

Breaking the targeted monotherapy myth: evolving precision medicine for heterogeneous cancers

Abstract

Precision oncology has revolutionized cancer treatment by targeting specific molecular alterations driving tumor growth. However, a fundamental limitation persists: no single “therapeutically actionable” biomarker is universally expressed by all tumor cells within a given cancer type. This intratumoral heterogeneity ensures that even highly effective targeted therapies leave residual disease, leading to therapeutic resistance and relapse. While precision monotherapy can induce deep initial responses, resistance mechanisms and clonal evolution allow tumor subpopulations to survive and repopulate. The persistence of residual disease following monotherapy underscores the critical need for innovative approaches that address tumor heterogeneity and optimize combination therapy strategies. Future directions include adaptive therapy regimens, guided by real-time molecular monitoring, and the development of polypharmacological agents capable of multi-target inhibition. Ultimately, overcoming therapeutic resistance requires a paradigm shift from monolithic targeting to dynamic, systems-based approaches that account for the evolving nature of cancer.

Keywords: Targeted monotherapy, therapeutically actionable biomarker, tumor heterogeneity, combination therapy, precision oncology

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Introduction

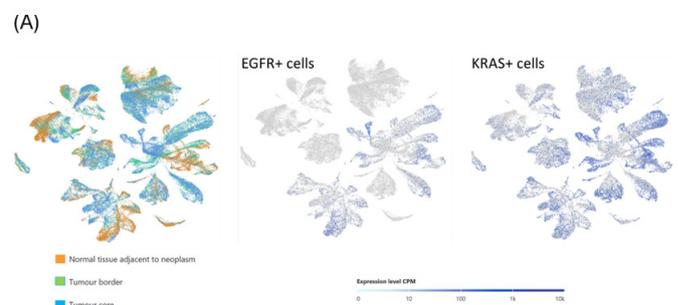
The paradox of precision oncology—successes and inherent limitations

The advent of precision oncology has revolutionized cancer treatment by enabling the development of therapies that target specific molecular alterations driving tumor growth. This paradigm shift, grounded in the identification of “therapeutically actionable” biomarkers, has yielded remarkable clinical successes, including EGFR tyrosine kinase inhibitors for EGFR-mutant non-small cell lung cancer (NSCLC), BRAF/MEK inhibitors for BRAF V600E-mutant melanoma, and PARP inhibitors for BRCA-mutant cancers.¹⁻³ However, despite these advances, a critical limitation persists: no single “therapeutically-actionable” biomarker is universally expressed by all tumor cells within a given cancer type.^{4,5} This biological reality—intratumoral heterogeneity—ensures that even the most effective targeted therapies leave behind residual disease, ultimately leading to therapeutic resistance and disease relapse.^{6,7} While precision monotherapy can induce profound initial responses, the inevitability of tumor cell escape underscores the need for a fundamental re-evaluation of current treatment strategies. This article provides a comprehensive examination of the biological basis of tumor heterogeneity, its clinical implications, and the emerging therapeutic approaches that may overcome these challenges.

The biological complexity of tumor heterogeneity: clonal architecture and evolutionary dynamics

Tumors are not monoclonal populations but rather complex ecosystems composed of genetically and phenotypically diverse subclones. Advances in next-generation sequencing and single-cell genomics and transcriptomics have revealed the staggering extent of intratumoral heterogeneity, demonstrating that individual tumors

harbor multiple subpopulations with distinct mutational profiles, transcriptional states, and epigenetic modifications.^{8,9} Multi-region sequencing studies in renal cell carcinoma, for example, have shown that only 30-60% of somatic mutations are consistently present across all tumor regions, with spatially distinct subclones exhibiting unique driver alterations.¹⁰ Similarly, in breast cancer, HER2 amplification—a well-established therapeutic target—frequently displays marked intratumoral heterogeneity, leading to incomplete responses to HER2-directed therapies such as trastuzumab.¹¹ Even in malignancies with highly prevalent biomarkers, such as ALK rearrangements in NSCLC or BRAF V600E mutations in melanoma, spatial heterogeneity ensures that a subset of tumor cells lack the target, thereby escaping therapeutic eradication.^{12,13} This clonal diversity is further exacerbated by Darwinian selection under therapeutic pressure, where resistant subpopulations are enriched, driving disease progression.¹⁴ The implications of this biological complexity are profound: precision monotherapy, by its very nature, cannot achieve complete tumor eradication due to the absence of universally expressed biomarkers (Figure 1).



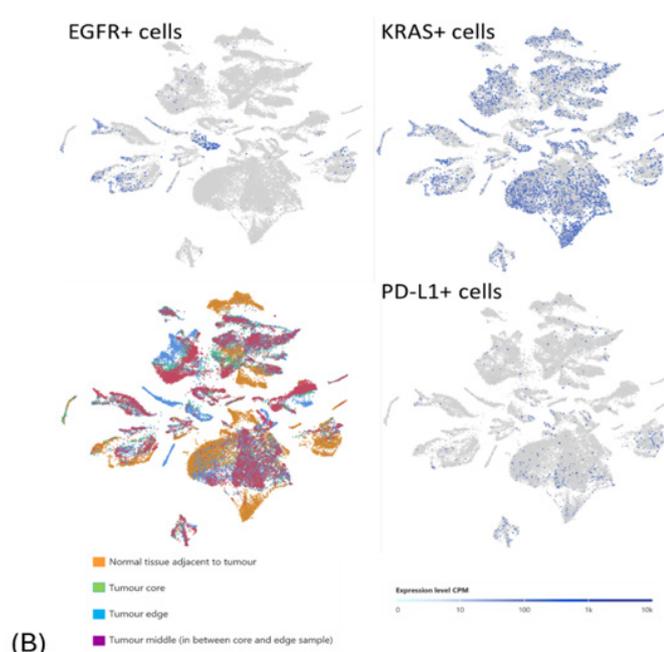


Figure 1 Not every tumor cell expressed therapeutically actionable biomarkers as illustrated by single-cell RNA sequencing of (A) colorectal tumors and adjacent non-malignant colon tissue; and (B) lung carcinomas and adjacent normal tissue. Spatial transcriptomic analysis here showed that some tumor cells don't express EGFR, KRAS or PD-L1, the hallmark genes utilized for treatment guidance for these two cancer types. Consequently, these tumor cells would evade targeted therapy due to the lacking of the target, enabling residual disease and progression.

Mechanisms of resistance: the molecular basis of therapeutic failure

The emergence of resistance to targeted therapy is governed by a multitude of molecular mechanisms, each contributing to the survival and eventual resurgence of residual tumor cells. Pre-existing subclones lacking the targeted biomarker represent a primary source of resistance, as exemplified by KRAS-mutant subpopulations in EGFR-driven NSCLC that persist despite EGFR inhibition.¹⁵ Acquired resistance mutations, such as EGFR T790M, ALK G1202R, or BRAF splice variants, further complicate treatment by rendering initially effective therapies futile.^{16,17} .-mutant melanoma, allowing them to circumvent targeted inhibition.^{18,19} Phenotypic plasticity—manifested through epithelial-mesenchymal transition (EMT), lineage switching, or epigenetic reprogramming—provides another avenue for escape, enabling tumor cells to adopt alternative transcriptional states that confer drug tolerance.²⁰ Single-cell RNA sequencing has further revealed the existence of drug-tolerant persister (DTP) cells, a transient but resilient subpopulation capable of surviving targeted therapy through metabolic and epigenetic adaptations.^{21,22} These DTPs serve as reservoirs for relapse, highlighting the inadequacy of monotherapy in achieving durable disease control. Collectively, these resistance mechanisms underscore the necessity of combinatorial strategies that simultaneously target multiple vulnerabilities within the tumor ecosystem.

Diagnostic challenges: the limitations of current biomarker detection technologies

Biopsy sampling, while essential for tumor diagnosis, has limitations in assessing tumor heterogeneity due to spatial and

temporal sampling biases. Single biopsies often capture only a small portion of the tumor, missing regional genetic and phenotypic variations. Intratumoral heterogeneity—driven by clonal evolution and microenvironmental influences—means that biopsy results may not represent the entire tumor's molecular profile. Additionally, sampling errors can occur if the biopsy targets necrotic or low-grade regions. Temporal heterogeneity further complicates assessment, as tumors evolve over time or in response to therapy. Consequently, biopsy-based analyses risk underestimating tumor diversity, potentially leading to incomplete therapeutic strategies or resistance mechanisms being overlooked.

While liquid biopsies and circulating tumor DNA (ctDNA) analysis have transformed the real-time monitoring of tumor dynamics, these approaches are not without significant limitations. ctDNA profiling, though invaluable for detecting resistance mutations and tracking clonal evolution, often fails to capture the full spectrum of spatial heterogeneity, as it predominantly reflects the most dominant or aggressive subclones.^{23,24} Moreover, residual disease frequently persists even in the absence of detectable ctDNA, indicating that liquid biopsies alone cannot reliably predict therapeutic cure.²⁵ Emerging technologies, such as multi-region sequencing and single-cell profiling, offer enhanced resolution in characterizing intratumoral heterogeneity but remain logistically challenging for routine clinical implementation.^{26,27} The diagnostic dilemma is further compounded by temporal heterogeneity, where tumors continuously evolve under treatment pressure, necessitating dynamic and adaptive monitoring strategies. These challenges emphasize the urgent need for integrative diagnostic platforms that combine genomic, transcriptomic, and proteomic data to comprehensively map tumor heterogeneity and guide therapeutic decision-making.

Overcoming monotherapy limitations: rational combination strategies

Given the inevitability of residual disease following precision monotherapy, the field is increasingly shifting toward rational combination strategies designed to target multiple oncogenic dependencies simultaneously (Table 1). Dual pathway inhibition, exemplified by the combination of BRAF and MEK inhibitors in melanoma, has demonstrated superior efficacy compared to single-agent therapy, delaying—though not preventing—the emergence of resistance.²⁸ Vertical and horizontal pathway blockade, such as concurrent EGFR and MET inhibition in NSCLC, represents another promising approach to mitigate bypass signaling.²⁹ Immunotherapy combinations, particularly the integration of PD-1/PD-L1 inhibitors with targeted therapies, have shown potential in engaging the immune system to eliminate residual tumor cells.³⁰ However, the clinical translation of these strategies is fraught with challenges, including overlapping toxicities and the unpredictable interplay between clonal subpopulations. Adaptive therapy, which modulates drug dosing to suppress dominant clones while preventing the outgrowth of resistant subpopulations, has shown promise in preclinical models but remains to be optimized for clinical use.³¹ Polypharmacology—the design of multi-targeted agents—and the exploitation of non-oncogene addictions, such as metabolic vulnerabilities in persister cells, are additional avenues being explored to overcome therapeutic resistance.^{32,33} These efforts collectively underscore the imperative to move beyond monotherapy and embrace multimodal treatment paradigms.

Table 1 Comparison of targeted monotherapy vs. rational combination therapy

Category	Targeted monotherapy	Rational combination therapy
Definition	Single-agent therapy targeting a specific molecular alteration (e.g., kinase inhibitor, monoclonal antibody).	Simultaneous use of two or more drugs targeting complementary pathways to enhance efficacy and reduce resistance.
Mechanism	Blocks a single driver pathway (e.g., EGFR inhibition in NSCLC).	Targets multiple pathways (e.g., EGFR + MEK inhibition) or combines targeted+ immune therapy (e.g., BRAF + MEK + PD-I inhibition).
Efficacy	High initial response in biomarker-selected patients Limited by resistance (e.g., secondary mutations, bypass signaling).	Higher response rates and deeper responses Delays or prevents resistance
Resistance Mechanisms	On-target mutations (e.g., T790M in EGFR) Off-target bypass (e.g., MET amplification)	Reduced likelihood of resistance due to multi- pathway inhibition Still possible if all targets are not fully suppressed
Toxicity	Generally lower than chemotherapy On-target toxicities (e.g., rash with EGFR inhibitors).	Higher risk due to overlapping toxicities (e.g., liver toxicity with BRAF + MEK inhibitors) Requires careful dose optimization
Biomarker Dependency	Requires strong predictive biomarkers (e.g., ALK fusions for ALK inhibitors)	May require multiple biomarkers (e.g., BRAFV600E+ immune context for combo therapy)
Clinical Use	First-line in defined molecular subsets (e.g., HER2 + breast cancer)	Used when monotherapy resistance is common (e.g., BRAF + MEK in melanoma) Emerging in front-line settings (e.g., PARP + immune checkpoint inhibitors)
Cost & Accessibility	High but often covered in biomarker-defined populations	Significantly higher cost Limited access in low-resource settings
Regulatory Approvals	Many FDA-approved (e.g., imatinib, osimertinib).	Increasing approvals (e.g., dabrafenib + trametinib, nivolumab + ipilimumab)
Examples	Trastuzumab (HER2+ breast cancer) Osimertinib (EGFR-mutated NSCLC)	Dabrafenib + trametinib (BRAF-mutant melanoma) Olaparib + bevacizumab (BRCA-mutant ovarian cancer)

The transformative potential of PGA technology to democratize precision combination therapy

The persistent challenge of tumor heterogeneity and the inevitable emergence of resistance have underscored the limitations of single-agent targeted therapies in oncology. Despite remarkable advances in precision medicine, monotherapy often fails to achieve durable responses due to the absence of universally expressed biomarkers and the dynamic clonal evolution of tumors.^{34,35} The Patient-derived Gene expression-informed Anticancer drug efficacy (PGA) technology represents a paradigm-shifting approach to this dilemma by leveraging functional genomics—using patient-specific gene expression signatures to predict drug sensitivity and optimize combination therapies.^{36–38} Unlike traditional biomarker-driven strategies, which rely on static genomic alterations, PGA integrates tumor and its microenvironment gene activities to identify potential drugs that target the diverse molecular vulnerabilities within a tumor (Figure 2). This approach not only addresses the shortcomings of monotherapy but also democratizes access to combination therapy by providing a data-driven, gene-to-drug mapping framework for identifying effective drug regimens without requiring prior knowledge of specific driver mutations.³⁷ Importantly, PGA circumvents the trial-and-error nature of empirical combination therapy by mapping out a list of the best drug candidates based on each patient’s gene signature. This is particularly impactful for refractory, metastatic or relapsed cancers, where conventional biomarker-driven approaches often fail due to a lack of established therapeutic targets. Furthermore, PGA’s integration with liquid biopsy-based dynamic monitoring enables adaptive therapy adjustments, ensuring that treatment evolves alongside the tumor’s molecular landscape. By shifting the focus

from single-target inhibition to network-based combinatorial disruption, PGA redefines precision oncology as a dynamic, patient-centric discipline capable of addressing the complexities of tumor heterogeneity.

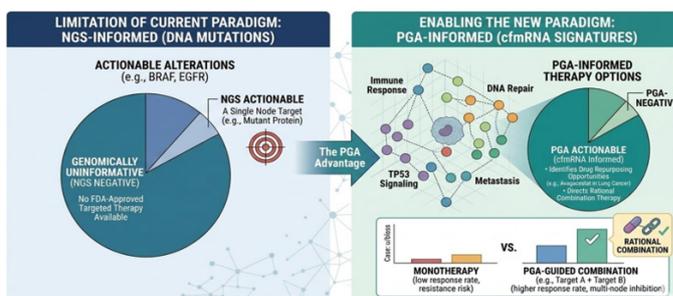


Figure 2 PGA as the bridge to rational combination therapy. This schematic illustrates the shift from DNA-based NGS, which leaves ~80% of patients without actionable targets, to PGA-informed treatment selection. While traditional targeted monotherapy often fails due to single-node resistance and compensatory signaling, PGA utilizes liquid biopsy cell-free mRNA signatures to map the tumor’s vulnerabilities. By interrogating multiple oncogenic pathways (e.g., DNA Repair, TP53), PGA identifies rational combination therapies and drug repurposing opportunities. This “multi-node” inhibition bypasses genomic limitations, effectively bridging the gap from ineffective monotherapy to high-response, personalized combinations that overcome acquired resistance.

Looking ahead, the widespread adoption of PGA technology has the potential to revolutionize cancer care by making precision combination therapy accessible to a broader patient population. Ultimately, PGA represents a transformative solution to the

monotherapy dilemma, offering a patient-tailored, evolution-aware drug-finding framework that maximizes therapeutic efficacy while minimizing unnecessary toxicity. By bridging the gap between functional genomics and clinical oncology, PGA not only enhances our understanding of tumor biology but also empowers clinicians to deliver truly personalized, combination-based precision medicine on a global scale.

Future directions: toward adaptive and evolution-informed multi-target therapies

The future of precision oncology lies in the development of dynamic, adaptive treatment strategies that account for the evolving nature of tumors. Artificial intelligence-driven real-time monitoring of clonal dynamics holds promise in predicting resistance patterns and informing therapeutic adjustments.³⁹ Functional precision diagnostics, which involves blood testing to inform drug efficacy such as PGA, could provide a more personalized approach to identifying effective combinations. Targeting the tumor microenvironment, particularly immune-suppressive niches that foster resistance, represents another critical frontier.⁴⁰ Furthermore, the integration of multi-omic profiling—encompassing genomic, transcriptomic, epigenomic, and proteomic data—will be essential in deciphering the complex interplay between clonal subpopulations and their microenvironmental context. While these advancements are still in their infancy, they collectively point toward a post-monotherapy era where multi-target treatment is continuously tailored to the evolving tumor landscape.

Conclusion: the imperative for a new therapeutic paradigm

The era of precision monotherapy, while transformative, has revealed its inherent limitations in the face of tumor heterogeneity. Residual disease is an inescapable consequence of single-agent targeted therapy, driven by the absence of universally expressed biomarkers and the relentless evolutionary pressure exerted by treatment. To overcome these challenges, the field must transition toward multimodal, adaptive treatment paradigms that integrate combinatorial targeted therapies, immunotherapy, and microenvironment modulation. Future research must prioritize the development of dynamic monitoring tools, evolution-aware therapeutic strategies, and novel agents capable of eradicating drug-tolerant persister cells. Only by embracing this comprehensive approach can we hope to achieve durable, if not curative, outcomes in oncology. The road ahead is complex, but the imperative is clear: precision medicine must evolve beyond monotherapy to confront the reality of tumor heterogeneity.

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None.

Conflict of interest

The authors declare no competing financial interests.

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