RESEARCH ARTICLE

Advances in Precision Oncology and Targeted Treatment

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ABSTRACT

Advances in precision oncology and targeted treatment have transformed cancer care by enabling therapies tailored to the molecular and microenvironmental characteristics of individual tumours. This narrative review summarizes key developments underpinning this paradigm shift, beginning with the biological foundations of cancer heterogeneity, the distinction between tumour genomics and the tumour microenvironment, and core concepts such as driver versus passenger mutations, clonal evolution and actionable alterations. We then discuss advances in genomic and molecular profiling, including next-generation sequencing (targeted panels, whole-exome and whole-genome sequencing), liquid biopsy for circulating tumour DNA and other analytes, and emerging multi-omics, single-cell and spatial technologies that refine patient stratification. Major classes of targeted therapies small-molecule inhibitors, monoclonal antibodies, antibody–drug conjugates, immune checkpoint inhibitors, cell-based therapies and novel modalities such as PROTACs, RNA therapeutics and gene-editing approaches are reviewed in the context of biomarker-guided treatment strategies, tumour-agnostic approvals and dynamic monitoring with ctDNA for minimal residual disease and resistance detection. Finally, we highlight key challenges, including tumour heterogeneity, resistance evolution, technical and economic barriers and health-system implementation gaps, and outline future directions aimed at integrating multi-omics, artificial intelligence and adaptive, evolutionary-informed treatment frameworks. Collectively, these advances underscore both the current impact and the unrealized potential of precision oncology to improve outcomes and quality of life across diverse cancer populations.

Keywords: Precision Oncology, Targeted Therapy, Biomarkers, Liquid Biopsy, Multi-Omics.

How to cite this article: Nigam GK, Kar P, Naik HY, Giri N, Fatma S. Advances in Precision Oncology and Targeted Treatment. Int J Drug Deliv Technol. 2026;16(69s):894-897. DOI: 10.25258/ijddt.16.69s.92

INTRODUCTION

Cancer remains one of the leading causes of morbidity and mortality worldwide, accounting for millions of new cases and deaths annually despite major advances in diagnosis and treatment (Brlek, P et al ; 2025). Conventional modalities such as surgery, radiotherapy and cytotoxic chemotherapy have improved survival for many tumour types but are limited by non-selective mechanisms of action, narrow therapeutic windows and substantial short- and long-term toxicities (Zafar, A et al ; 2025). Moreover, inter- and intra-tumour heterogeneity, variable drug metabolism and the emergence of resistance frequently lead to suboptimal response and treatment failure under traditional "one-size-fits-all" approaches (Zhang, J et al ; 2018 ; Chen, M et al ; 2019). Precision oncology has emerged as a paradigm shift, aiming to tailor therapy to the individual patient by integrating molecular, genomic and microenvironmental features of the tumour and host (Zafar, A et al ; 2025). Recent advances in next-generation sequencing, multi-omics profiling, liquid biopsy and sophisticated bioinformatics now enable routine identification of actionable alterations and biomarker-defined subgroups across many solid and haematologic malignancies (Qiao, D et al ; 2025 ; Tsimberidou, A. M et al ; 2020). At the same time, an expanding arsenal of targeted agents, antibody–drug conjugates, immunotherapies and cell-based treatments has transformed the therapeutic landscape, enabling more selective interventions that can deliver deeper and more durable responses in appropriately stratified patients (Brlek, P et al ; 2025) .

Thus, the aim was to synthesize current developments across three interconnected domains which includes biomarkers, targeted therapies and enabling technologies.

ADVANCES IN GENOMIC AND MOLECULAR PROFILING

Next-generation sequencing (NGS) technologies, including targeted gene panels, whole-exome sequencing (WES) and whole-genome sequencing (WGS), have transformed clinical oncology by enabling comprehensive characterization of tumour genomes at scale (Akhoundova, D et al ; 2022). Targeted panels are now widely implemented in routine practice to detect recurrent, clinically actionable alterations such as oncogenic mutations, gene fusions and copy-number changes, providing rapid, cost-effective information to guide targeted therapy selection and enrolment in molecularly stratified trials (Hofman, P. ; 2021 ; Di Sario, G et al ; 2023). WES and WGS, although more resource-intensive, further capture rare drivers, mutational signatures and genome-wide structural variants, refining molecular taxonomy and supporting discovery of new therapeutic targets and resistance mechanisms (Shibata, T. ; 2015).

Liquid biopsy has emerged as a complementary, minimally invasive approach that leverages analysis of circulating tumour DNA (ctDNA), circulating tumour cells (CTCs) and tumour-derived extracellular vesicles or exosomes in blood and other body fluids. NGS-based profiling of ctDNA permits real-time monitoring of tumour burden, detection of molecular residual disease and identification of emergent resistance alterations, often preceding radiological progression (Shibata, T. ; 2015). Multi-omic interrogation of liquid biopsy samples combining genomics, epigenomics, fragmentomics and proteomics that have shown promise for early cancer detection, dynamic treatment response assessment and longitudinal surveillance, particularly when integrated with machine-learning approaches for signal interpretation (Chen, G et al ; 2023). These developments position liquid biopsy as a key tool for serially informing precision treatment decisions across the disease course (Chen, G et al ; 2023 ; Shibata, T. ; 2015).

Beyond DNA, advanced transcriptomic, epigenomic and proteomic platforms now enable detailed mapping of gene expression programmes, chromatin states and protein networks that drive tumour behaviour and therapeutic sensitivity (Chen, G et al ; 2023). Integration of these layers in multi-omics frameworks provides a more holistic view of tumour architecture, revealing convergent pathway activation, lineage states and microenvironmental interactions that may not be apparent from genome sequencing alone (Akhoundova, D et al ; 2022). Single-cell sequencing and spatial transcriptomics further dissect intra-tumour heterogeneity and cellular ecosystems at high resolution, distinguishing malignant subclones, stromal populations and immune cell subsets, and linking spatially organized niches to treatment response and resistance (Akhoundova, D et al ; 2022). Although clinical translation of these cutting-edge profiling technologies remains challenging, ongoing efforts in analytical validation, standardization and data integration are steadily

bringing multi-omics and spatial approaches closer to routine precision oncology (Shibata, T. ; 2015).

TARGETED THERAPIES: MODALITIES AND MECHANISMS

Small-molecule inhibitors represent the earliest and most established class of targeted therapies, designed to selectively modulate dysregulated signalling pathways and DNA repair processes in cancer cells. Kinase inhibitors directed against EGFR, ALK, BRAF and other oncogenic drivers, as well as agents targeting the PI3K/AKT/mTOR axis, have demonstrated substantial clinical benefit in biomarker-selected populations across multiple tumour types Shibata, T. ; 2015). PARP inhibitors exploit defects in homologous recombination repair, particularly in BRCA1/2-mutated and other homologous recombination-deficient cancers, exemplifying the concept of synthetic lethality in precision treatment (Pei, H et al ; 2019). More recently, proteolysis-targeting chimeras (PROTACs) have emerged as a novel small-molecule modality that induces selective degradation, rather than inhibition, of pathogenic proteins, offering a strategy to target previously "undruggable" oncoproteins (Akhoundova, D et al ; 2022).

Monoclonal antibodies and antibody drug conjugates (ADCs) expand the targeted therapy toolbox by recognizing specific cell-surface antigens and delivering effector functions or cytotoxic payloads directly to tumour cells (Akhoundova, D et al ; 2022). Classical examples include anti-HER2 and anti-EGFR antibodies, which block ligand–receptor interactions and downstream signalling in HER2- and EGFR-driven cancers, respectively. ADCs couple antigen-specific antibodies to potent chemotherapeutic agents via cleavable linkers, enabling highly selective delivery of cytotoxins while sparing normal tissues, and have shown remarkable activity in HER2-low breast cancer and other antigen-defined settings (Shibata, T. ; 2015). In parallel, immune checkpoint inhibitors targeting PD-1/PD-L1 and CTLA-4 unleash anti-tumour T-cell responses by reversing tumour-mediated immune suppression, and their use is increasingly guided by biomarkers such as PD-L1 expression, tumour mutational burden and mismatch-repair deficiency (Chen, G et al ; 2023).

Cell therapies and engineered immune cells further illustrate the convergence of immunology and precision medicine, with chimeric antigen receptor T-cell (CAR-T) products and T-cell receptor (TCR)-engineered therapies offering highly specific, living drugs directed against defined tumour antigens (Pei, H et al ; 2019). CAR-T therapies have achieved transformative outcomes in certain haematologic malignancies, and ongoing work seeks to extend their benefit to solid tumours through improved target selection, modulation of exhaustion and microenvironmental barriers (Chen, G et al ; 2023). Novel biologics such as bispecific antibodies can simultaneously engage tumour antigens and immune effectors, enhancing synapse formation and cytotoxicity, while RNA-based therapeutics and CRISPR-mediated genome editing open new avenues for directly modulating oncogenic drivers, resistance pathways and immune regulators at the nucleic acid level. Together, these modalities form a rapidly expanding, mechanistically diverse arsenal of targeted treatments, underscoring the need for precise biomarker-guided selection and rational combination strategies within modern precision oncology (Pei, H et al ; 2019).

BIOMARKER-GUIDED TREATMENT STRATEGIES

Companion diagnostics (CDx) are in vitro tests co-developed with targeted therapies to identify patients who are most likely to benefit, and they are tightly regulated as medical devices in major jurisdictions (Kadam, H et al ; 2025). Regulatory agencies such as the US FDA and EMA typically require robust analytical validity, clinical validity and clinical utility data, and most CDx for oncology drugs are approved through stringent pathways like Premarket Approval, often in parallel with the associated therapeutic label (Semenkovich, N. P et al ; 2023). These diagnostics now span tissue-based assays (e.g., immunohistochemistry, in situ hybridization, NGS panels) and liquid biopsy-based platforms for ctDNA, reflecting the shift toward molecular stratification as a prerequisite for prescribing many targeted agents (Shibata, T. ; 2015).

A key milestone in biomarker-guided care has been the advent of tumour-agnostic approvals, where therapies are authorised based on the presence of a specific biomarker regardless of tumour histology. Examples include agents directed at microsatellite instability-high (MSI-H) or mismatch-repair-deficient tumours, as well as TRK inhibitors for NTRK gene fusions, and more recently therapies for high tumour mutational burden or other rare genomic alterations (Shibata, T. ; 2015). These approvals are particularly impactful for rare cancers and molecular subsets that cannot be feasibly studied in traditional histology-specific trials, reinforcing the central role of comprehensive biomarker testing to uncover actionable drivers across the cancer spectrum. Predictive biomarkers such as activating EGFR mutations, ALK rearrangements, BRAF V600 mutations, HER2 amplification and BRCA1/2 or other homologous recombination repair defects illustrate the clinical impact of biomarker-driven treatment selection (Akhoundova, D et al ; 2022).

EGFR and ALK alterations guide the use of first- and next-generation tyrosine kinase inhibitors in non-small cell lung cancer, yielding higher response rates and longer progression-free survival compared with chemotherapy when present. BRAF V600 mutations identify candidates for BRAF/MEK inhibitor combinations in melanoma and selected other tumours, HER2 amplification remains a cornerstone biomarker for anti-HER2 antibodies and ADCs, and BRCA/HRD status predicts benefit from PARP inhibition in ovarian, breast and other cancers. Increasingly, these markers are detected using NGS-based panels and integrated into clinical decision pathways and molecular tumour boards (Semenkovich, N. P et al ; 2023 ; Akhoundova, D et al ; 2022 ; Shibata, T. ; 2015).

Dynamic monitoring with ctDNA has expanded the concept of biomarker-guided therapy beyond baseline selection to longitudinal disease management (Semenkovich, N. P et al ; 2023). Ultra-sensitive NGS assays enable detection of minimal residual disease (MRD) following curative-intent therapy, allowing identification of patients at high risk of relapse and informing adjuvant treatment decisions or intensified surveillance (Semenkovich, N. P et al ; 2023). Serial ctDNA profiling also permits early detection of emergent resistance mutations, such as EGFR T790M or ALK secondary alterations, thereby facilitating timely switch to next-line targeted agents or enrolment in appropriate trials before overt radiological progression (Rohlfing, S et al ; 2026). Case-based and cohort studies across tumour types, including pancreatic and lung cancers, underscore how ctDNA-based MRD and resistance monitoring can refine risk stratification and personalize treatment duration and sequencing within precision oncology frameworks (Chen, G et al ; 2023).

OVERCOMING RESISTANCE TO TARGETED THERAPY

Despite major advances, primary and acquired resistance remain ubiquitous challenges to targeted therapies (Hu, H et al ; 2026). Primary resistance may arise from tumour-intrinsic factors such as absence of true dependency on the targeted pathway, co-occurring alterations that activate parallel signalling, or microenvironmental cues that blunt drug effects (Hu, H et al ; 2026). Acquired resistance encompasses on-target mechanisms (e.g., secondary mutations in the drug binding site, target amplification), activation of bypass pathways (such as MET or HER2 upregulation, alternative RTK activation) and broader phenomena like phenotypic plasticity, lineage switching and epithelial mesenchymal transition that enable tumour cells to escape therapeutic pressure (Tomasik, B et al ; 2024). These processes occur against a backdrop of clonal evolution and heterogeneous selection, leading to complex resistance landscapes that differ between and within patients (Tomasik, B et al ; 2024 ; Zhang, J et al ; 2018).

To mitigate resistance, sequential and combination strategies are increasingly employed, leveraging both vertical and horizontal pathway inhibition as well as cross-modality combinations (Kudek, M. R et al ; 2025). Sequential use of first-, second- and

third-generation kinase inhibitors, guided by evolving mutational profiles, has become standard in several oncogene-addicted tumours, exemplifying a stepwise approach to overcoming specific resistance mutations (Akhoundova, D et al ; 2022). Combination regimens pair targeted therapies with chemotherapy or radiotherapy to reduce the likelihood of resistant clones emerging, and targeted agents are also being combined with immune checkpoint inhibitors to exploit potential synergy between direct oncogenic pathway blockade and immune activation (Qiao, D et al ; 2025). Rational combinations informed by preclinical models, multi-omics profiling and early-phase trials aim to delay or prevent resistance while balancing toxicity and cost (Shibata, T. ; 2015).

Adaptive therapy and evolutionary-informed treatment strategies represent emerging approaches that explicitly account for tumour ecology and clonal dynamics (Chen, G et al ; 2023). Instead of continuous maximal dosing, adaptive protocols adjust therapy intensity or alternate agents based on biomarkers such as ctDNA levels, imaging and other dynamic indicators, with the goal of maintaining a controllable tumour population and suppressing highly resistant clones (Tomasik, B et al ; 2024). Mathematical modelling, single-cell and spatial profiling, and longitudinal liquid biopsy data are increasingly used to design such strategies and to test concepts like cycling targeted therapies, intermittent dosing and early introduction of combination partners in response to specific resistance signatures (Qiao, D et al ; 2025). While still largely investigational, these evolutionary-informed paradigms highlight a future in which overcoming resistance relies not only on new drugs but also on smarter, biomarker-driven deployment of existing targeted and immunotherapeutic agents (Hu, H et al ; 2026).

CHALLENGES

a. Limited proportion of patients with truly actionable alterations and durable benefit.

b. High intra- and inter-tumour heterogeneity complicating biomarker interpretation and response prediction.

c. Technical and analytical variability across assays, platforms and bioinformatics pipelines.

d. High costs and uncertain cost-effectiveness of genomic testing and targeted therapies.

e. Unequal access and infrastructure gaps, especially in low- and middle-income settings.

f. Insufficient clinical validation and standardization of advanced multi-omics and spatial technologies.

g. Logistical complexity and slow accrual in biomarker-stratified trials (basket, umbrella, platform).

h. Regulatory and co-development challenges for companion diagnostics and targeted drugs.

i. Limited genomics literacy and implementation capacity in routine clinical practice.

FUTURE DIRECTIONS

Future directions in precision oncology and targeted treatment focus on integrating increasingly sophisticated molecular profiling with next-generation therapeutic modalities to deliver more precise, durable and equitable cancer care (Qiao, D et al ; 2025). Key priorities include routine incorporation of multi-omics and spatial technologies, expansion of tumour-agnostic and age-agnostic biomarker-based approvals, wider use of ctDNA-guided minimal residual disease monitoring, and the rational development of novel targeted agents such as advanced antibody–drug conjugates, PROTACs, RNA therapeutics and gene-editing approaches, all supported by artificial intelligence–driven decision tools and learning health system (Rulten, S. L et al ; 2023 ; Mai N, et al ; 2025 ; Qiao, D et al ; 2025).

CONCLUSION

Advances in precision oncology and targeted treatment have fundamentally reshaped cancer care by shifting from empirical, histology-based approaches to biomarker-driven, individualized strategies that exploit the molecular and microenvironmental features of each tumour. Integrated genomic and multi-omics profiling, liquid biopsy–based monitoring and sophisticated companion diagnostics now enable more accurate patient selection, dynamic assessment of minimal residual disease and earlier detection of resistance, while an expanding arsenal of targeted agents, antibody drug conjugates, immunotherapies and engineered cell therapies offers the potential for deeper and more durable responses. However, persistent challenges including tumour heterogeneity, resistance evolution, cost and access barriers, and limited implementation capacity underscore that these innovations must be accompanied by robust evidence generation, health-system adaptation and equitable deployment to fully realize their promise. Collectively, the emerging science and technologies reviewed here highlight a future in which precision oncology is increasingly integrated across the cancer continuum, from early detection and risk stratification to personalized treatment sequencing and survivorship, ultimately aiming to improve outcomes and quality of life for diverse patient populations.

DECLARATIONS

Funding

There was no sponsorship from any other sources, and this essay about conception was published without any financial compensation.

Conflict of Interest

There is no declaration of any conflicts of interest made by the authors.

Data Availability Statement

No empirical datasets were created or examined in this paper. Policy-driven literature analysis and conceptual synthesis underpin this research.

Author Contributions

.....helped with the development of ideas, the construction of the framework, and the composition of the text.....also assisted with the development of theories, supervision, and editing of the final result.

Ethics Statement

This study does not contain human participation, human data, animal subjects, or clinical materials. Consequently, authorization from the ethical community was not required.

Declaration of generative AI and AI-assisted technologies in the manuscript preparation process

All authors above have contributed equally to this paper. It was not edited or written using any generative AI or AI-assisted

technology. The writers are entirely responsible for the contents of their contributions.

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