Biomarkers: Key to Precision Therapy for Cancer

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ABSTRACT

In recent years, biomarkers have significantly transformed the field of oncology, offering crucial resources for rapid diagnosis, patient grouping, and personalized care. These biological indicators in body fluids and tissues facilitate differentiation between healthy and diseased states, predict clinical outcomes, and track therapeutic responses. This article delves into their utility for advancing precision medicine, from discovering important molecules such as carcinoembryonic antigen (CEA) to revolutionary advances in genomics, proteomics, and nanotechnology. It also investigates their use in various cancer types, including lung, breast, and prostate cancers, shedding light on emerging biomarkers and obstacles such as tumor diversity and sensitivity limitations. Despite these obstacles, biomarkers have the potential to reshape cancer treatment, elucidating the path to more efficient and less invasive solutions and revolutionizing both research and clinical efforts.

Keywords: Biomarkers, Precision therapy, Oncology, Genomics, Proteomics

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Background

Biomarkers are biological indicators that arise from internal processes within the organism.[1] The National Cancer Institute (NCI) characterizes biomarkers as biological indicators found in body fluids, including blood or tissues, that reveal a particular health problem, condition, or standard or unusual body function. This facilitates the identification of patients affected by a disease versus those who are not affected. They also allow monitoring of how that condition changes in an individual in response to therapies and predicting relevant or intermediate clinical outcomes. Fluctuations in biomarkers between individuals suffering from a disease may arise due to germline or somatic alterations, transcriptional errors, or modifications after translation.[2,3] Nucleic acids (including DNA and/or RNA) are frequently used markers of biological importance, followed by proteins (such as receptors, enzymes, hormones, cytokines, etc.), metabolites, carbohydrates, and other components.[3] This means that diagnosis ranges from simple laboratory determinations to complex molecular fingerprints obtained using advanced technologies such as proteomics, genomics, and metabolomics.[1]

The application of biomarkers has been a significant advancement in various areas of contemporary medicine, offering an accurate and impartial means of differentiating between the physiological (normal/healthy) and pathological conditions in an individual, along with their subsequent monitoring. Biomarkers enable early diagnosis and are fundamental to personalized medicine and pharmacovigilance. The use of biomarkers in clinical practice is essential because they provide relevant information that helps healthcare professionals make simpler, clearer, and faster measurable medical decisions, often in a more cost-effective way.[4] Many countries have begun to invest in the creation of national cohorts for data collection and the development of regulations on biomarkers, allowing for better personalization of medical treatments.[5]

The pharmaceutical industry has greatly benefited from the emergence of biomarkers, as losses due to drug failures have been significantly reduced by biomarker diagnostic tools that allow for more accurate selection of drug candidates and even pharmacokinetic assessment.[6] In addition to refining compound selection, they allow for the design of effective dosing regimens, assessment of drug-target interactions, and prediction of clinical outcomes. On the other hand, they allow for the categorization and profiling of patient cohorts, delve into the intricate pathophysiological processes that develop within these groups when exposed to a drug, and juxtapose them with their healthy counterparts. These benefits have significantly contributed to reducing the financial burden and risks of drug development while decreasing the failure rate in clinical trials. An example of these benefits can be seen in diseases such as Alzheimer's, where these indicators can differentiate between palliative treatments and those that produce some change in the disease, thus reducing development times and optimizing resources.[7,8]

Biomarkers play a key role in several areas of oncology. Cancer is the leading cause of mortality worldwide, with an estimated 20 million new diagnoses in 2020 and a staggering 9.7 million deaths as a result of this disease.[9] Cancer can manifest itself in more than 200 variants and affect approximately 60 organs of the human body. Although certain tumors can remain latent, 90% of cancer deaths are related to metastasis, a formidable challenge to address in its most advanced stages. Early detection is, therefore, essential to expand therapeutic options and improve survival.[10]

The carcinoembryonic antigen (CEA), identified by Phil Gold and Samuel Freedman in 1965, was one of the first recognized biomarkers. This antigen, discovered in people battling colorectal cancer but absent in those in robust health, prompted the creation of biomarker-based diagnostics (Figure 1). By the late 1970s, several serum assays for various forms of cancer had emerged, confirming the value of biomarkers in the diagnostic setting.[10,11]

In this review, we explore the fundamental role of biomarkers in oncology, from their different types and advancements as well as the benefits they bring to clinical strategies to treat and understand cancer. We will delve deeper into the world of biomarkers, exploring their fundamental role not only in measuring the likelihood of cancer onset but also in revealing hidden

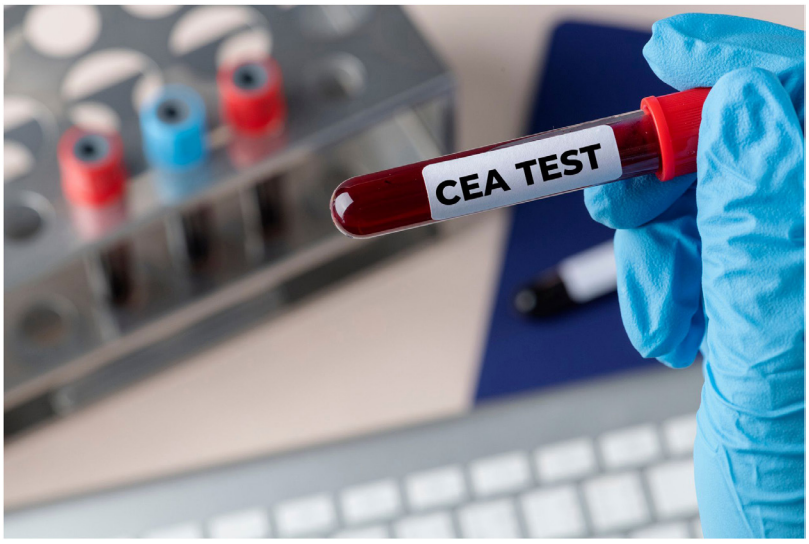

Fig 1 | Carcinoembryonic antigen (CEA) test, a blood test that measures the amount of CEA protein in the blood to help detect colorectal cancer

tumors, distinguishing between harmless and harmful lesions, predicting outcomes, anticipating treatment responses, monitoring disease progression, aiding in the discovery of recurrences, and evaluating the success of therapeutic interventions.

Potential Applications of Biomarkers in Oncology

In oncology, biomarkers are key players in improving diagnosis and treatment, which has important implications for many facets of cancer care. Advancements in many technologies, including pharmacogenomics and proteomics, have amplified the power of biomarkers to revolutionize cancer treatment, contributing to the inclusion of new strategies to improve personalized medicine.

Early Detection of Cancer Using Biomarkers

Early detection of cancer using biomarkers allows the identification of the disease before the onset of symptoms, thus enabling more effective and less invasive therapies. Identification of biomarkers in body fluids is a viable and noninvasive strategy.[12] Examples of biomarkers include CEA in colorectal cancer[10] and EGFR mutations in lung cancer, which are capable of predicting the disease before symptoms.[13]

Next-generation sequencing (NGS) has improved the accuracy of early diagnosis.[14] Serum proteomics combined with bioinformatics tools has shown potential for detecting breast cancer in its early stages.[12] One example is RS/DJ-1, a PTEN regulator detected in the serum of 37% of breast cancer patients but absent in healthy individuals.[15,16] Emerging biomarkers such as circulating miRNAs, circulating tumor DNA (ctDNA), and exosomes have demonstrated high sensitivity and specificity in early detection,[17] although they still require clinical validation.

Another promising strategy is the study of post-translational modifications in glycoproteins, especially glycosylation, which reflects changes in tumor metabolism and may induce the generation of autoantibodies detectable before symptoms.[18] Some key alterations include:

- N-glycan branching: favors tumor invasion and is associated with worse clinical outcomes.[19–22]
- Incomplete O-glycan synthesis: truncated antigens such as Tn, STn, and T are abundant in cancer cells and useful for therapies and diagnostics.[21,22]
- Alterations in mucins: facilitate immune evasion and metastasis, exposing immunogenic epitopes relevant for diagnosis.[23,24]

Despite these advancements, the identification of effective biomarkers remains a challenge. Some biomarkers have presented limitations when used in early cancer detection, such as PSA for prostate cancer, which has been criticized for its high rate of false positives, which can lead to erroneous diagnoses.[25] Similarly, CA125 and CA19-9, used to monitor ovarian and pancreatic cancer, have limited specificity.[26,27] However, a study evaluating serum samples before diagnosis failed to identify reliable biomarkers, highlighting the difficulty of their clinical application.[28] However, the development of new biomedical technologies and the integrated approach of multiple biomarkers will allow for improving the sensitivity and accuracy in early cancer detection.

Monitoring and Relapse

Biomarkers are used not only in diagnosis and treatment selection but also in monitoring disease progression during and after treatment. This includes early detection of recurrence, allowing for rapid and effective intervention. Biomarkers such as CEA and CA19-9, used in gastrointestinal cancers, allow for monitoring disease progression and adjusting therapies based on patient response.[10] CA125 is also widely used to assess treatment response in ovarian cancer.[25] This innovative monitoring feature allows medical experts to continuously assess the impact of therapies and implement modifications when necessary.

Prognostic Biomarkers

Prognostic biomarkers predict the clinical course of the disease, independent of treatment. For example, alterations in KRAS correlate with worse clinical outcomes in colorectal cancer and offer crucial information for designing treatment strategies.[29] Likewise, HER2/neu has played a fundamental role in the identification of patients with aggressive breast cancer, guiding the application of targeted therapies such as trastuzumab, which may be a beneficial option in HER2+ cases, where some cases have shown progression-free survival.[30,31]

The biomarkers OPN and GP73 have shown great potential in the diagnosis and prognosis of hepatocellular carcinoma (HCC). OPN is found at significantly elevated levels in patients with HCC compared to individuals with non-malignant chronic liver disease, suggesting its diagnostic utility. Furthermore, a meta-analysis associated its increase with a lower overall and relapse-free survival, indicating its prognostic value beyond alpha-fetoprotein (AFP).[32,33] On the other hand, GP73, a Golgi complex

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protein, is expressed at elevated levels in patients with HCC and has demonstrated a sensitivity of 74.6% and a specificity of 97.4%, surpassing AFP values of 58.2% and 85.3%, respectively. Furthermore, its serum levels decrease after surgical resection and increase with tumor recurrence, reinforcing its usefulness as a biomarker in detecting HCC in high-risk populations.[34,35]

Pharmacodynamic Biomarkers

Pharmacodynamic biomarkers serve as crucial cancer biomarkers, supporting the identification of ideal chemotherapy doses tailored to specific tumors and individual characteristics. These indicators are essential for adjusting medication levels to remain below harmful thresholds while advancing clinical trials into later stages.[36]

Predictive Biomarkers

These biomarkers reveal the likelihood that a patient will respond favorably to a specific treatment, allowing for the optimization of therapeutic options. EGFR mutations predict the efficacy of tyrosine kinase inhibitors in the treatment of lung cancer.[13] An increase in PD-L1 expression indicates better outcomes for therapies targeting immune checkpoints, such as nivolumab and pembrolizumab.[37]

Furthermore, biomarkers such as EGFR and ALK are essential for guiding targeted therapies in non-small-cell lung cancer (NSCLC), contributing to improved overall survival rates and minimizing adverse reactions.[26]

However, mutations in the Kirsten rat sarcoma (KRAS) and neuroblastoma RAS (NRAS) oncogenes, which are downstream modulators of the EGFR signaling pathway, activate independent pathways in which EGFR-targeted drugs are ineffective. Consequently, patients with these mutations have a low response to monoclonal antibody (MAb) therapies. Given the medical relevance of KRAS and NRAS in colorectal cancer, a study evaluated the ability to detect these mutations using Sanger sequencing, which is considered the gold standard method for this type of diagnosis in much of Latin America. The results were compared with the SNaPshot sequencing technique, finding that the latter showed greater accuracy, sensitivity, and specificity in the detection of single nucleotide polymorphisms compared to the Sanger method.[38]

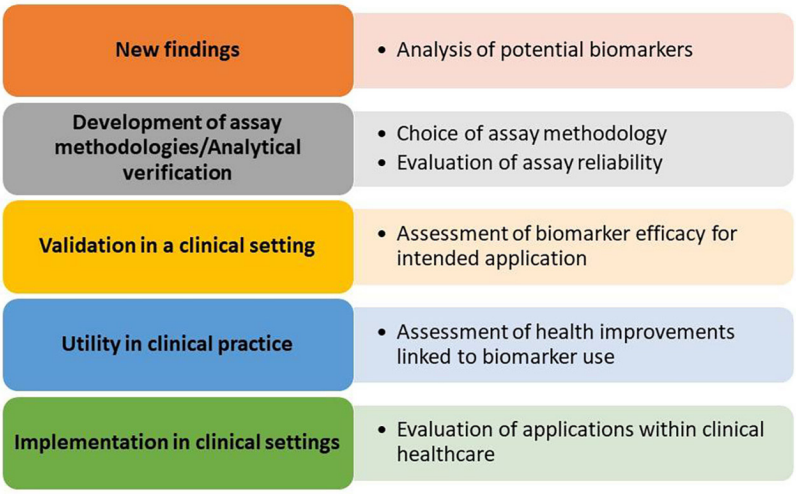

Fig 2 | Steps for the discovery and implementation of new biomarkers

Process for Discovering New Oncological Biomarkers

Biomarker detection plays a pivotal role in early cancer diagnosis, treatment response assessment, and disease monitoring. This process faces inherent challenges due to the biological heterogeneity and the complexity of validation procedures.[39]

Biomarker detection can be performed using qualitative as well as quantitative methodologies. Quantitative methods assess the exact amounts of disease-related biomarkers, while qualitative methods shed light on the relationships between biomarkers and clinical traits of the disease, although they do not provide precise readouts. Both methodologies are instrumental in unraveling the intricate ways in which biomarkers can reflect complex biological dynamics.[40] For a biomarker to be considered validated, it must meet three crucial criteria:

1. Content validity reflects how accurately the biomarker embodies the biological phenomenon under investigation.
2. Construct validity demonstrates its link to several crucial clinical factors related to the disease.
3. Criterion validity assesses its ability to align with the disease through measures such as sensitivity, specificity, and predictive capacity.

Stages of Biomarker Development

The biomarker innovation process is guided by a meticulously crafted five-step framework established by the National Cancer Institute (NCI) (Figure 2). This framework ensures that discovered biomarkers have significant clinical relevance and practical application in healthcare:

Preclinical discovery: During this initial stage, potential biomarkers are revealed through the examination of biological samples, taking advantage of cutting-edge techniques such as genomics and proteomics.[39]

Initial clinical validation: In this phase, the biomarker is examined for accuracy and consistency within a fundamental clinical framework by developing reliable detection techniques.[41]

Retrospective evaluation: This stage examines samples obtained before disease manifestation to establish a link between the biomarker and the disease trajectory.

Prospective study: The effectiveness of the biomarker is evaluated in real time by analyzing its sensitivity and specificity within expansive, population-focused clinical trials.[39]

Implementation in population controls: Ultimately, the biomarker is examined in a broader spectrum, weighing its advantages and disadvantages concerning public health implications and economic ramifications.

In addition, the NCI has promoted initiatives such as the Program for the Assessment of Clinical Trials in Cancer (PACCT) and the Clinical Trials Advancement Initiative, both of which are dedicated to improving the creation and verification of biomarkers to ensure their relevance in medical practice.[41]

Validation Standards for the Application of New Biomarkers

Accurate reporting of biomarker research results is essential to enable researchers to critically appraise the study setting and data and to provide sufficient detail to independently verify conclusions. To achieve this goal, several guidelines have been developed to harmonize reporting approaches:

- Biospecimen Reporting for Improved Study Quality (BRISQ) and Reporting Recommendations for Tumor Marker Prognostic Studies (REMARK): These protocols organize the description of preanalytical and analytical details in prognostic biomarker research.[42–45]
- Standards for Reporting of Diagnostic Accuracy Studies (STARD) emphasize the importance of accuracy and transparency in documenting diagnostic tests.[46,47]
- The Minimum Information About a Microarray Experiment (MIAME) and Minimum Information About a Next-Generation Sequencing Experiment (MINSEQE): These establish essential benchmarks for detailing experiments using microarrays or sequencing studies.[48,49]

In addition, initiatives have been launched to classify biomarker findings into various levels of evidence (LoE) based on their clinical importance. In 1996, the American Society of Clinical Oncology (ASCO) Tumor Marker Guidelines Committee released the Tumor Marker Utility Grading System (TMUGS) framework,[50] which assigns the highest level of evidence (Level I) to prospective studies explicitly designed to evaluate a biomarker, along with meta-analyses of rigorously executed studies.[51]

Scientific Research and Technological Advancements for the Discovery and Diagnosis of Biomarkers

Revolutionary technological advancements have changed the landscape of biomarker research in oncology, facilitating accurate diagnoses, personalized treatments, and a deeper understanding of the molecular basis of cancer. In addition, biomarkers are indispensable in clinical research, facilitating the evaluation of the efficacy of novel therapies and the discovery of new therapeutic strategies.[6]

Genomics and Proteomics

The cheapening of genetic sequencing and other omics technologies has allowed the generation of large volumes of molecular data, facilitating the identification of new biomarkers and the classification of patients into specific subtypes.[5] These tools have also played a crucial role in the discovery of global changes in gene expression and the distinction of previously elusive tumor stages and types.[51] For example, analysis of cytokeratin-19 mRNA has significantly improved the identification of epithelial tumors.[52] These advancements have enriched our understanding of the pathophysiological complexities of cancer, paving the way for the creation of more precise and potent therapies.[6]

Molecular Imaging

The alliance of biomarkers with cutting-edge imaging technologies, especially positron emission tomography (PET), has dramatically increased the efficiency of cancer diagnosis and assessment. This noninvasive approach measures FDG-labeled glucose consumption and links its uptake to the level of tumor aggressiveness and response to treatment.[53] Furthermore, imaging technologies can identify the location of tumors and track the efficacy of new experimental treatments.

Epigenetic Biomarkers

Alterations in epigenetic structure, particularly increased levels of DNA methylation in tumor suppressor genes, are important indicators of cancer. For example, hypermethylation of p16 has been linked to recurrent colorectal cancer, serving as a valuable tool for both diagnosis and prediction of therapeutic outcomes.[54] These biomarkers not only identify vulnerable patients but also help discern the most appropriate treatments.

Circulating Tumor Cells (CTCs)

The appearance of circulating tumor cells (CTCs) represents a vital advancement that allows observing cancer dynamics and assessing therapeutic efficacy. The detection of CTCs in individuals with metastatic cancer correlates with a dismal prognosis, while their eradication during therapy means a favorable reaction.[55] These cells serve as a vital instrument to identify which patients are most likely to benefit from innovative treatments.[6]

Mass Spectrometry and Proteomic Analysis

Mass spectrometry reveals the hidden complexities of tumor-associated proteins, allowing for the creation of unique profiles that are essential for accurate diagnosis and the development of personalized therapies.[56] These investigations have also paved the way for discovering new therapeutic targets and tailored treatment approaches.

Biosensors and Nanotechnology

The main obstacle in the quest to identify cancer biomarkers lies in the low levels of analytes found in non-tumor tissue samples, including blood and other body fluids. To address this problem, the domains of biosensors and nanotechnology are being leveraged to elevate the sensitivity and accuracy of detection. Biosensors detect biomarkers through chemical processes that generate electrical signals, which are then processed and amplified.[57] Furthermore, the fascinating realm of gold nanoparticles, quantum dots, nanotubes, and nanoribbons boast an extraordinary surface-to-volume ratio, allowing a multitude of molecules (such as antibodies, linkers, and small compounds) to adhere firmly, thus amplifying the sensitivity of biosensors. These innovative technologies serve as powerful tools to reveal cancer biomarkers, including ctDNA/RNA/miRNAs, e.g., miR-141 found in prostate cancer serum,[58] or the intriguing DNA methylation in ctDNA for cancer identification,[59] along with

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proteins, circulating tumor cells (CTCs), and extracellular vesicles (EVs) present in body fluids.[60] Nanotechnology can also identify CTCs using proteins such as EpCAM, PTK7, HER2, and Cd2/Cd3.

Overall, biomarker detection techniques are essential for early diagnosis, treatment selection, and cancer monitoring. Each method has advantages and limitations that determine its clinical use. The following table compares various detection technologies, such as NGS, liquid biopsy, proteomics, and nanotechnology biosensors, highlighting their benefits and challenges in oncology (Table 1).

Table 1 | Comparison of biomarker detection techniques

Method	Advantages	Disadvantages
Next-Generation Sequencing (NGS)	High genetic resolution, detection of rare mutations	Expensive, requires advanced computational analysis
Proteomics by Mass Spectrometry	Identification of key proteins, tumor profiling	Complex data analysis, limited to known proteins
PET Imaging	Real-time detection, useful for staging and monitoring	Requires radioactive isotopes, does not detect molecular mutations
Liquid Biopsy	Minimally invasive, enables continuous tumor tracking	Lower sensitivity in early cancer stages
Microarrays	Allows gene expression analysis in large sample volumes	Does not detect point mutations and requires PCR confirmation
Digital PCR	High sensitivity and specificity for specific mutations	Limited to specific genes, does not allow global detection
Nanopore Sequencing	Rapid and portable sequencing, useful in clinical and field settings	Less accurate than NGS for complex structural variants
Flow Cytometry	Allows analysis of circulating tumor cells in blood	Requires high specialization, expensive for large volumes
Nanotechnology-Based Biosensors	High sensitivity for biomarkers in biological fluids, potential miniaturization	Emerging technology, still under clinical validation

Table 2 |Some recent clinical trials on cancer biomarkers

ClinicalTrials.gov ID	Cancer Type	Biomarker(s)	Objective	Last Update
NCT06726070	Prostate Cancer	miR-107, miR-134-5p, miR-149-5p, miR-370-3p, miR-221	Evaluate miRNA expression in blood to distinguish PCa from BPH and reduce unnecessary biopsies.	2024-12-10
NCT06629831	Ovarian Cancer	NLR, PLR, LMR (Inflammatory Markers)	Determine the prognostic value of inflammatory biomarkers in ovarian cancer surgery.	2024-10-09
NCT06601205	Prostate Cancer	Finasteride, Flutamide (Tissue Biomarkers)	Assess the effects of Finasteride and Flutamide in pre-surgical prostate cancer patients.	2024-09-19
NCT06432413	Colorectal Cancer	SNHG3, LUNAR1 (lncRNAs)	Investigate NOTCH-related lncRNAs as prognostic biomarkers in CRC.	2024-05-29
NCT06427720	Breast Cancer	LINC00511, miR-185-3p, miR-301a-3p (miRNAs & lncRNAs)	Evaluate the diagnostic potential of the LINC00511/miR-185-3p/miR-301a-3p axis in breast cancer	2024-05-24
NCT06091592	Colorectal Cancer	Serum Autotaxin	Investigate the diagnostic value of serum autotaxin levels in colorectal cancer.	2024-10-09
NCT05326906	Lung Cancer (Immune-related Hepatitis)	Predictive Biomarkers for Severe Immune-related Hepatitis	Identify predictive biomarkers for severe immune-related hepatitis in lung cancer patients.	2023-10-19

The aforementioned tools have enabled major advancements in the discovery of new biomarkers, driving the development of new strategies for cancer diagnosis and treatment. Recent clinical trials have explored innovative biomarkers, from microRNAs and long non-coding RNAs (lncRNAs) to inflammatory biomarkers and serum enzymes, to improve diagnostic accuracy and the selection of personalized therapies. The following table summarizes several recent clinical trials, highlighting the type of cancer, the biomarkers evaluated, and the study objectives (Table 2). These studies reflect the growing interest in noninvasive biomarkers and their potential impact on oncology precision medicine.

Biomarkers in Various Types of Cancer

Lung Cancer

Lung-cancer-related biomarkers present a diverse tapestry of indicators such as squamous cell carcinoma antigen, CEA, CA-125, NSE, chromogranin A, RBP, and α1-antitrypsin, along with genetic variations such as increased activation of oncogenes (K-ras, Myc, EGFR, Met) and downregulation of tumor suppressor genes (p53, Rb).[52] DNA amplification (TTF-1, Pax9, Nkx-8) and genetic hypermethylation (p16, RARB, DAPK) are also emerging as predictive markers. Mutations of p53 and β-2 microglobulin are associated with prognosis in lung cancer and lymphoma.[61]

Prostate Cancer

PSA is the main indicator of prostate cancer, although complementary markers such as fPSA and tPSA variants are vital to assess disease severity. Other promising biomarkers for metastatic prostate cancer include thymosin β-15, antizyme, collagen XXIII, hK2, EPCA, AMACR, IGFBPs, and TGF-β1, with both thymosin β-15 and PSA demonstrating increased sensitivity for predicting recurrence.[62–64] Genomic changes such as p53 and bcl-2 expression correlate with poor outcomes.[62]

Breast Cancer

Breast cancer biomarkers span a spectrum including CA 15-3, CA 27-29, CEA, ER, PR, HER2, uPA, and PAI-1, along with rising stars such as BRCA1/2 mutations, miRNAs, p53, and cyclin E, all of which contribute to the art of risk assessment and treatment strategy.[65,66] The presence of Her-2 is essential to guide therapeutic pathways such as Herceptin®, while the microvessel density (MVD) and MMP landscape reveal the secrets of tumor expansion. Osteopontin also emerges as a beacon of prognostic knowledge.[67]

In this type of cancer, the identification of tumor subtypes that allow patient stratification is often complex. In one study, they performed a High-throughput proteomics analysis of breast cancer subtypes using panels to identify differentially expressed proteins as subtype biomarkers. These panels achieved performances with at least 75% sensitivity and 92% specificity. In the validation cohort, the panels obtained acceptable to outstanding performances (AUC = 0.740–1.00).[68]

Ovarian Cancer

Uncovering the shadows of ovarian cancer in its early stages presents a formidable challenge. Although CA-125 is considered a conventional biomarker, its accuracy leaves much to be desired. Increased presence of cyclin D1 and tumor-associated trypsin inhibitors are emerging as promising indicators of more aggressive disease and its prognosis.[69,70]

Colorectal Cancer

The presence of microsatellite instability resulting from alterations in DNA repair genes (MLH1, MSH2, MSH6) is a significant prognostic indicator for colorectal cancer. In addition, elevated levels of D-dimer are a promising biomarker but are not specific enough.[71]

Other Cancers

Indicators such as modifications of p53, β-2 microglobulin, and caspase-3 show the potential to predict a variety of malignancies. Advancements in genomic and proteomic innovations are constantly revealing markers, although no single biomarker accurately predicts outcomes. Future research is expected to be based on a combination of biomarkers to assess metastasis, recurrence, and disease progression.[72]

The following table summarizes some important biomarkers, associated treatments, and their impact on breast, lung, and colorectal cancers, among others (Table 3). Their use optimizes clinical decisions, thus improving patient outcomes.

Challenges and Prospects for Oncological Biomarkers

The discovery and use of biomarkers offer promising opportunities for improving medical care. However, their integration into clinical practice faces multiple challenges of various kinds, ranging from biological and technical aspects to regulatory and economic barriers. One of the main obstacles in the development of biomarkers is the enormous tumor diversity. The great variability of genetic and epigenetic changes between different types of cancer makes it difficult to identify universal biomarkers, which complicates the creation of effective diagnostic tools to address all varieties of the disease. The intricate molecular heterogeneity of tumors amplifies this difficulty, making it almost impossible to find biomarkers that faithfully represent each cancer subtype.[25,73,74]

Technical discrepancies constitute another significant impediment. Factors such as sample collection techniques, storage practices, and analysis methods can influence the reliability of the results, generating inconsistencies that affect the reproducibility and credibility of biomarker studies. Furthermore, commonly used biomarkers such as PSA and CA-125 have accuracy issues, limiting their effectiveness as definitive diagnostic tools in clinical settings.[75] Errors in biomarker sensitivity and specificity can lead to false positives and negatives, leading to inaccurate diagnoses, unnecessary treatments, and significant emotional burdens for patients.[4,76] Furthermore, the lack of validation in independent cohorts and the low representation of rare subtypes in studies affect the reliability of these biomarkers and their widespread application.[5] Another relevant problem is the management of the huge amounts of data generated by biomolecular analysis. The absence of standards in clinical procedures hinders the integration of biomarkers into healthcare systems, underlining the need to develop uniform and reliable protocols for their clinical use.[75] Regulations vary considerably across countries, posing an additional challenge to the implementation of biomarkers in medical practice. In the United States, the FDA requires rigorous validation before commercialization, whereas in Europe, the CE-IVD framework allows for more flexible but still extensive, protocol-driven procedures. In low-income countries, accessibility to these technologies is limited due to the high costs of tools such as next-generation sequencing (NGS). Initiatives such as The Cancer Moonshot have begun to address this gap through subsidy programs for biomarker technologies in low-resource settings. In addition to regulatory barriers, the costs associated with biomarker research, development, and approval represent a significant financial challenge. High costs, coupled with strict regulatory requirements, delay the introduction of new biomarkers into medical practice and limit their availability to patients.[19,26]

Despite these challenges, biomarkers have proven their value in precision medicine, allowing the identification of patients who can most benefit from personalized therapies, thereby improving clinical outcomes and reducing unnecessary side effects. Emerging technologies, particularly artificial intelligence, are beginning to address some of these limitations. Deep neural networks are enabling advancement in cancer research by integrating multiple types of data, from medical images to molecular data and clinical records, using predictive and personalized models, which can be beneficial for detection, diagnosis, and treatment. These innovations facilitate the efficient analysis of large biomolecular data sets and accelerate the adoption of

Table 3 | Comparison of some biomarkers and treatments in different types of cancer

Cancer Type	Biomarkers	Targeted Therapy	Survival Improvement (%) or Benefit
Breast	HER2	Trastuzumab, Pertuzumab	+33% reduction in recurrence
Lung	EGFR, ALK, ROS1	Erlotinib, Gefitinib, Crizotinib	+10 months median survival
Colorectal	KRAS/NRAS, BRAF	Anti-EGFR (only in KRAS wild-type), BRAF Inhibitors	Only in patients without KRAS/NRAS mutations
Hepatocellular	AFP, OPN, GP73	No specific targeted treatment	Not reported
Ovarian	CA-125, HE4	Bevacizumab, Olaparib	Better response in selected subgroups
Prostate	PSA, PCA3	Enzalutamide, Abiraterone	Tumor progression reduction
Chronic Myeloid Leukemia	BCR-ABL	Imatinib, Nilotinib, Dasatinib	Transformed CML into a chronic disease
Melanoma	BRAF V600E	Vemurafenib, Dabrafenib	Better response in metastatic melanoma
Kidney Cancer	VEGF	Sunitinib, Pazopanib	Improved survival in advanced stages

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biomarkers in personalized medicine, offering a promising future for their application in healthcare.[76,77]

Conclusion

In cancer research, biomarkers have markedly changed the dynamics of personalized medicine by enabling accurate diagnostic techniques, comprehensive prognostic assessments, and tailored treatment strategies. Their remarkable role in early cancer identification, monitoring therapeutic responses, and assessing recurrences has profoundly transformed the structure of clinical practice. However, obstacles such as the diverse nature of tumors, the insufficient specificity of certain biomarkers, and high costs associated with clinical validation underscore the need for continued exploration and refinement of their application.

Despite these limitations, the future of biomarkers is promising. Emerging technologies such as artificial intelligence and omics analyses have enabled crucial advancements, from the identification of specific molecular alterations to the development of targeted therapies. The integration of clinical and molecular data into electronic medical records will be key to advancing precision medicine and ensuring the effective application of biomarkers in medical practice. With a well-designed strategy, biomarkers promise to improve clinical outcomes while mitigating the economic strains associated with cancer research and treatment. This underscores their indispensable role in moving toward truly personalized and efficient medicine.

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