REVIEW / DERLEME

DOI: 10.4274/turkjsurgoncol.galenos.2026.18480
Turk J Surg Oncol 2026;2(2):43-51

Medical Oncology in the Era of Molecular Biomarkers: Clinical Integration, Organ-specific Translation, Immuno-oncology, and Future Perspective

Moleküler Biyomarkırlar Çağında Tıbbi Onkoloji: Klinik Entegrasyon, Organ-spesifik Uyarlama, İmmüno-onkoloji, ve Gelecek Perspektif

İsmail Oğuz Kara

Çukurova University Faculty of Medicine, Department of Medical Oncology, Adana, Türkiye

Abstract

The rapid expansion of molecular biomarkers has fundamentally reshaped contemporary oncology practice, transitioning it from morphology-based classification toward biologically driven precision medicine. In line with current scientific advancements, oncology treatment practices will increasingly be patient-centered, driven by genetic analysis and targeted therapy. Personalized treatment based on next-generation sequencing (NGS) will assume a central role. A narrative review of recent literature was conducted, focusing on NGS, liquid biopsy and circulating tumor DNA (ctDNA), minimal residual disease (MRD), immuno-oncology biomarkers, and organ-specific clinical implementation. Biomarker-driven oncology now informs systemic therapy selection, adjuvant strategies, recurrence risk stratification, and multidisciplinary sequencing across major solid tumors, including lung, colorectal, breast, gastric, hepatobiliary, and prostate cancers. ctDNA-based MRD detection has emerged as a dynamic risk stratification tool, while immuno-oncology biomarkers such as programmed death-ligand 1, tumor mutational burden, and microsatellite instability guide checkpoint inhibitor therapy; these biomarkers have varying predictive performance. Future oncology practice will rely on integrated biomarker ecosystems combining genomics, dynamic monitoring, immunologic profiling, and artificial intelligence-assisted decision support systems.

Keywords: Molecular biomarkers, precision oncology, ctDNA, liquid biopsy, minimal residual disease, immuno-oncology, TMB, MSI, digital pathology, multi-omics, AI

Öz

Moleküler biyobelirteçlerdeki hızlı gelişmeler, çağdaş onkoloji pratiğini yeniden şekillendirmiş ve klinik uygulamayı morfolojiye dayandıran sınıflandırmadan biyolojik temelli hassas tıbba doğru kaydırmıştır. Mevcut bilimsel gelişmeler doğrultusunda, onkoloji tedavi uygulamaları giderek daha çok hasta merkezli olacak ve genetik analiz ve hedefe yönelik tedavi ile yönlendirilecektir. Yeni nesil dizileme (NGS) temelli kişiselleştirilmiş tedavi gelecekte esas rolü üstlenecektir. Bu çalışmada, NGS, sıvı biyopsi ve dolaşımdaki tümör DNA'sı (ctDNA), minimal rezidüel hastalık (MRD), immüno-onkoloji biyobelirteçleri ve organa özgü klinik uygulamaya odaklanan yakın zamandaki literatürden derleme incelemesi yapılmıştır. Biyobelirteç odaklı onkoloji, artık akciğer, kolorektal, meme, mide, hepatobiliyer ve prostat kanserleri de dahil olmak üzere başlıca solid tümörlerde sistemik tedavi seçimi, adjuvant stratejiler, nüks riski sınıflandırması ve multidisipliner yaklaşım konusunda yaklaşım salamaktadır. ctDNA bazlı MRD tespiti, dinamik bir risk sınıflandırma aracı olarak ortaya çıkarken, programmed death-ligand 1, tümör mutasyon yükü ve mikrosatellitinstabilitesi gibi immüno-onkoloji biyobelirteçleri, farklı prediktif özellikleri ile immünkontrol inhibitör tedavilerine rehberlik etmektedir.

Address for Correspondence: Prof. MD., İsmail Oğuz Kara, Çukurova University Faculty of Medicine, Department of Medical Oncology, Adana, Türkiye
E-mail: ioguzkara@gmail.com **ORCID ID:** orcid.org/0000-0003-4963-2028
Received: 19.02.2026 **Accepted:** 12.03.2026 **Publication Date:** 15.06.2026

Cite this article as: Kara İO. Medical oncology in the era of molecular biomarkers: clinical integration, organ-specific translation, immuno-oncology, and future perspective. Turk J Surg Oncol. 2026;2(2):43-51

Geleceğin onkoloji pratiği, genomik, dinamik izleme, immünolojik profil oluşturma ve yapay zeka destekli kararları birleştiren entegre biyobelirteç ekosistemlerine dayanacaktır.

Anahtar Kelimeler: Moleküler biyobelirteçler, kişselleştirilmiş onkoloji, ctDNA, sıvı biyopsi, minimal rezidüel hastalık, immüno-onkoloji, TBM, MSI, dijital patoloji, çoklu-omikler, YZ

Introduction

Oncology is undergoing a structural reorganization of its decision-making language to treat the diseas faced. Historically, tumor histology and anatomic stage were the primary coordinates for prognosis and treatment selection. On the other hand, in the molecular biomarker era, these coordinates remain essential, but they are increasingly complemented and sometimes superseded by biological features that predict therapeutic vulnerability, resistance, and recurrence risk (1-4) as well. This transition is not merely technological; it changes how clinicians conceptualize risk. A "high-risk" tumor is no longer defined only by size, nodal status, or grade, but in the age modern treatment era also by driver alterations, immune contexture, and the presence of molecular residual disease after definitive therapy (Figure 1) (5-11).

From a medical oncology daily perspective, biomarkers are matter for three practical reasons. First, they compress uncertainty: a predictive biomarker increases the probability that a treatment works for a given patient while reducing exposure to ineffective therapy and to avoid toxicity. Second, biomarkers can convert time into an actionable resource: longitudinal measurements [e.g., circulating tumor DNA (ctDNA)] allow clinicians to detect disease relapse earlier or to show resistance mechanisms without re-biopsy. Third, biomarkers reshape multidisciplinary care by influencing neoadjuvant sequencing, adjuvant intensification or de-escalation, and postoperative surveillance strategies areas where surgical oncology and medical oncology increasingly intersect together (5,6,9,11,12).

The last five years have been particularly dynamic in terms of oncology practice. Precision oncology reviews highlight a steady expansion of targeted therapies and a maturing ecosystem of trial designs (basket, umbrella, platform studies) that operationalize biomarker-driven hypotheses (2,3). In conjuction with this, minimal residual disease (MRD) concepts have moved from hematologic malignancies into solid tumors, with ctDNA technologies enabling molecular detection below radiographic thresholds (5-11). Finally, artificial intelligence (AI) and multi-omics integration are shifting biomarker work from single assays to fused, multimodal predictors that may support clinical decision-making in clinical evaluation (13-15).

Biomarker Taxonomy and the Shift from Static to Dynamic Risk

As known that clinically, biomarkers are often categorized as diagnostic, prognostic, predictive, and monitoring biomarkers. In real daily practice these categories overlap, and the same biomarker can serve multiple roles. For example, microsatellite instability (MSI) can act as a prognostic marker in certain settings as in lung cancer, a predictive biomarker for immune checkpoint inhibitors as in colorectal cancer (CRC), and a clue to inherited cancer risk via mismatch repair deficiency pathways as in Lynch syndrome (16).

A useful contemporary distinction is between static biomarkers (typically measured once from baseline tissue) and dynamic biomarkers (measured repeatedly to capture evolution). Static biomarkers [e.g., epidermal growth factor receptor (EGFR) mutation in non-small cell lung cancer (NSCLC), human epidermal growth factor receptor 2 (HER2) amplification in breast or gastric cancer, *breast cancer gene 2* alterations in prostate cancer] are foundational to targeted therapy selection and often guide first-line strategy (17-23). Dynamic biomarkers especially ctDNA capture changing tumor burden and emergent resistance, and are increasingly discussed as tools for MRD detection after curative-intent surgery or chemoradiation, respectively (5-11).

The dynamic view reframes postoperative surveillance: rather than waiting for radiographic recurrence, clinicians may stratify recurrence risk molecularly and tailor surveillance intensity and adjuvant therapy. However, earlier detection does not automatically imply improved outcomes; clinical utility ultimately depends on whether an intervention triggered by MRD status changes survival or quality of life, a point emphasized in emerging analyses of ctDNA-led recurrence detection (10,11).

Enabling Technologies: Next-generation Sequencing (NGS), Liquid Biopsy, Digital Pathology, and Multi-omics NGS

NGS has become the main platform for identifying actionable alterations, characterizing resistance mechanisms, and enabling tumor-agnostic therapies in oncology practice. Contemporary reviews highlight the clinical translation of diverse biomarker classes oncogenic drivers, homologous recombination deficiency, gene fusions, and mutational signatures that often within panel based workflows that can be deployed across tumor types (1-4). The real-world challenge is less about the existence of sequencing and more about the operational pipeline: tissue adequacy, turnaround time, bioinformatics standardization, and how possible results are integrated into multidisciplinary decision pathways (18,24).

Figure 1. Evolution from histology-based oncology to dynamic biomarker ecosystems combining NGS, ctDNA MRD, and immuno-oncology biomarkers (1-3,5-11)

ctDNA: Circulating tumor DNA, MRD: Minimal residual disease, NGS: Next-generation sequencing, EGFR: Epidermal growth factor receptor, HER2: Human epidermal growth factor receptor 2, PCR: Polymerase chain reaction, BRC-ABL: Breakpoint cluster region-Abelson murine leukemia viral oncogene homolog, CTCs: Circulating tumor cells

Liquid Biopsy and ctDNA

Liquid biopsy encompasses multiple analytes: ctDNA, circulating tumor cells, extracellular vesicles, and other cell-free components. Among these, ctDNA has emerged as the most measurable clinical tool due to assay sensitivity, relative standardization, and direct linkage to tumor genomics (6-9). Narrative and systematic reviews describe applications in (I) baseline genotyping when tissue is unavailable, (II) monitoring treatment response and resistance, and (III) detecting MRD after curative-intent therapy (6-9,11).

The field distinguishes tumor-informed assays (custom panels based on the patient's tumor) from tumor-agnostic assays (fixed panels without prior tumor sequencing). Tumor-informed approaches may offer higher specificity for MRD, while tumor-agnostic assays favor speed and simplicity; both approaches remain under active evaluation for clinical utility and cost-effectiveness as well (10,11).

Digital Pathology and AI

Digital pathology is increasingly considered as a biomarker platform. AI models applied on hematoxylin and eosin images can predict genomic alterations, immune phenotypes, and even immunotherapy response in specific contexts, potentially reducing barriers where molecular testing is delayed or inaccessible (14,15). Importantly, AI outputs should be treated as probabilistic decision aids rather than definitive biomarkers, and prospective validation plus interpretability remain prerequisites for clinical deployment (13-15).

Multi-omics and Multimodal Fusion

Multi-omics integration combines genomics, transcriptomics, epigenomics, proteomics, metabolomics, imaging, and clinical data to build more robust predictors than any single data layer. Recent reviews summarize AI-driven approaches in which including graph-based models and transformers for cross modal fusion and emphasize the need for standardization, reproducibility, and clinically meaningful endpoints (14,15).

Organ-specific Translation: What Actually Changes in Clinical Practice (Figure 2, Table 1) (17,20,21,24-26)

NSCLC

NSCLC represents the model of biomarker-driven systemic therapy. Contemporary guidelines and implementation reviews emphasize comprehensive molecular profiling for key drivers [EGFR, anaplastic lymphoma kinase, ROS proto-oncogene 1,

Table 1. Organ-specific molecular biomarkers and clinical implications in contemporary oncology

Tumor type	Key molecular biomarkers	Primary clinical role	Impact on clinical management
NSCLC	EGFR, ALK, ROS1, RET, MET exon 14, KRAS G12C, PD-L1	Predictive	Genotype-matched targeted therapy; immunotherapy stratification; longitudinal ctDNA monitoring
Colorectal cancer	KRAS/NRAS, BRAF, MSI/dMMR, ctDNA (MRD)	Predictive+monitoring	Anti-EGFR selection; immunotherapy eligibility (MSI-H); adjuvant risk stratification; MRD-guided decisions
Breast cancer	ER, PR, HER2, ESR1 (ctDNA), genomic signatures	Predictive+prognostic	Endocrine therapy guidance; anti-HER2 therapy; resistance monitoring; recurrence risk assessment
Gastric/GEJ cancer	HER2, MSI, CLDN18.2	Predictive	HER2-directed therapy; immunotherapy in MSI-high disease; CLDN18.2-targeted therapy (e.g., zolbetuximab)
Cholangiocarcinoma	FGFR2 fusions, IDH1 mutations	Predictive	FGFR inhibitor therapy; IDH1-targeted treatment
Prostate cancer	BRCA1/2, HRR/DDR genes, AR alterations	Predictive	PARP inhibitor eligibility; treatment sequencing; resistance monitoring

NSCLC: Non-small cell lung cancer, GEJ: Gastroesophageal junction, EGFR: Epidermal growth factor receptor, ALK: Anaplastic lymphoma kinase, ROS1: ROS proto-oncogene 1, RET: Rearranged during transfection, MET exon 14: MET proto-oncogene, receptor tyrosine kinase exon 14 alteration, KRAS G12C: Kirsten rat sarcoma viral oncogene G12C mutation, KRAS: Kirsten rat sarcoma viral oncogene, NRAS: Neuroblastoma RAS viral oncogene homolog, BRAF: B-Raf proto-oncogene, serine/threonine kinase, MSI/dMMR: Microsatellite instability/mismatch repair deficiency, ctDNA: Circulating tumor DNA, MRD: Minimal residual disease, ER: Estrogen receptor, PR: Progesterone receptor, HER2: Human epidermal growth factor receptor 2, ESR1: Estrogen receptor 1, FGFR2: Fibroblast growth factor receptor 2, IDH1: Isocitrate dehydrogenase 1, AR: Androgen receptor, HRR/DD: Homologous recombination repair/DNA damage response, CLDN18.2: Claudin 18.2 (a cell surface protein), PD-L1: Programmed death-ligand 1, BRCA1/2: Breast cancer gene 1/2, PARP: Poly (ADP-ribose) polymerase

B-Raf proto-oncogene (BRAF), MET exon 14 skipping, rearranged during transfection, neurotrophic tyrosine receptor kinase (NTRK), Kirsten rat sarcoma viral oncogene G12C mutation) because targeted therapy selection depends on accurate identification of actionable subsets and resistance pathways (18-20,25). Transactionally, delays and inconsistent testing remain major barriers; practical solutions include reflex testing, standardized pathways, and early integration of liquid biopsy when tissue is limited (18,24).

In the perioperative setting, the biomarker story is expanding from driver genotyping to dynamic assessment of response and residual disease. ctDNA-based monitoring after curative-intent therapy has shown prognostic value in early-stage NSCLC and may enable risk adapted adjuvant strategies, although prospective interventional evidence is still emerging (7,10). The clinical potential is clear: how to integrate molecular relapse signals without over-treatment or anxiety, and how to act when an MRD-positive result appears months before radiographic disease is detectable (5-11).

CRC

CRC biomarker practice involves both static and dynamic components. Static biomarkers include rat sarcoma virus and BRAF for targeted therapy selection and MSI status for immunotherapy eligibility and prognostic stratification (17). The most disruptive addition is ctDNA-based MRD. Multiple reviews synthesize evidence that postoperative ctDNA positivity is strongly associated with recurrence risk and may outperform clinicopathologic risk factors for MRD assessment (5,6,10,11,27,28).

A key next-step question is whether MRD-guided treatment changes survival. Prospective work has begun to link MRD status to overall survival and to evaluate intervention strategies based on ctDNA results (11,29). However, clinical utility requires more than prognostic correlation; pathways especially for adjuvant escalation, de-escalation, and the definition of actionable thresholds must be standardized (10,11,27-29).

Breast Cancer

Breast cancer remains structured by receptor biomarkers (estrogen receptor/progesterone receptor and HER2) as in luminal classification and genomic risk signatures, but molecular biomarker practice is evolving in two directions: resistance mapping in advanced disease and ctDNA applications in early-stage surveillance (20,30-33). Estrogen receptor 1 mutations in ctDNA illustrate how liquid biopsy can operationalize endocrine resistance mechanisms and support treatment selection in hormone receptor-positive disease especially in progressive disease (30-32). Meanwhile, ctDNA MRD concepts in early-stage breast cancer are being actively investigated; reviews emphasize the consistent association between ctDNA positivity and recurrence risk while highlighting assay sensitivity, standardization, and interventional trial evidence as key gaps (33-35).

Gastric and Gastroesophageal Junction (GEJ) Cancers

In gastric/GEJ cancers, the biomarker landscape is expanding beyond HER2 and MSI to include Claudin 18.2 (CLDN18.2) as a therapeutic target. Recentlly, phase 3 trials have shown clinical benefit for zolbetuximab plus chemotherapy in CLDN18.2-positive, HER2-negative disease, motivating routine testing considerations (20-23). Reviews and prevalence studies suggest CLDN18.2 is

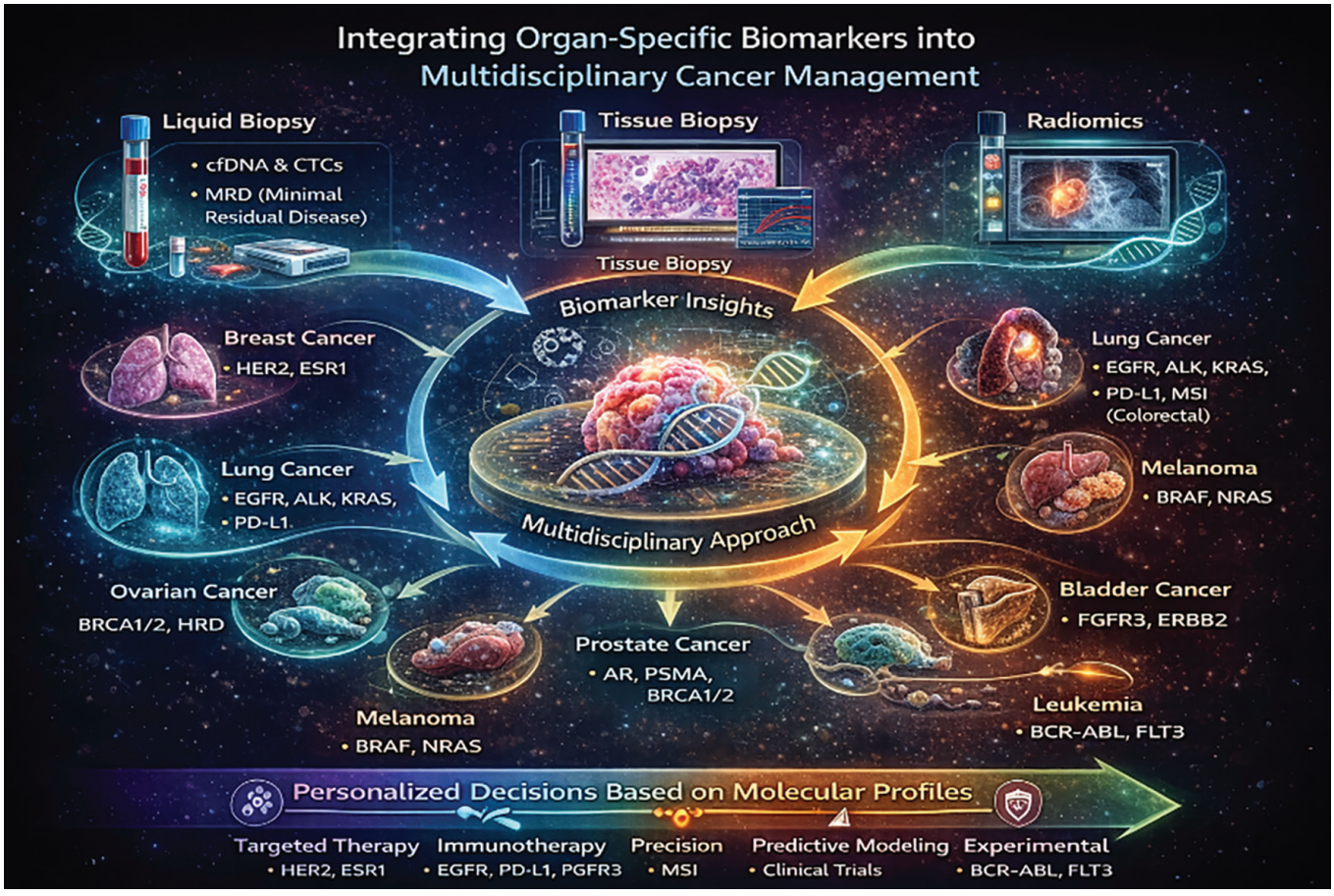

Figure 2. Organ-specific integration of biomarkers into multidisciplinary pathways across NSCLC, CRC, breast, gastric/GEJ, hepatobiliary, and prostate cancers (17-29,36-38)

NSCLC: Non-small cell lung cancer, CRC: Colorectal cancer, GEJ: Gastroesophageal junction, BRAF: B-Raf proto-oncogene, serine/threonine kinase, KRAS: Kirsten rat sarcoma viral oncogene, NRAS: Neuroblastoma RAS viral oncogene homolog, ALK: Anaplastic lymphoma kinase, AR: Androgen receptor, EGFR: Epidermal growth factor receptor, HER2: Human epidermal growth factor receptor 2, ESR1: Estrogen receptor 1, FGFR3: Fibroblast growth factor receptor 3, MSI: Microsatellite instability, HRD: Homologous recombination deficiency, ERBB: Epidermal growth factor receptor, PD-L1: Programmed death-ligand 1, BRCA1/2: Breast cancer gene 1/2, cfDNA: Cell free DNA, CTCs: Circulating tumor cells, PSMA: Prostate-specific membrane antigen, BRC-ABL: Breakpoint cluster region-Abelson murine leukemia viral oncogene homolog, FLT3: Fms-like tyrosine kinase 3

common and may remain relatively stable over time, supporting its feasibility as a clinical biomarker (22,23).

Hepatobiliary Cancers and Cholangiocarcinoma

Cholangiocarcinoma illustrates the value of biomarker stratification in rare, aggressive tumors. Fibroblast growth factor receptor 2 (FGFR2) rearrangements and isocitrate dehydrogenase 1 mutations are clinically actionable subsets. Targeted therapies (including FGFR inhibitors) have demonstrated activity in FGFR-altered disease, and multiple reviews address resistance mechanisms and safety profiles, emphasizing the importance of longitudinal molecular monitoring (25,36,37).

Prostate Cancer and Genitourinary Malignancies

Prostate cancer biomarkers increasingly span inherited and acquired alterations in DNA damage repair pathways, with poly (ADP-ribose) polymerase inhibitors demonstrating benefit in selected molecular subsets. Recent reviews summarize emerging biomarkers across genetic, RNA-based, metabolic, and epigenetic classes and discuss how molecular stratification may refine prognosis and therapy (26,38). The near-term clinical direction is toward more systematic germline and somatic testing pipelines, earlier integration of targeted therapies, and biomarker guided combinations, while retaining careful toxicity management and validation (38).

Immuno-oncology Biomarkers: Promise, Friction, and Composite Approaches (Table 2) (12-16,39)

The immunotherapy era introduced biomarkers that reflect tumor immune interaction rather than solely tumor-intrinsic genetics. PD-L1 expression, tumor mutational burden (TMB), tumor-infiltrating lymphocytes, and MSI are the most widely discussed in oncology practice. Narrative reviews emphasize

Table 2. Immuno-oncology biomarkers: utility and limitations

Biomarker	Method	Clinical use	Limitations
PD-L1	IHC	Checkpoint inhibitor selection	Intratumoral heterogeneity; assay variability; dynamic expression changes
TMB	NGS-based assay	Immunotherapy stratification (selected tumor types)	Platform variability; lack of standardized thresholds
MSI/dMMR	IHC/PCR/NGS	Strong predictor of PD-1/PD-L1 inhibitor response	Tumor-type dependent prevalence; variable sensitivity
TILs	Histopathology/RNA-based profiling	Prognostic value; emerging predictive utility	Lack of universal scoring standardization

PD-L1: Programmed death-ligand 1, TMB: Tumor mutational burden, MSI/dMMR: Microsatellite instability/mismatch repair deficiency, TILs: Tumor-infiltrating lymphocytes, IHC: Immunohistochemistry, NGS: Next-generation sequencing, PCR: Polymerase chain reaction

that predictive performance is inconsistent across tumor types and disease stages, limited by assay variability, sampling bias, and dynamic expression (12,16,39). MSI remains one of the most robust predictors of response to PD-1 blockade in several contexts, and guideline recommendations emphasize standardized MSI testing approaches (17).

Beyond baseline prediction, biomarkers are increasingly used to understand resistance to therapy. In NSCLC, for example, reviews dissect tumor-intrinsic and microenvironmental drivers of immunotherapy resistance even in PD-L1-high disease, underscoring why single marker strategies often fail and motivating composite or longitudinal biomarker approaches (12).

Composite biomarker strategies combine tumor genomics (TMB/MSI), immunohistochemistry, spatial immune architecture, and dynamic signals such as ctDNA kinetics. This reflects a broader principle: immunotherapy response is a systems property, not a single gene event. Multimodal AI approaches that integrate histopathology, omics, and imaging may become particularly useful here, provided prospective validation demonstrates incremental value over existing clinical models (13-15).

MRD: From Prognostic Signal to Interventional Tool (Figure 3)

MRD in solid tumors is often termed molecular residual disease and refers to tumor derived fragments that persist after definitive therapy but remain below detection of conventional imaging. Reviews describe ctDNA MRD as a dynamic biomarker that can identify recurrence risk earlier than radiology and may support risk adapted adjuvant strategies (5,6,8-11).

CRC provides the most mature MRD evidence base, with prospective data linking MRD to outcomes and ongoing trials testing ctDNA-guided adjuvant therapy strategies (10,11,27-29). Breast and lung cancer are rapidly following, but the key obstacles are consistent: assay sensitivity (especially in low-shedding tumors), pre-analytic variables, false positives from clonal hematopoiesis, and the need for clinically actionable algorithms (8-11,33-35).

From a multidisciplinary viewpoint, MRD has surgical implications. It could influence adjuvant therapy decisions after R0 resection, surveillance intensity, and selection for clinical trials. Until now the field must avoid premature over reliance: MRD is a powerful risk stratifier, but patient benefit depends on evidence that MRD-guided actions improve survival, reduce toxicity, or meaningfully enhance quality of life (10,11,29).

Tumor-agnostic Biomarkers and the Expansion of "Biology-First" Treatment

Tumor-agnostic therapy targets are specific molecular alterations of whom independent of the tumor's site of origin. Reviews highlight both the clinical promise and practical challenges: assay standardization, rare biomarker prevalence, equitable access to testing, and the need for multidisciplinary interpretation (40). NTRK fusions represent a canonical example of a biomarker enabling tumor-agnostic targeted therapy; clinical translation depends on robust fusion detection and careful diagnostic workflows (41).

Future Perspective

From Single Biomarkers to Biomarker Ecosystems (Table 3) (13-15)

The next phase of biomarker oncology is likely to be characterized by integration rather than proliferation. Instead of adding isolated markers, clinical value will come from (I) standardized pipelines, (II) longitudinal monitoring frameworks, and (III) multimodal fusion of omics, imaging, histopathology, and real-world clinical data for decision support (13-15).

AI-driven multi-omics integration reviews emphasize two themes. First, model performance must translate into clinical utility, meaning measurable improvement in decisions compared with current standards. Second, interpretability, robustness, and governance are not optional; they determine whether a model can be trusted in heterogeneous real-world settings (13-15).

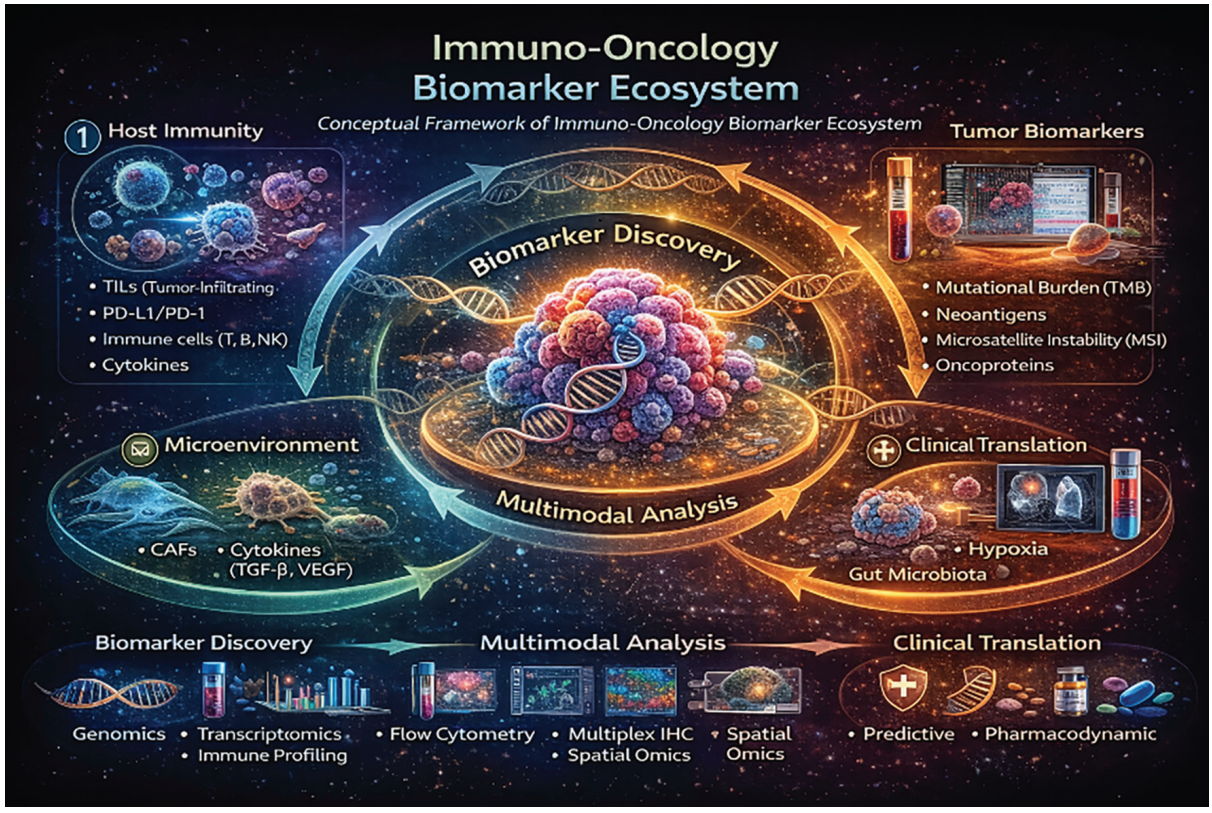

Figure 3. Immuno-oncology biomarker ecosystem: tumor-intrinsic genomics (TMB/MSI), microenvironment, and dynamic monitoring approaches (12-16,39)

TMB: Tumor mutational burden, MSI: Microsatellite instability, IHC: Immunohistochemistry, TGF-β: Transforming growth factor-beta, VEGF: Vascular endothelial growth factor, CAFs: Cancer-associated fibroblasts, TILs: Tumor-infiltrating lymphocytes, PD-L1: Programmed death-ligand 1, PD-1: Programmed cell death-1, T: T lymphocyte, B: B lymphocyte, NK: Naturel killer

Table 3. Emerging directions in molecular oncology

Emerging field	Technology	Potential application	Current challenge
ctDNA MRD-guided therapy	Tumor-informed ctDNA assays	Adjuvant therapy escalation or de-escalation	Requirement for long-term survival validation
AI-based histopathology	Deep learning applied to H&E slides	Immunotherapy response prediction	Need for prospective clinical validation
Multi-omics integration	Genomics+transcriptomics+imaging platforms	Composite predictive modeling	Data harmonization and standardization challenges
Tumor-agnostic treatment strategies	Comprehensive NGS panels	Biology-first, mutation-driven therapy selection	Access limitations and cost barriers

ctDNA: Circulating tumor DNA, MRD: Minimal residual disease, AI: Artificial intelligence, H&E: Hematoxylin and eosin, NGS: Next-generation sequencing

Transactionally, the future is also about systems: turnaround time, reimbursement, laboratory capacity, and multidisciplinary tumor boards capable of interpreting complex results. Biomarker innovation will not achieve its potential unless health systems can deliver timely, standardized testing and embed results into care pathways.

Practical Recommendations for Clinical Integration

• Use guideline concordant comprehensive profiling in biomarker-driven diseases (e.g., NSCLC) and ensure reflex testing pathways in daily practice (17-19,24).

• Prefer validated, clinically actionable biomarkers; treat exploratory multi-omics predictors as decision aids until prospectively validated (13-15).

• For MRD/ctDNA, integrate results into predefined clinical pathways (adjuvant escalation/de-escalation, trial referral) and communicate uncertainty clearly (5-11,27-29,33-35).

• Anticipate tumor heterogeneity: when tissue is limited, consider liquid biopsy as complementary rather than substitutive when feasible (6-9,11).

• Maintain multidisciplinary review of complex findings, especially for tumor-agnostic indications and rare alterations (40,41).

Footnotes

Financial Disclosure: The author declared that this study received no financial support.

References

1. AlDoughaim M, AlSuhebany N, AlZahrani M, et al. Cancer biomarkers and precision oncology: a review of recent trend and innovations. Clinical Medicine Insights: Oncology. 2024;18:1-15.
2. Murciano-Goroff YR, Suehnholz SP, Drilon A, Chakravarty D. Precision oncology: 2023 in review. Cancer Discov. 2023;13:2525-31.
3. Rosen E, Drilon A, Chakravarty D. Precision oncology: 2022 in review. Cancer Discov. 2022;12:2747-53.
4. Brlek P, Škaro V, Hrvatin N, et al. Advances in precision oncology: from molecular profiling to regulatory-approved targeted therapies. Cancers (Basel). 2025;17:1-41.
5. Pantel K, Alix-Panabières C. Minimal residual disease as a target for liquid biopsy in patients with solid tumours. Nat Rev Clin Oncol. 2025;22:65-77.
6. Shen F, Zailaie SA, Chiu B, Magliocco A, Sergi CM. Liquid biopsy - a narrative review with an update on current US governmental clinical trials targeting immunotherapy. Future Science OA. 2025;11:1-35.
7. Pellini B, Chaudhuri AA. Circulating tumor DNA minimal residual disease detection of non-small-cell lung cancer treated with curative intent. J Clin Oncol. 2022;40:567-75.
8. Parums DV. A review of circulating tumor DNA (ctDNA) and the liquid biopsy in cancer diagnosis, screening, and monitoring treatment response. Med Sci Monit. 2025;31:e949300.
9. Rolfo C, Mack P, Scagliotti GV, et al. Liquid Biopsy for Advanced NSCLC: a consensus statement from the International Association for the Study of Lung Cancer. J Thorac Oncol. 2021;16:1647-62.
10. Soueidy C, Zaanan A, Gelli M, et al. Clinical impact of circulating tumor DNA to track minimal residual disease in colorectal cancer patients. Hopes and limitations. ESMO Gastrointest Oncol. 2024;4:1-16.
11. Nakamura Y, Watanabe J, Akazawa N, et al. ctDNA-based molecular residual disease and survival in resectable colorectal cancer. Nat Med. 2024;30:3272-83.
12. Liu J, Cai Y, Liu J, Chen D, Wu X. Immunotherapy resistance and therapeutic strategies in PD-L1 high expression non-small cell lung cancer. Onco Targets Ther. 2025;18:953-66.
13. Hsu CY, Askar S, Alshkarchy SS, et al. AI-driven multi-omics integration in precision oncology: bridging the data deluge to clinical decisions. Clin Exp Med. 2025;26:29.
14. Marouf AA, Rokne JG, Alhajj R. Integrating multi-omics and medical imaging in artificial intelligence-based cancer research: an umbrella review of fusion strategies and applications. Cancers (Basel). 2025:17:3638.
15. Ran D, Li J, Zhao M, Du L, Zhang Y, Zhu J. Artificial intelligence integrates multi-omics data for precision stratification and drug resistance prediction in breast cancer. Front Oncol. 2025;15:1612474.
16. Luchini C, Bibeau F, Ligtenberg MJL, et al. ESMO recommendations on microsatellite instability testing for immunotherapy in cancer, and its relationship with PD-1/PD-L1 expression and tumour mutational burden: a systematic review-based approach. Ann Oncol. 2019;30:1232-43.
17. Hendriks LE, Kerr KM, Menis J, et al. Oncogene-addicted metastatic non-small-cell lung cancer: ESMO clinical practice guideline for diagnosis, treatment and follow-up. Ann Oncol. 2023;34:339-57.
18. Salazar AS, Noy J, Reynolds JM, et al. Strategies for improving biomarker testing rates in non-small cell lung cancer in North America: a scoping review. J Thorac Dis. 2025;17:9225-39.
19. Shuangshoti S, Prasongsook N, Thamlikitkul L, et al. Expert recommendations for biomarker evaluation of advanced non-small cell lung cancer in Thailand. Transl Lung Cancer Res. 2025;14:2387-402.
20. Gao Y, Yu Y, Zhang M, Yu W, Kang L. Mechanisms of endocrine resistance in hormone receptor-positive breast cancer. Front Oncol. 2024;14:1448687.
21. Shitara K, Lordick F, Bang YJ, et al Zolbetuximab plus mFOLFOX6 in patients with CLDN18.2-positive, HER2-negative, untreated, locally advanced unresectable or metastatic gastric or gastro-oesophageal junction adenocarcinoma (SPOTLIGHT): a multicentre, randomised, double-blind, phase 3 trial. Lancet. 2023;401:1655-68.
22. Shah MA, Shitara K, Ajani JA, et al. Zolbetuximab plus CAPOX in CLDN18.2-positive gastric or gastroesophageal junction adenocarcinoma: the randomized, phase 3 GLOW trial. Nat Med. 2023;29:2133-41.
23. Mathias-Machado MC, de Jesus VHF, Jácome A, et al. Claudin 18.2 as a new biomarker in gastric cancer-what should we know? Cancers (Basel). 2024;16:1-18.
24. Huang Q, Li Y, Huang Y, et al. Advances in molecular pathology and therapy of non-small cell lung cancer. Sig Transduct Target Ther. 2025;10:1-72.
25. Goyal L, Meric-Bernstam F, Hollebecque A, et al. Futibatinib for FGFR2-rearranged intrahepatic cholangiocarcinoma. N Engl J Med. 2023;388:228-39.
26. Huang Y, Mao J, Li X. Emerging biomarkers in prostate cancer diagnosis and management: Insights into genetic, RNA and metabolic markers (Review). Intern J Oncol. 2025;68:1-17.
27. Ma D, Gao X, Wang L, Yin H, Feng L, Zhu Y. Circulating tumor DNA for MRD detection in colorectal cancer: recent advances and clinical implications. Biomark Res. 2025;13:89.
28. Lonardi S, Nimeiri H, Xu C, et al. Comprehensive genomic profiling (CGP)-informed personalized molecular residual disease (MRD) detection: an exploratory analysis from the PREDATOR study of metastatic colorectal cancer (mCRC) patients undergoing surgical resection. Int J Mol Sci. 2022;23:11529.
29. André T, Shiu KK, Kim TW, et al. Pembrolizumab in microsatellite-instability-high advanced colorectal cancer. N Engl J Med. 2020:2207-18.
30. Yarunin A, Ahlgren H, Chaki M, Morrow C, Li X, Longshore J. *ESR1* ctDNA testing: literature review and comparison of assays for ESR1 mutation detection in advanced hormone receptor-positive breast cancer. Expert Rev Mol Diagn. 2025;25:903-14.
31. Borkar S, Markus F, Oetting A, et al. Detection of *ESR1* mutations in tissue and liquid biopsy with novel next-generation sequencing and digital droplet PCR assays: insights from multi-center real life data of almost 6000 patients. Cancers (Basel). 2025;17:1266.

32. Lu Y, Ren L, Yang M, Liu J. Clinical management of circulating tumor DNA in breast cancer: detection, prediction, and monitoring. Breast Cancer (Dove Med Press). 2025;17:851-61.

33. Ozaki Y, Iwata H. Current status and perspective of ctDNA-based MRD testing in breast cancer: a systematic review. Jpn J Clin Oncol. 2025;55:1210-6.

34. Easaw S, Hsu J, Steuerwald N, Heeke AL. Liquid clues: tracking early-stage breast cancer with ctDNA - a mini review. Front Oncol. 2025;15:1634859.

35. Abdo T, Alhalabi A, Yaghi S, et al. Minimal residual disease in solid tumors: clinical applications and future directions. Cancer. 2026;132:e70286.

36. Matranga G, Carollo A, Alaimo M, Cutaia S, Rizzo S, Provenzani A. Safety profiles of the new target therapies-pemigatinib, futibatinib, and ivosidenib-for the treatment of cholangiocarcinoma: a systematic review. Ther Adv Drug Saf. 2025;16:20420986251347376.

37. Xin X, Miao R. FGFR2-rearranged biliary tract cancer: biology, resistance mechanisms, and emerging therapeutic strategies. Cancers (Basel). 2026;18:531.

38. Lobianco L, Calvanese G, D'Ausilio D, et al. The emerging role of PARP inhibitors in prostate cancer: a narrative review. Cancer Treat Rev. 2025;140:103000.

39. Puntambekar M, Shery N, Parokkaran I, Al-Hamas M. Predictive biomarkers in cancer immunotherapy: a narrative review across selected solid tu mors. Cureus. 2025;17:e88647.

40. Wu S, Thawani R. Tumor-agnostic therapies in practice: challenges, innovations, and future perspectives. Cancers (Basel). 2025;17:801.

41. Gouda MA, Thein KZ, Hong DS. Tissue-agnostic targeting of neurotrophic tyrosine receptor kinase fusions: current approvals and future directions. Cancers (Basel). 2024;16:3395.