGA LUNG's ability to predict drug efficacies/responses for treatment-unresponsive cancer patients with high accuracy provides a critical clinical advantage.

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1. Introduction

According to the World Health Organization, cancer is the second leading cause of death globally, highlighting the urgent need to predict responses to anticancer drugs. Various databases, such as The Cancer Genome Atlas (TCGA),¹ the Cancer Cell Line Encyclopedia (CCLE),² and the Catalogue of Somatic Mutations in Cancer (COSMIC),³

aim to comprehensively study genomic changes and catalog genetic mutations involved in human cancer through genotype-phenotype analysis technologies. While these initiatives provide a substantial amount of publicly accessible data, the heterogeneity within and between tumors makes research a complex and exhaustive process. Thus, the development of novel gene-drug mapping tools is crucial for identifying potential cancer biomarkers and drug targets, facilitating the drug discovery process, and reducing the experimental workload.

Predicting the efficacy of anticancer drugs is a formidable challenge due to the need to integrate diverse data types, including genomic profiles, therapeutic intervention, and clinical characteristics and outcomes. Genomic profiles (mutations, copy number variations) identify oncogenic drivers, while transcriptomic data (RNA-seq) reveal gene expression patterns influencing drug sensitivity. Epigenomic modifications (methylation, chromatin states) regulate gene activity, and proteomic/metabolomic data reflect functional protein and metabolic pathways. Therapeutic intervention details (drug mechanisms, pharmacokinetics) guide treatment selection, and clinical characteristics (tumor stage, histology, comorbidities) contextualize patient-specific factors. Finally, clinical outcomes (survival, toxicity) validate predictions. Integrating these multi-omics and clinical datasets enhances precision but demands advanced computational methods to overcome heterogeneity and improve predictive accuracy in oncology. The outcomes of drug therapy can be unpredictable, ranging from beneficial to toxic, and are largely driven by the tumor's molecular profile.⁴ Responses to anticancer drugs can be influenced by both germline and acquired somatic mutations, as well as the status of gene expression and signaling pathways.⁵⁻⁷ This suggests that therapies targeting an individual's genomic landscape are more effective than one-size-fits-all approaches. Recent advances in high-throughput drug screening, along with the availability of pharmacological and omics data (genomic, transcriptomic, proteomic, and metabolomic), have paved the way for identifying genetic biomarkers associated with treatment responses.⁸ These datasets have helped assess the sensitivity of many compounds, including FDA-approved drugs *in vitro*, and have enabled collective analysis of drug sensitivity and gene expression data to uncover novel gene-drug relationships.⁶ Numerous studies have demonstrated that machine learning models can achieve high accuracy in predicting drug activity against cancer cell lines.^{9,10} However, they are all still in the digital modeling phase, far from clinical application.

Despite advancements in genomics-based drug

sensitivity analysis, the practical application of genomic profiling for selecting appropriate drugs remains limited. The breakthrough PGA (patient-derived gene expression-informed anticancer drug efficacy) technology offers a novel method to predict drug sensitivity through personalized gene expression signatures.⁶ To the best of our knowledge, this is the first and only study to validate predicting patients' sensitivity to the existing ~700 anticancer drugs using gene activation patterns derived from individual patients.

The majority of lung cancers (~85%) are grouped broadly as non-small cell lung cancer (NSCLC). In this heterogeneous class, the prognosis is particularly poor when cancer has spread to contralateral lymph nodes (stage IIIB) or distant sites (stage IV), because it indicates advanced metastatic spread, reduced resectability, and increased tumor aggressiveness, often leading to systemic therapy resistance and higher recurrence rates post-treatment. The five-year survival rate drops dramatically—from 61% in earlier stages (IA–IIA) to just 6% in advanced stages.¹¹ Since more than half of new cases are diagnosed at the metastatic disease stage, effective treatment in this setting is crucial. The NCCN Clinical Practice Guidelines in Oncology recommend biomarker testing for eligible patients with metastatic NSCLC, if clinically feasible, to identify the most appropriate treatment options.¹² However, there is limited information on whether and to what extent real-world clinicians have adopted these recommendations and altered the treatment of advanced NSCLC patients.

Biomarker testing often fails to predict treatment efficacy due to tumor heterogeneity, where a single biopsy may not capture the full molecular diversity of the cancer. Additionally, biomarkers typically focus on a limited set of mutations (e.g., EGFR, ALK), ignoring complex gene expression patterns and dynamic tumor-microenvironment interactions that influence drug response. Static biomarkers also fail to account for acquired resistance mechanisms that emerge during therapy. In contrast, PGA LUNG leverages a patient's unique gene expression signature, providing a more comprehensive and dynamic assessment of drug sensitivity, potentially overcoming the limitations of conventional biomarker-driven approaches.

To further validate PGA technology in a real-world setting, we explored a reality check and the extent to which a NSCLC patient's tumor response to multiple approved and experimental drugs (or drug efficacies) can be predicted based on the patient's gene expression profile obtained through targeted transcriptomic profiling, as gene expression signatures often correlate with drug sensitivity,

resistance mechanisms, and tumor heterogeneity, providing a clinically actionable basis for personalized therapy selection beyond genomic mutations alone. Mapping patient-specific gene signatures to drug efficacies is highly transformative, as it paves the way for the transcriptomic characterization of treatment responses. This approach also has the potential to exclude certain drugs from being used in a patient's treatment based on his/her functional genomic profile. In this study, PGA LUNG test results were compared to the current treatment trends in NSCLC, as the systematic review of publications and TCGA databases captured the evolving treatment patterns in the United States (U.S.).

2. Materials and methods

2.1. PGA LUNG testing

The details of sample processing, patient-derived transcriptomic profiling, the entire testing procedure, and digital data analytics of PGA LUNG have been reported previously.^{6,13} All patient plasma samples used for cell-free RNA extraction were subjected to one freeze-thaw cycle and stored at -80°C until PGA LUNG test analysis. Plasma samples were stored at -80°C to preserve RNA integrity, minimizing degradation and ensuring reliable cell-free RNA extraction. This temperature inhibits enzymatic activity and reduces RNA fragmentation, maintaining sample stability for subsequent PGA LUNG test analysis. Circulating cell-free RNA was extracted from 400 μL double-spun plasma using the MagMAX[™] Viral/Pathogen Nucleic Acid Isolation Kit (Applied Biosystems, Foster City, CA, USA). Double-stranded cDNA was synthesized using the NEBNext RNA First Strand Synthesis Module and NEBNext Ultra[™] II Non-Directional RNA Second Strand Synthesis Module (New England Biolabs, Ipswich, MA) following the manufacturer's protocol. For PGA LUNG profiling, we used the TaqMan gene expression assay (Applied Biosystems, Foster City, CA, USA) on selected lung cancer-specific biomarkers to establish a patient-unique gene signature. Relative gene expression changes were calculated using the $\Delta\Delta\text{Ct}$ method via Sequence Detection System (SDS) 2.1 software (Applied Biosystems). The SDS 2.1 software is a real-time PCR data analysis tool that automates threshold cycle (Ct) determination, enables $\Delta\Delta\text{Ct}$ -based relative quantification of gene expression, and provides quality control metrics for accurate, reproducible results in qPCR experiments. SDS 2.1 software was selected for its robust data analysis capabilities, high reproducibility, and compatibility with next-generation sequencing platforms. Its performance ensures accurate variant calling, efficient data processing, and reliable quality control for genomic applications.

PGA LUNG gene-to-drug mapping was then performed using a proprietary algorithm via *in silico* data fusion and computation.⁶ Top-performing candidates were identified from screening of more than 700 existing cancer drugs, either approved, in clinical trials, or investigational. These drugs were further ranked into three categories—excellent, good, or fair—based on predictive drug efficacy/response by Z-scores, ensuring a quick and seamless clinical treatment decision-making.⁶ The classification of drug efficacies was to enable clinicians to quickly prioritize treatments with the highest likelihood of success while accounting for varying levels of supporting evidence, thus streamlining decision-making in precision medicine.

2.2. Manual curation of TCGA treatment data

TCGA data were accessed via the NCI Genomic Data Commons (GDC) data portal. The GDC Data Portal provides a subset of TCGA data harmonized with GRCh38 (hg38) using GDC Bioinformatics Pipelines. These pipelines standardize biospecimen and clinical data, realign DNA and RNA sequences to a common reference genome (GRCh38), and generate derived data. The open-access GDC data does not require authentication or authorization and typically includes high-level genomic data that is not individually identifiable, along with most clinical and all biospecimen data elements. The GDC provides de-identified genomic, clinical, and biospecimen data, ensuring patient privacy by removing personal identifiers. Since no sensitive information is exposed, authentication is unnecessary, facilitating unrestricted open-access research while maintaining ethical compliance with data-sharing regulations.

The data frames detailing the drug therapy response data for TCGA samples were extracted and curated (total 1,145 treatment records). Drug names in the drug-specific data frame were manually curated to correct and harmonize treatment names. Manual curation of drug names was necessary to standardize inconsistent terminology, correct misspellings, resolve synonyms, and ensure accurate matching across datasets for reliable drug efficacy analysis. This involved changing brand names to generic names and correcting typographical errors. In cases of multiple generic names for a drug, the name found in Drugbank was selected to facilitate cross-referencing between the two databases.

2.3. Real-world data on NSCLC treatment patterns

The systematic literature review sought to examine real-world treatment patterns in NSCLC. This review adhered to a pre-specified study protocol and followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines¹⁴ and was registered in the

PROSPERO systematic review registry (<https://www.crd.york.ac.uk/PROSPERO/view/CRD420251143466>). Since the study focused on publicly accessible medical literature, no institutional ethics approval or patient informed consent was necessary. Two electronic databases, MEDLINE (both Epub Ahead of Print and In-Process database subsets) and TCGA, were methodically searched for peer-reviewed articles published between January 1, 2012, and November 15, 2024. Eligibility criteria were established in advance using the Population, Interventions, Comparators, Outcomes, and Study design (PICOS) framework for evidence-based literature review and incorporated into the study protocol.¹⁴ In this review, we focused exclusively on studies that provided information on treatment patterns in the U.S. We included studies that documented all regimens available at the baseline. The treatment patterns were qualitatively summarized using descriptive statistics and presented in both text and table formats.

Two independent reviewers initially screened the titles and abstracts of identified records. Full-text articles for abstracts that passed the initial screening were then independently reviewed based on PICOS criteria, with eligible studies being included. Relevant international and local conference proceedings published between 2012 and 2024 were manually searched and added to the list of included peer-reviewed publications. Reference lists of all included records were also hand-screened to identify additional relevant publications. While studies were included based on PICOS criteria, data were only extracted for those that met both the primary and additional eligibility criteria. Data extraction was conducted by two reviewers, with a third independent reviewer providing consensus to resolve any discrepancies. A PRISMA flow diagram for the systematic review of NSCLC treatment trends in clinical practice is shown below. The PRISMA flow diagram (Figure 1) outlines the systematic review process

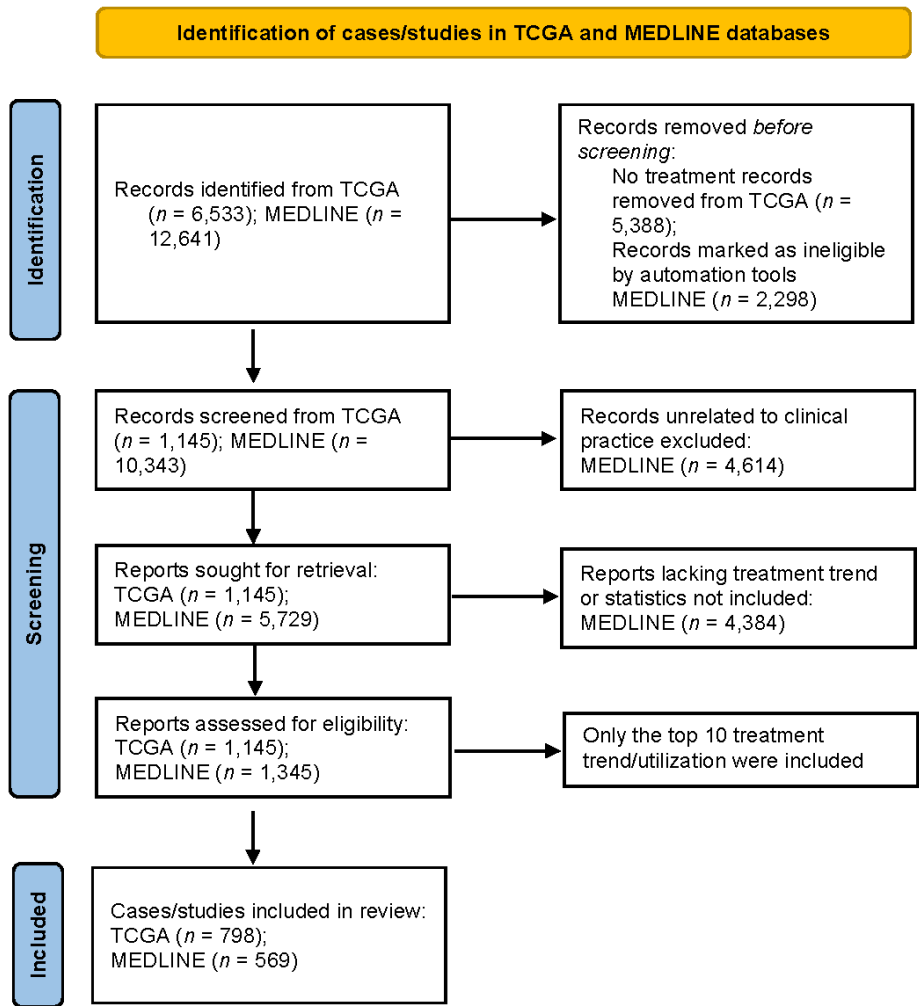


Figure 1. The PRISMA flow diagram used to identify eligible cases/studies in the TCGA and MEDLINE databases for the current study

for NSCLC treatment trends, detailing the initial database search, screening of records, eligibility assessment, and final study inclusion, while also documenting excluded studies and reasons for exclusion to ensure transparency and reproducibility in the selection methodology.

2.4. Statistical analysis

Survival time was calculated from treatment initiation (with/without PGA guidance) to death or study censoring. All analyses used SPSS v20.0 (IBM, Chicago, IL). Progression-free survival (PFS) was estimated via the Kaplan–Meier method, with between-group comparisons assessed by two-sided log-rank tests. The Kaplan–Meier method provides unbiased survival estimates with censored data, while the log-rank test efficiently compares PFS between groups without assuming proportional hazards, making both robust for clinical trials with variable follow-up times and dropouts. Their non-parametric nature ensures reliability across diverse cancer populations. Multivariate Cox proportional hazards models evaluated covariate effects on PFS. $p < 0.05$ was considered to indicate a statistically significant difference.

3. Results

3.1. A revolutionary gene-to-drug technology

Our main goal was to use a patient-derived gene expression signature, coupled with *in silico* computational analytics, to predict drug efficacy/response for individual patients

with cancer. An overview of the breakthrough gene-to-drug technology PGA was shown in Figure 2 (complete development and technical details were published in Ref.⁶). PGA performed consistently as the best predictor, with the added advantage of being highly computationally efficient, which is crucial for accurate gene-drug mapping. Furthermore, our data demonstrated that blood-based transcriptomic profiling can capture far more information about tumor microenvironment and immune cell interaction than may have been previously appreciated beyond tumor mutations. Leveraging advanced liquid biopsy know-how and disruptive technologies, we have maximized the PGA's panel capacity, enabling a high payload capacity for both tumor and non-tumor microenvironment biomarkers. The system integrates real-time patient testing that allows it to establish the patient's gene expression signature with precision, meaning the drug screening and mapping can then be made digitally, connected with data sources, and merged with the reporting system. A laboratory can offer multiple PGA tests for different cancer types, e.g., PGA LUNG, PGA BREAST, and PGA PANCREATIC. With this diverse biomarker detection capability, PGA is capable of making accurate drug efficacy/response prediction following thorough interrogation of ~700 existing cancer drugs, either approved, in clinical trial, or investigational.

The PGA's ability to report out multiple classes, top-ranking cancer drugs from a single run, as opposed to the traditional one-class-of-drugs-per-test approach

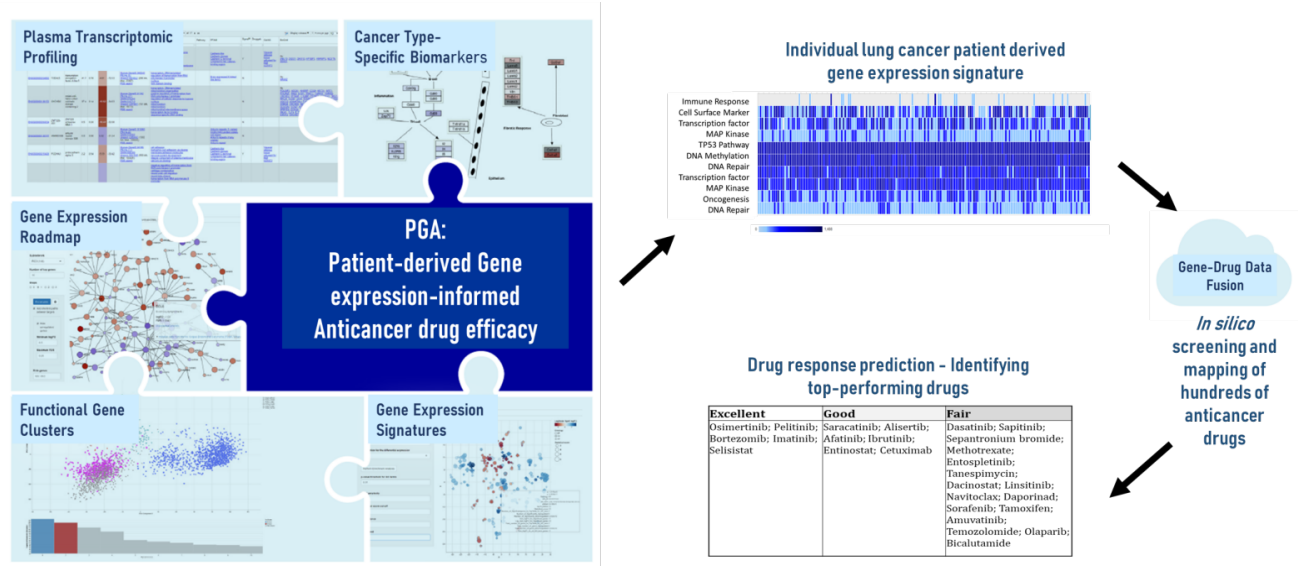


Figure 2. Overview of the PGA gene-to-drug mapping platform from *in vitro* patient testing and *in silico* data fusion analytics to the identification of top-performing drugs. Cancer type-specific biomarker selection was performed through patient plasma transcriptomic profiling, gene expression roadmap, and functional gene clusters. A patient-derived gene signature was further established on the selected cancer panel. Incorporating proprietary gene-to-drug mapping algorithms enhanced PGA's abilities to screen, match, and identify the best candidates for individual patients from the existing pool of over 700 cancer drugs. As a result, clinicians can quickly reach treatment decision-making within 3 days without delay.

(i.e., companion diagnostics or biomarker testing for targeted therapy or immunotherapy), represents a major breakthrough: a single system for a wide variety of cancer drugs and combinations. The PGA test is particularly suited for cancer patients who are not qualified for precision therapy or have refractory, metastatic, or relapsed disease, or when the standard of care has been exhausted. Relapsed disease occurs when cancer returns after a period of remission, either at the original site (local recurrence) or in distant organs (metastatic recurrence), often due to residual tumor cells evading treatment or developing resistance mechanisms, necessitating alternative therapeutic strategies like PGA testing. It greatly enhances alternative treatment options and provides flexibility with personalized drug selection.

Both the PGA and biomarker testing (or companion diagnostics) offer distinct advantages, making them formidable technologies in their own right. The biomarker testing with its NGS-informed targeted therapy features, advanced bioinformatics, and cutting-edge tumor genome profiling systems excels in modern, networked clinical decision-making. Meanwhile, the PGA, known for its versatility, quick turnaround, low cost, and powerful drug efficacy/response prediction capabilities, remains a patient-tested gene-to-drug technology capable of screening all existing cancer drugs in a single run.

While the biomarker testing and companion diagnostics have long been a symbol of precision medicine, their limitations are becoming increasingly apparent. The lack of full-spectrum patient coverage puts biomarker testing and precision therapy at a significant disadvantage in the clinical reality where they can only qualify 20–30% of cancer patients while benefiting only 10–20% of patients.¹⁵ Without targeted therapy, the remaining 70–80%, who are the non-responders, remain vulnerable to the lack of reliable tools for predicting drug efficacy, thereby limiting treatment options (Figure 3). Although targeted therapy remains effective in many scenarios, the benefit gap between responders and non-responders is growing. The rapid advancements in tumor clonal evolution and disease progression, including low response rate, drug resistance, metastasis, and relapse, are making the situation more dire.

These situations have shifted the balance of power in the fight against cancer, and for the first time since the approval of the first targeted drug, the revolution in precision medicine has been subject to debate. Precision oncology, in particular, is feeling the strain as the fleet of biomarker-targeted drugs—good though they are—lacks the therapeutic edge or diversity to benefit the entire patient population and fails to deliver their promise of ‘no patient left behind’. Most significantly, in the event of

therapeutic exhaustion, clinicians will struggle to sustain any treatment plans beyond the standard of care.

For precision diagnostic laboratories, the decision to potentially implement PGA could mark a significant expansion in its precision treatment selection capabilities, integrating it with the current precision oncology testing workup. On the other hand, the biomarker testing, already in service with some molecular laboratories, continues to be a reliable and effective assay, offering a proven platform tailored to patients’ clinical needs. Yet, here is the real-life situation of today’s precision oncology biomarker testing: Apart from the few glaringly obvious actionable mutations, most end up receiving the blanket “mutation not detected” label, effectively leaving patients without any more treatment answers compared to their initial presentation at the clinic, even as precious time ticks away.

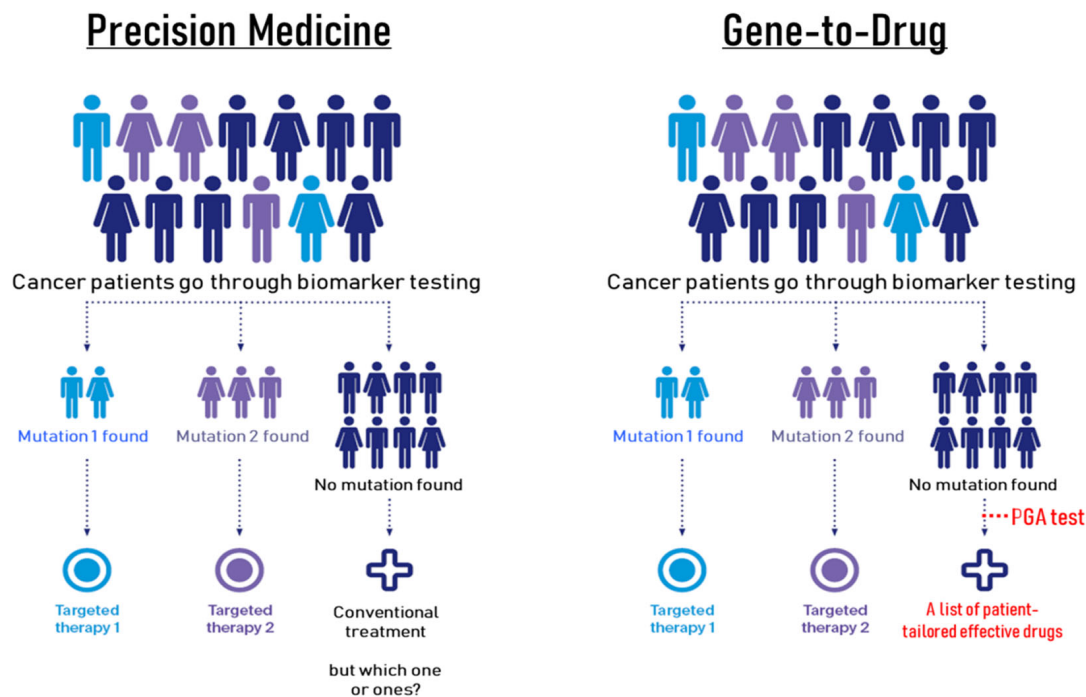
Much more than a laboratory-developed test, PGA offers a real-time, gene-to-drug mapping capability. The platform can smoothly integrate a patient’s own gene signature, enhancing and improving therapeutic efficacy and responses. Decision-making time is shortened from weeks to days, potentially saving lives by giving early warnings and actionable options to patients sooner rather than later. Designed to benefit the patients who are not responding to current precision medicine, PGA marks a significant development of technology innovation into a transformative system aligned with modern clinical requirements.

3.2. Personalized drug efficacy/response results

We performed the PGA LUNG test in NSCLC patients through a pilot study to identify the top-ranking drugs for each patient. PGA LUNG classified drug responses as excellent, good, and fair based on the confidence levels of 95%, 90%, and 80% of Z-scores, respectively. As shown in Table 1, for the five representative patients, PGA LUNG predicted positive responses of drugs, including cisplatin, oxaliplatin, paclitaxel, docetaxel, irinotecan, topotecan, gemcitabine, 5-fluorouracil, bleomycin, cyclophosphamide, and temozolomide, all of which are very common chemotherapy drugs used to treat NSCLC. Similarly, some targeted therapy drugs approved by the FDA for NSCLC were also picked up by PGA LUNG, such as erlotinib, gefitinib, afatinib, osimertinib, cetuximab, and trametinib, suggesting that PGA LUNG could enrich for drug responders, regardless of any known actionable mutations.

Additionally, PGA LUNG predicted efficacies of other cancer drugs that could potentially be used as off-label or for drug repurposing (repositioning), like poly (ADP-ribose) polymerase (PARP) and histone deacetylase

A



B

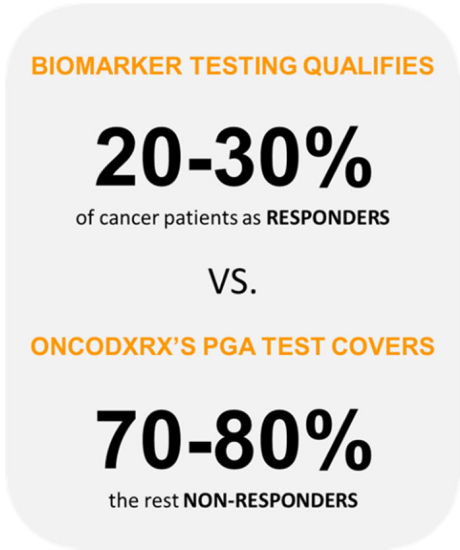


Figure 3. PGA fills the gaps of biomarker testing and completes precision medicine through its gene-to-drug mapping power. (A) Despite the promises of biomarker testing and targeted therapy as core pillars of modern oncology, their capacity to benefit all cancer patients remains limited. Moreover, precision medicine—often positioned as a comprehensive solution—likely faces significant drawbacks and issues, due to challenges in patient eligibility, patient response rate, and drug resistance, making it an unreliable solution for individual patient’s needs. (B) With its remarkable accuracy, accessibility, affordability, and ability to be integrated into precision oncology testing workup, PGA could offer excellent drug selection capabilities via gene-to-drug mapping. With its comprehensive profiling capacity, PGA can identify the most effective drugs from a pool of more than 700 cancer drugs that are approved, in clinical trials, or under investigation.

Table 1. Representative lists of cancer drugs identified and ranked by the PGA LUNG test for individual NSCLC patients

PGA LUNG DRP	Excellent	Good	Fair
Patient #1	Temozolomide ; bosutinib; bleomycin	Talazoparib; niraparib; irinotecan ; erlotinib ; doramapimod	Cyclophosphamide ; avagacestat; tanespimycin; alpelisib; gemcitabine ; ruxolitinib; cetuximab ; 5-fluorouracil ; pilaralisib; gefitinib ; afatinib ; tanespimycin
Patient #2	Zoledronate (ZOMETA); olaparib; talazoparib; rucaparib; cisplatin	Alisertib; irinotecan	Ruxolitinib; cetuximab ; 5-fluorouracil ; vismodegib (ERIVEDGE); savolitinib; niraparib; topotecan ; lenalidomide (Revlimid); cytarabine; mitoxantrone; cyclophosphamide ; camptothecin; uprosertib; oxaliplatin ; docetaxel ; capivasertib
Patient #3	Ulixertinib; refametinib; trametinib ; selumetinib; obatoclox mesylate; midostaurin; ibrutinib; sapitinib; cetuximab ; bexarotene	Pictilisib; pilaralisib; avagacestat; fulvestrant	Elesclomol; osimertinib
Patient #4	Temozolomide ; talazoparib; niraparib; olaparib; irinotecan ; cisplatin ; trichostatin A	Panobinostat; entinostat; avagacestat	Ruxolitinib
Patient #5	Olaparib; talazoparib; rucaparib; cisplatin ; doramapimod; refametinib; trametinib ; tipifarnib	Selumetinib; idelalisib; paclitaxel	

Note: NCCN guideline chemotherapeutic agents and targeted drugs are indicated in boldface and underlined, respectively.

(HDAC) inhibitors, among others. Drug repurposing or repositioning is a method for identifying new therapeutic uses of existing drugs. Repositioning potent candidate drugs in NSCLC treatment is one of the important topics in personalized medicine. A recent meta-analysis suggested that PARP inhibitor-containing regimens can improve overall survival, particularly in NSCLC.¹⁶ While HDAC inhibitors are not highly efficacious as single agents for the treatment of NSCLC, the results of early phase clinical trials utilizing combination strategies have been encouraging, especially the combination with tyrosine kinase inhibitors and immune checkpoint inhibitors.¹⁷

The current study showcased PGA LUNG's drug repurposing capability to identify candidate drugs to treat NSCLC patients. Our results here showed that the PGA LUNG test, derived from a patient's own gene signature, has superior power to predict drug efficacy/response of a full spectrum of cancer drugs from standard-of-care to off-label, in contrast to other one-model-one-drug deep learning computational algorithms.

3.3. Treatment trends for NSCLC in archived datasets and the real world

The TCGA database searches identified 1,145 records that reported treatment patterns in NSCLC patients. Of these, 286 patients received platinum-based therapies, 71 patients paclitaxel, 66 patients pemetrexed, 56 patients gemcitabine, and 53 patients docetaxel (Table 2). Approximately 24% of patients were deceased, while 62% are still alive. The majority of the patients were in the 45–85 age range, and their cancers were localized and had not metastasized to other organs (M0/N0 stages). Chemotherapy was the most common first-line treatment among this cohort of NSCLC patients in the TCGA databases. NSCLC is the most common type of epithelial lung cancer, often diagnosed after 40% of lung tissue invasion. According to the World Health Organization, 30% of NSCLC cases can be cured if detected and treated early. Currently, treatment decisions rely heavily on genomic alterations and mutations. Achieving optimal outcomes requires considering available therapeutics in current anticancer approaches to enhance the quality of life and treatment results for NSCLC

patients. Importantly, the PGA LUNG-proposed drug list was in agreement with the treatment trends in the TCGA databases.

Table 2. The top 10 treatment drugs of NSCLC in the TCGA databases

Treatment	No. of cases
Radiation	163
Cisplatin	154
Carboplatin	132
Paclitaxel	71
Pemetrexed	66
Gemcitabine	56
Docetaxel	53
Vincristine	45
Etoposide	30
Erlotinib	28

The choice of treatment for NSCLC in the real world depends on several factors, including tumor grade, size, location, lymph node status, overall patient health, and lung function (Table 3). For stage 0 NSCLC, surgery is typically curative, with no need for chemotherapy or radiation therapy. For stage I NSCLC, surgery remains the primary treatment option, and postoperative radiation therapy or adjuvant chemotherapy may reduce cancer recurrence. In stage II NSCLC, surgery may be followed by adjuvant chemotherapy, radiation, and immunotherapy. Initial treatment for stage IIIA NSCLC often involves a combination of chemotherapy, radiation therapy, and/or surgery, supplemented by immunotherapy. For patients with specific *EGFR* gene mutations, adjuvant therapy with the targeted drug osimertinib may be considered. Stage IIIB NSCLC, which cannot be entirely removed by surgery, benefits from chemoradiotherapy and immunotherapy. Stage IVA or IVB NSCLC is more challenging to cure, but treatments such as surgery, photodynamic therapy, laser therapy, radiation therapy, chemotherapy, immunotherapy, and targeted therapy can help relieve symptoms. Compared to best supportive care, platinum-based chemotherapy extends survival, improves symptom control, and enhances quality of life for patients with metastatic disease. For patients with advanced, incurable NSCLC, cisplatin-based combinations have shown improved survival rates. Combining platinum with newer agents such as vinorelbine, paclitaxel, docetaxel, gemcitabine, or irinotecan has proven more effective than older platinum-based combinations. For patients whose disease progresses during or after first-line therapy, single-

agent docetaxel and pemetrexed are preferred second-line therapies. Pemetrexed has demonstrated comparable efficacy to docetaxel with a more favorable adverse-effect profile.¹⁸ For stage IVB cancers that have metastasized throughout the body, cancer cells will be tested for specific gene mutations, including those in the *VEGF*, *KRAS*, *EGFR*, *ALK*, *ROS1*, *BRAF*, *RET*, *MET*, and *NTRK* genes. If any of these genes are mutated, targeted therapy drugs like epidermal growth factor receptor (EGFR) tyrosine kinase inhibitors will likely be the first line of treatment.¹⁹

3.4. Commonly used real-world NSCLC therapies identified by the PGA LUNG test

Real-world data are becoming increasingly important in the evaluation of modern therapeutics. They allow for a pragmatic assessment of treatment patterns found in a variety of conditions and are particularly insightful in oncology, where multiple lines of different treatments can be offered to the patient. Nevertheless, a growing literature describes the poor clinical outcomes among patients with NSCLC who experience progression on the frontline treatments, highlighting the large unmet need for additional treatment options that may improve survival in later lines of therapy. Therefore, clinical trials of novel agents that may offer benefit in this patient population are needed. Given the heterogeneous monitoring and treatment approaches in real-world clinical practice, it is noteworthy that certain PGA LUNG-identified drugs, either chemotherapy or targeted therapy, were found to be frequently used in real-world settings (Figure 4). The PGA LUNG test accurately identified the most commonly prescribed real-world NSCLC treatments, including platinum-based and taxane-based chemotherapies and targeted therapies (e.g., erlotinib, gefitinib, osimertinib for *EGFR*-mutated tumors), demonstrating its clinical relevance in predicting standard-of-care drug efficacy based on patient-specific gene expression profiles. Together, the PGA LUNG test represents an unprecedented tool to support clinical decision-making of treatment selection.

3.5. PGA LUNG provided vital insights for combination therapy

In the past decade, advances in molecular pathology have deepened our understanding of NSCLC's pathophysiology and heterogeneity, leading to significant improvements in treatment methods. Despite the control provided by targeted therapies, drug resistance in tumors remains inevitable. To enhance treatment effectiveness, the development of combination therapies and a better understanding of resistance mechanisms are essential. Numerous clinical trials evaluating chemotherapy and targeted therapy agents are currently underway, and the results have been

Table 3. The most common classes of drugs used to treat NSCLC in the real world

Class	Representative drug(s)	Target	Applications
Platinums (alkylating agents)	Cisplatin, carboplatin	DNA	Adjuvant therapy; combination regimens
Taxanes	Paclitaxel, docetaxel	Tubulin (mitotic spindle formation)	Second-line chemotherapy; combination regimens
Vinca alkaloids	Vinorelbine, vinoblastine	Microtubule formation	Second-line chemotherapy
Antimetabolites	Gemcitabine	DNA polymerase	Second-line chemotherapy; combination regimens
Topoisomerase I inhibitors	Irinotecan, topotecan	Topoisomerase I	Combination regimens
Podophyllotoxins	Etoposide, teniposide	Topoisomerase II	Combination regimens
Antifolate	Pemetrexed	Folate-dependent pathways	Second-line chemotherapy
EGFR tyrosine kinase inhibitors	Gefitinib, erlotinib, afatinib, osimertinib	EGFR tyrosine kinase	NSCLC with an <i>EGFR</i> mutation

Abbreviations: EGFR: Epidermal growth factor receptor; NSCLC: Non-small cell lung cancer.

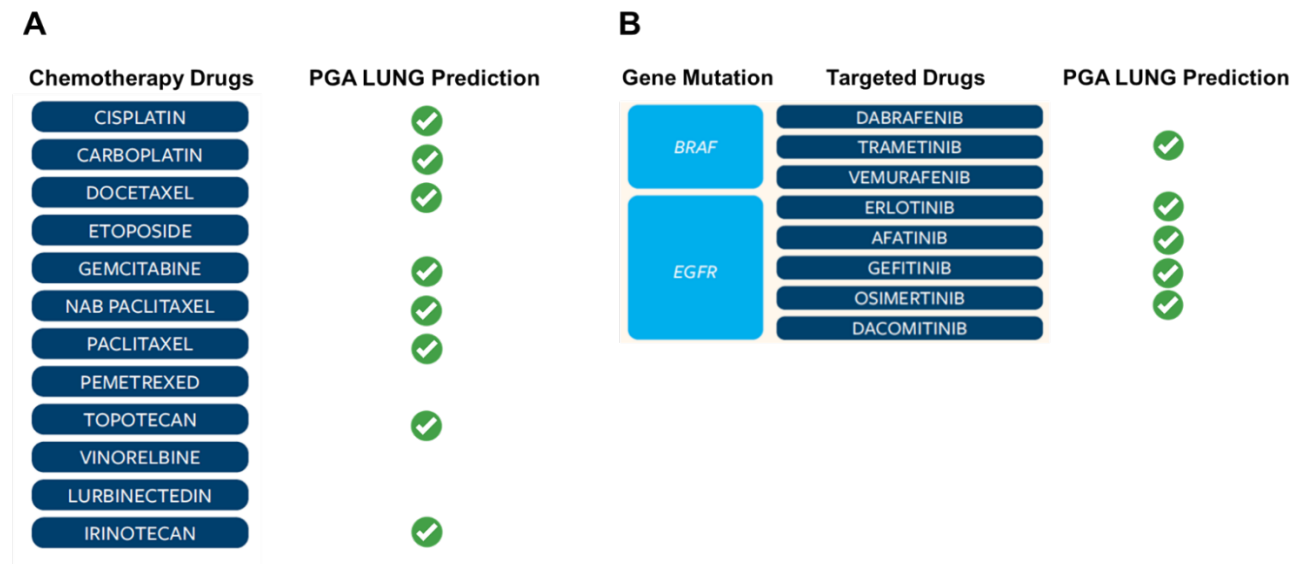


Figure 4. Excellent alignment between PGA LUNG drug efficacy/response prediction and the real-world drug usage trends in NSCLC. (A) Chemotherapy drugs; (B) targeted therapy drugs.

encouraging (Table 4). Developing combination therapy is a complex endeavor that can greatly benefit from PGA LUNG, which matches patients' transcriptional signatures with extensive drug efficacy/response data. This innovative gene-drug mapping approach allows for the identification of drugs and drug combinations tailored to target specific tumor pathways, networks, or vulnerabilities in individual patients, making it highly suitable for developing personalized cancer treatment strategies.

Going forward, enhanced knowledge of predictive biomarkers and the development of combination therapies can provide the most effective treatments. Proper patient selection using PGA LUNG could be crucial

for personalized oncological intervention, maximizing benefits, and reducing toxicities. Future improvements in patient survival are anticipated if resistance is addressed, suitable drugs or combinations of drugs are used, and side effects are minimized.

3.6. Clinical performance of the PGA LUNG test in a small real-world trial

Progression-free survival (PFS) serves as the preferred endpoint in small-scale, short-duration oncology trials due to three key advantages over overall survival (OS)²⁰: (i) PFS events manifest earlier than OS events, enabling interim analysis within compressed trial timelines; (ii)

Table 4. Approved and investigational drugs for chemotherapy and targeted therapy in NSCLC

Therapy	Drugs	Indication	Status
Chemotherapy	RG-4733 plus erlotinib	Advanced NSCLC	Phase I/II
Chemotherapy	Sulforaphane plus cisplatin and doxorubicin	NSCLC	Preclinical
Chemotherapy	Acetyl-11-keto-beta-boswellic acid plus cisplatin	NSCLC	Preclinical
Chemoradiotherapy/ Immunotherapy	Conventional chemoradiotherapy (platinum-based chemotherapy and radiotherapy) plus durvalumab	Stage III NSCLC	Phase III
Targeted therapy	Gefitinib, erlotinib, afatinib, and dacomitinib	NSCLC with <i>EGFR</i> mutation (exon 19 deletions, exon 21 substitution mutations)	Approved
Targeted therapy	Osimertinib	Metastatic NSCLC with <i>EGFR</i> mutation (T790M mutation)	Approved
Targeted therapy	Crizotinib, lorlatinib	<i>ALK</i> -positive or <i>ROS1</i> -positive NSCLC	Approved
Targeted therapy	Alectinib, ceritinib	<i>ALK</i> -positive metastatic NSCLC	Approved
Targeted therapy	Brigatinib	NSCLC with <i>ALK</i> -positive, <i>ROS1</i> -positive, or <i>EGFR</i> mutation-positive	Approved
Targeted therapy	Dabrafenib plus trametinib	<i>BRAF</i> V600E mutant metastatic NSCLC	Phase II
Targeted therapy	Larotrectinib	Metastatic NSCLC harboring an <i>NTRK</i> fusion without acquired mutation for resistance	Phase II
Targeted therapy	Entrectinib	Metastatic <i>ROS1</i> -positive NSCLC	Approved
Targeted therapy	Entrectinib	NSCLC harboring an <i>NTRK1/2/3</i> , <i>ROS1</i> , or <i>ALK</i> gene fusion	Phase II
Targeted therapy	Crizotinib	<i>ROS1</i> - or <i>MET</i> -mutated NSCLC	Phase II
Targeted therapy	Pralsetinib, selpercatinib	Metastatic <i>RET</i> fusion-positive NSCLC	Approved
Targeted therapy	Pyrotinib	Advanced NSCLC with <i>HER2</i> mutation	Phase II
Targeted therapy	Tucatinib	<i>HER2</i> -expressing NSCLC	Phase II
Targeted therapy	Trastuzumab	NSCLC	Phase II
Targeted therapy	Trastuzumab deruxtecan	<i>HER2</i> -mutated metastatic NSCLC	Phase II
Targeted therapy	Adagrasib	NSCLC harboring the <i>KRAS</i> G12C mutation	Phase III
Targeted therapy	Sotorasib	Stage IV NSCLC with <i>KRAS</i> p.G12C mutation	Phase II
Targeted therapy	Docetaxel, cisplatin, and pemetrexed plus gefitinib	NSCLC	Preclinical
Targeted therapy/ Anti-angiogenic therapy	Erlotinib plus bevacizumab	Untreated metastatic <i>EGFR</i> -mutated NSCLC	Phase III
Targeted therapy/ Anti-angiogenic therapy	Gefitinib plus apatinib	Advanced NSCLC with <i>EGFR</i> mutation	Phase III
Targeted therapy	Osimertinib plus dacomitinib	Advanced <i>EGFR</i> mutant lung cancer	Phase I/II
Targeted therapy	Osimertinib and navitoclax	<i>EGFR</i> -mutated NSCLC	Phase IB

Abbreviations: ALK: Anaplastic lymphoma kinase; BRAF: B-Raf proto-oncogene, serine/threonine kinase; EGFR: Epidermal growth factor receptor; HER2: Human epidermal growth factor receptor 2; KRAS: Kirsten rat sarcoma viral oncogene homolog; MET: Mesenchymal-epithelial transition factor; NSCLC: Non-small cell lung cancer; NTRK: Neurotrophic tyrosine receptor kinase; RET: Rearranged during transfection; ROS: c-ros oncogene.

Determination of PFS requires fewer participants and abbreviated follow-up as progression events, compared to OS analysis. PFS occurs more frequently than deaths and presents earlier in the disease trajectory, reducing trial costs by 30–50% and accelerating development cycles; (iii) PFS is less confounded by subsequent treatment lines, non-cancer mortality, providing a cleaner signal of the investigational therapy's efficacy.

To evaluate the clinical performance of PGA LUNG in a real-world setting, we analyzed 24 patients with recurrent/progressive lung cancer who had limited therapy options. Patients were prospectively stratified into two matched cohorts (placebo: $n = 12$; experimental: $n = 12$) balanced by age, gender, and disease stage. In the placebo group, patients received standard-of-care therapy without PGA guidance; while in the experimental cohort, patients went through the PGA LUNG test and received PGA-informed treatment selection. The Kaplan–Meier method and a log-rank test were used to analyze the univariate discrimination of PFS as the primary outcome by demographic data, baseline clinical information, and toxicities. Kaplan–Meier analysis in our small trial demonstrated significantly prolonged PFS (HR = 1.67; 95% CI: 1.3–2.14; $p = 0.043$) in PGA LUNG-guided versus non-guided lung cancer patients (Figure 5). These findings confirmed PGA LUNG's clinical utility, showing a substantial survival impact in

real-world settings.

4. Discussion

The complexity of cancer arises from the intricate interplay of genetic and epigenetic factors, biological networks, compensatory mechanisms, and environmental influences, making it unlikely that each patient will respond similarly to the same drug(s). The outcomes of drug therapy in oncology vary widely, from therapeutic efficacy to severe toxicity, primarily due to the tumor's molecular heterogeneity. Genetic mutations, epigenetic alterations, and signaling pathway dysregulation influence drug response, often leading to unpredictable results. Precision medicine, guided by molecular profiling, aims to optimize treatment by targeting specific tumor biomarkers, thereby improving efficacy and minimizing adverse effects. Over the past few decades, there has been a lack of new treatment mechanisms for cancer patients who do not respond to precision therapies, *i.e.*, non-responders. This is largely because modern medicine has focused primarily on the development of target-based therapies. Even patients with the same cancer type need personalized treatments due to factors like genetic predisposition, lifestyle, and immune response. Therapeutic outcomes range from complete remission to treatment resistance, and cancer cells often develop drug resistance through genetic mutations,

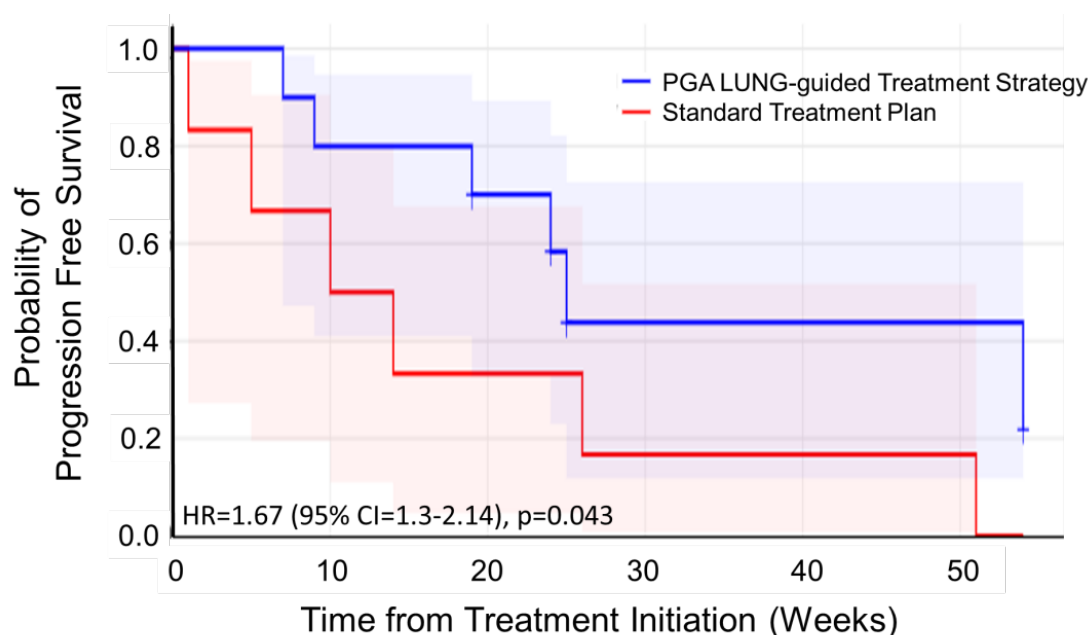


Figure 5. Kaplan–Meier analysis of progression-free survival (PFS) for the treatment of real-world lung cancer patients with or without the support from the PGA LUNG test.

Abbreviations: CI: Confidence interval; HR: Hazard ratio.

making therapy ineffective.

Today, there are more than 60 companion diagnostics approved by the FDA, most of which are in the field of oncology. Most drugs that are available in the market are beneficial to a fraction of patients who receive them; identifying the fraction that will respond to these drugs is incredibly important. Biomarker testing often fails to predict treatment efficacy due to tumor heterogeneity, as a single biopsy may not represent the cancer's full molecular diversity. Spatial and temporal variations in genetic and phenotypic profiles lead to sampling bias, resulting in incomplete or misleading data. This limitation underscores the need for multi-region sequencing and longitudinal monitoring to improve predictive accuracy. Most companion/biomarker tests in the market today target a single biomarker, and therefore, lack the ability to tackle the vast heterogeneity seen across patients and within individual tumors. These constraints contribute to the fact that, even today, many patients who receive targeted treatments fail to respond to them. Therefore, it is of paramount importance to initiate the appropriate therapy for a patient as promptly as possible.

We have demonstrated a breakthrough technology, PGA LUNG, for the prediction of drug efficacy/response in NSCLC patients using a patient-derived gene expression signature. First, we established a lung cancer-specific gene overexpression panel using liquid biopsy transcriptomic profiling. Following patient testing with data homogenization and filtering, the patient-unique gene pattern was used to map out the best-fitting drugs from a library of ~700 cancer drugs, yielding a list of potential drugs with excellent, good, or fair responses.

PGA LUNG captured a statistically significant proportion of potentially effective drugs. Regardless of standard-of-care or off-label, and in all cases, results were consistent with those treatment trends in the TCGA databases, NCCN guidelines, and real-world patients. Overall, our results here suggested that PGA LUNG, created on a patient's own gene signature, can complement or even surpass the performance of companion diagnostics biomarker testing. To our knowledge, this is the first time that a drug response prediction technology capable of this function has been described.

In NSCLC, standard treatments yield poor outcomes, except in the most localized cases. Newly diagnosed NSCLC patients are potential candidates for studies exploring new treatment methods. Surgery offers the most curative potential for this disease. Postoperative chemotherapy may further benefit patients with resected NSCLC. Radiation therapy combined with chemotherapy can cure a small number of patients and provide palliation

for many. Prophylactic cranial irradiation may reduce the incidence of brain metastases, but there is no evidence of a survival benefit, and its impact on quality of life remains unknown.²¹ In advanced-stage disease, chemotherapy or EGFR kinase inhibitors provide modest improvements in median survival, though overall survival remains poor.²²

Chemotherapy has led to short-term improvements in disease-related symptoms for patients with advanced NSCLC. Numerous clinical trials have evaluated the impact of chemotherapy on tumor-related symptoms and quality of life. Collectively, these studies indicate that chemotherapy can manage tumor-related symptoms without negatively affecting overall quality of life.^{23–28} However, further research is needed to fully understand its impact on quality of life. Generally, older patients who are medically eligible and have good performance status experience the same benefits from treatment as younger patients.

The discovery of gene mutations in lung cancer has paved the way for molecularly targeted therapies, improving the survival rates of certain patients with metastatic disease.^{29–33} Specifically, genetic abnormalities in the EGFR, MAPK, and PI3K signaling pathways in subsets of NSCLC can define mechanisms of drug sensitivity and resistance, both primary and acquired, to kinase inhibitors. *EGFR* mutations significantly predict an enhanced response rate and PFS with EGFR inhibitors. *ALK* fusions with *EML4* and other genes, found in about 3–7% of unselected NSCLC cases, respond well to ALK inhibitors like alectinib. The *MET* oncogene, encoding the hepatocyte growth factor receptor, is linked to secondary resistance to EGFR tyrosine kinase inhibitors. Recurrent *ROS1* gene fusions, observed in up to 2% of NSCLCs, respond to crizotinib and entrectinib. *NTRK* gene fusions, present in up to 1% of NSCLCs, can be treated with TRK inhibitors, such as larotrectinib and entrectinib.^{19,34–36}

A systematic review of the TCGA databases and real-world statistics revealed that the primary chemotherapeutics used in NSCLC are platinum analogs (cisplatin and carboplatin), vinca alkaloids (vinorelbine, vinblastine, vindesine), etoposide, gemcitabine, pemetrexed, topoisomerase I inhibitors (irinotecan, topotecan), and taxanes (paclitaxel, docetaxel). While chemotherapy monotherapy is less commonly employed as a first-line treatment, it is most frequently administered to elderly patients aged 65 years and above. Conversely, targeted therapies, including TKIs, such as gefitinib, erlotinib, afatinib, and osimertinib, showed the highest utilization as first-line treatments.^{37–40}

With the recent expansion of personalized treatment options for NSCLC, the adoption of immunotherapy has

steadily increased in frontline treatment within real-world practice. Most patients receiving immunotherapy were treated with pembrolizumab, either as monotherapy or in combination with chemotherapy. Combination therapy is expected to grow in popularity over the coming years. For second-line treatment, unspecified chemotherapy regimens remained the primary therapy in studies, closely followed by chemotherapy monotherapy.

In this study, the PGA LUNG test successfully passed a reality check and demonstrated its accuracy by aligning its results with TCGA data and real-world treatment trends in NSCLC. PGA LUNG goes beyond merely predicting drug responses; it enables the identification and ranking of the most effective drugs, whether approved, in clinical trials, or investigational. Our findings also indicated that real-world treatment patterns shift as new therapies are introduced and as U.S. treatment guidelines evolve. Clinical practice treatment decisions appear more adaptable to therapies designed to target cellular signaling and/or modulate the immune microenvironment, as the PGA LUNG test does.

Blood-based transcriptomic profiling provides a comprehensive view of the tumor microenvironment and immune-tumor interactions by analyzing circulating RNA from immune cells, stromal components, and tumor-derived signals. Unlike mutation-focused assays, it captures dynamic immune responses, cytokine activity, and cellular heterogeneity, offering deeper insights into disease progression, treatment resistance, and potential therapeutic targets. This approach enhances precision oncology by revealing systemic and local tumor microenvironment interactions previously overlooked by genomic analyses alone.

The “tumor vulnerability” biomarkers included in PGA LUNG highlighted key genes and signaling pathways that may play significant roles in the mechanisms of action of various lung cancer drugs. These findings suggested that our gene-to-drug mapping technology can generate biologically relevant genes and pathways, enhancing the understanding of mechanisms underlying drug efficacy and response. Furthermore, it may provide additional combinatorial therapeutic strategies to overcome certain drug resistances.

A significant strength of the PGA LUNG test lies in its robust, streamlined, and reproducible approach to mapping, identifying, and ranking the best cancer drugs for individual patients. *In silico* deep learning drug response models can only predict limited numbers or certain classes of drugs, while PGA screens and maps out over 700 existing cancer drugs in a single run (ALL-IN approach). Notably, while all *in silico* digital training models are still

in the development stage and far from clinical application, PGA LUNG has shown promising results ready for its prime time in clinical settings.

By incorporating patient-specific gene signatures, PGA LUNG offers more precise drug efficacy/response information. Furthermore, it highlights the efficacy of certain off-label cancer drugs, such as inhibitors of PARP, MEK (mitogen-activated extracellular signal-regulated kinase), and HDAC. Despite significant advancements in surgical, radiological, chemical, and immunological approaches that have improved cancer treatment outcomes, the drug regimen remains a key therapeutic strategy. However, its clinical efficacy is often limited by drug resistance and severe toxic side effects, highlighting the critical need for novel cancer therapeutics. One promising strategy gaining attention is drug repurposing, which involves identifying new applications for existing, clinically approved drugs. This approach offers several advantages in cancer treatment, as repurposed drugs are typically cost-effective, proven to be safe, and can expedite the drug development process due to their established safety profiles. In this regard, PGA LUNG could provide an unprecedented and unmatched power for cancer drug repurposing or repositioning, advancing the field of precision medicine and showcasing its potential to provide more effective and less toxic therapeutic options for cancer patients.

PGA LUNG testing results demonstrated exceptional performance in predicting clinical drug efficacy/response, aligning with real-world treatment patterns and potentially having a profound impact on patient care. For example, predicting therapeutic efficacy/response *in vitro* is significantly less costly and time-consuming than conducting large clinical trials. Additionally, *in vitro* patient testing is typically conducted under controlled experimental conditions, leading to greater accuracy. The ability to test a larger number of patients with greater accuracy, lower costs, and faster turnaround times can enhance statistical power compared to *in vivo* animal models, which rely on smaller sample sizes and often yield noisy clinical response data. Overall, the PGA LUNG approach represents a revolutionary breakthrough in personalizing drug treatment.

There is no limit to the number of drugs that could be mapped out against a patient's gene expression profile. With PGA LUNG, predictive efficacies of all existing anticancer compounds can be obtained, meaning that, given a liquid biopsy, it would be game-changing and disruptive to use this approach to estimate response to every drug prior to any course of clinical treatment. The affordability and accessibility of PGA LUNG make it feasible to incorporate

this technology into the standard of care.

Our findings also have significant implications for drug development, where the PGA approach could be utilized to identify likely drug responders before conducting clinical trials. There is growing interest in developing drugs alongside companion diagnostic tests. While the benefits of identifying potential drug responders are clear, developing accurate biomarkers without exposing the drug to patients is challenging. PGA LUNG holds tremendous potential as a companion diagnostic, especially for patients unresponsive to precision therapy. Additionally, there is a clear ethical advantage, as this diagnostic method can be developed without exposing potentially unresponsive patients to toxic drug candidates.

PGA technology represents a promising approach to personalized oncology by leveraging gene expression profiling to predict drug responses. However, several limitations and challenges must be considered regarding its accuracy, generalizability, and clinical utility. False positives may arise if the gene expression signatures used to predict drug sensitivity do not fully account for tumor heterogeneity, microenvironmental influences, or post-transcriptional modifications that alter protein function. Conversely, false negatives could occur if the PGA platform fails to detect rare but actionable molecular subtypes or if the gene expression thresholds for drug resistance are overly stringent. Additionally, the clinical utility of PGA depends on the availability of matched targeted therapies; even if the technology accurately predicts drug efficacy, patients may lack access to the recommended treatments due to cost, regulatory restrictions, or off-label use barriers.

The applicability of PGA across diverse cancer populations remains another critical consideration. Disparities in tumor genetic expression patterns may affect the generalizability of PGA's predictive power. We therefore designed and developed individual PGA technologies, such as PGA LUNG, PGA BREAST, and PGA PANCREATIC, to address each corresponding cancer type.

Despite these challenges, PGA holds significant potential if integrated with complementary biomarker testing or companion diagnostics and validated in prospective clinical trials. While it might not be a standalone solution, PGA could enhance precision oncology by providing an additional layer of evidence to guide therapeutic decision-making, particularly when combined with genomic and clinical data. Future iterations of the technology need to prioritize transparency in validation metrics, particularly positive predictive value and survival benefit, to establish its role in routine clinical practice.

5. Conclusion

In conclusion, the PGA LUNG test results have significantly mirrored the evolving NSCLC treatment landscape in the U.S. over recent years. For the first time, we demonstrated the possibility of accurately predicting drug efficacy/response in a clinical cohort using patients' own gene expression signatures through gene-drug mapping computational analytics. Additionally, we showed that the PGA LUNG test results align with real-world and NCCN guideline treatment patterns. These findings carry profound implications for personalized medicine and drug development. Future PGA efforts will aim to enhance predictions with more rigorous transcriptome quantification and further validation in prospective clinical trials.

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Conflict of interest

The authors declare that they have no competing interests.

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Ethics approval and consent to participate

The study was conducted according to the guidelines of the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use Guideline for Good Clinical Practice (ICH-GCP), and approved by the Institutional Research Board of Shin Kong Wu Ho-Su Memorial Hospital, Taipei, Taiwan, IRB 20180804Rv2. Written informed consent was obtained from all subjects involved in the study for the use and publication of data (2018-08-28 version 2). All experiments were carried out in accordance with the ICH-GCP in its last revised version.

Consent for publication

Written informed consent was obtained from all subjects involved in the study for the use and publication of data (2018-08-28 version 2).

Availability of data

The raw data supporting the conclusions of this manuscript will be made available by the authors, without undue reservation, to any qualified researcher upon reasonable request.

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