Cancer Biomarkers and Precision Oncology: A Review of Recent Trends and Innovations

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ABSTRACT: The discovery of cancer-specific biomarkers has resulted in major advancements in the field of cancer diagnostics and therapeutics, therefore significantly lowering cancer-related morbidity and mortality. Cancer biomarkers can be generally classified as prognostic biomarkers that predict specific disease outcomes and predictive biomarkers that predict disease response to targeted therapeutic interventions. As research in the area of predictive biomarkers continues to grow, precision medicine becomes far more integrated in cancer treatment. This article presents a general overview on the most recent advancements in the area of cancer biomarkers, immunotherapy, artificial intelligence, and pharmacogenomics of the Middle East.

KEYWORDS: Cancer biomarkers, precision medicine, targeted therapy, artificial intelligence, pharmacogenomics

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Introduction

Cancer biomarkers have become integral in cancer research and drug development, playing a crucial role in guiding decision-making and ensuring the success of novel antitumor therapeutics.[1] There are 2 main types of biomarkers: disease-related and drug-related biomarkers. Disease-related biomarkers aid in risk stratification, identifying patients with cancer within the general population, staging cancer, and predicting disease outcomes.[2] Conversely, drug-related biomarkers provide valuable information about prognosis and survival following clinical intervention.[2,3] These predictive factors assist in identifying patients who are most likely to benefit from specific treatments and assessing treatment effectiveness and potential side effects.[2,3] Despite some progress in biomarker discovery, only a few biomarkers have been translated into routine clinical use. An ideal biomarker should be easily and reliably measured with high analytical specificity and sensitivity in a noninvasive or minimally invasive manner and at a low cost.[4] However, the translation of biomarkers from the laboratory to clinical practice faces challenges such as small sample sizes; mismatched case and control specimens; and errors in sample collection, handling, storage, preparation, and analysis.[4]

The discovery of biomarkers is significant in the era of targeted therapy, where personalized medicine aims to predict the response to medical treatment and tailor interventions based on individual biological information.[4,5] Cancer mortality rate continued to decline from 2019 to 2020 by 1.5%, and this decline contributed to a 33% overall reduction in cancer deaths, preventing an estimated 3.8 million fatalities.[6] This progress is largely attributed to advancements in cancer treatment, especially noticeable in the decrease in mortality rates for cancer diseases such as leukemia, melanoma, and kidney cancer, with an approximately 2% annual decline from 2016 to 2020.[6]

Recent trends and innovations in cancer biomarkers have revolutionized cancer treatment. This comprehensive review article aims to provide an in-depth overview of these biomarkers while also discussing the successes and obstacles encountered with targeted therapies. In addition, we provide insight into utilizing artificial intelligence (AI) in the field of cancer biomarkers. Finally, we discuss the current state and trends of cancer biomarkers in underrepresented Middle Eastern populations.

Precision Medicine and Targeted Therapies

Precision medicine represents a shift from the one-size-fits-all approach of traditional cancer treatments to more personalized, targeted interventions, which has shown promise in improving treatment outcomes and reducing the side effects associated with cancer therapies.[7] Targeted cancer therapies are generally divided into 2 groups: small molecule drugs and monoclonal antibodies (mAbs).[8] Small molecules (<900 Da) exert their effects by penetrating the cell and binding to specific cellular proteins to alter downstream signaling pathways. Monoclonal antibodies are larger proteins produced through recombinant technologies, and mAbs exert their therapeutic action by interacting with extracellular targets.[9-11] Antibody drug conjugates (ADCs) are mAbs linked with a cytotoxic payload. This novel concept, which was introduced in the year 2000, has led to precise cancer cell

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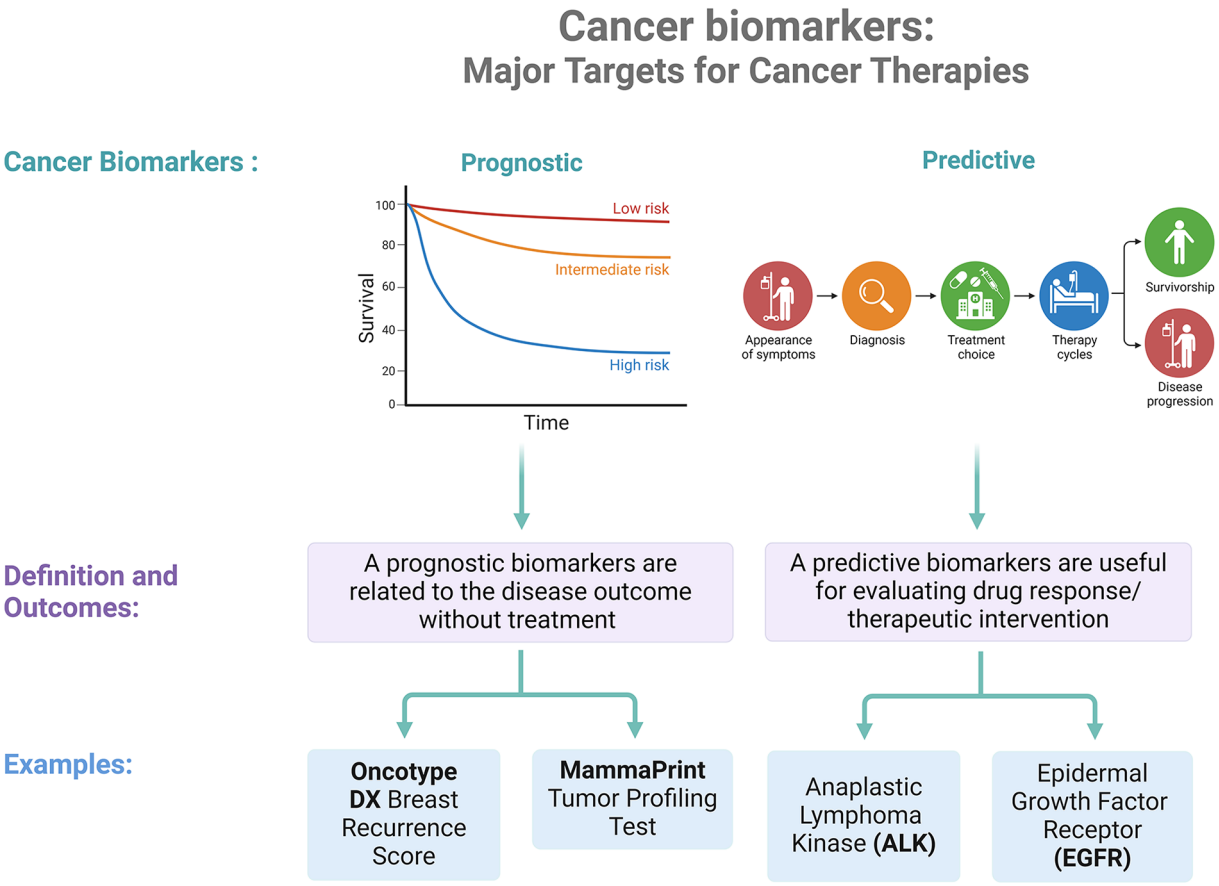

Figure 1. Biomarker classification based on treatment response. Prognostic biomarkers may be detected by standardized tests (eg, Oncotype Dx, Mammaprint). Predictive biomarkers that predict the response to targeted therapies including ALK and EGFR.

targeting with less cytotoxic chemotherapy-associated toxicity than conventional chemotherapy.[12,13] In contrast to chemotherapy, targeted therapies are designed to specifically target some molecular structures within cells, often resulting in fewer and less severe side effects.[8]

In the realm of precision medicine, patients with cancer who receive treatment based on biomarker-guided approaches have shown improved outcomes compared with those receiving traditional treatment methods.[14] The hallmarks of cancer, as described by Hanahan and Weinberg, provide a foundational framework for understanding cancer biology and have significantly influenced the development of rational drug designs. Among these hallmarks, selective growth and proliferative advantage are critical.[14] An improved understanding of the hallmarks of cancer has led to a shift from nonselective, traditional therapies to more effective targeted treatments, which will be discussed in this section.

Biomarker classification

Cancer biomarkers are divided into prognostic and predictive biomarkers. Prognostic biomarkers provide insights into disease outcomes, while predictive biomarkers are useful for evaluating drug responses[15,16] (Figure 1). Biomarkers may also be categorized based on patient genetics as either germline or somatic. Furthermore, a more complex framework exists for categorizing the significance and pathogenicity of various biomarkers[16,17] (Figure 2).

Biomarkers in solid cancers

The fast-growing field of targeted therapies for cancer can be categorized according to their effect on one or more of the hallmarks of cancer.[14] This section will discuss the role of cancer biomarkers in the top 3 reported solid cancers worldwide, which are breast, lung, and colorectal cancers (CRCs).[6] In Table 1, we summarize the most common treatment-driven biomarkers and their targeted cancer therapies.

Lung cancer. Lung cancer, which includes small and non–small cell cancer types, is the leading cause of cancer deaths globally, with 1.8 million deaths/year.[16] Despite advances in targeted therapies improving the prognosis of patients with advanced lung cancer, late-stage patients still face poor outcomes, highlighting the importance of early detection and aggressive treatment.[15] In lung cancer treatment, personalized therapy based on molecular profiling has become crucial and used in multiple treatment algorithms, such as in the National Comprehensive Cancer Network (NCCN) and European Society for Medical Oncology (ESMO) guidelines.[18,19]

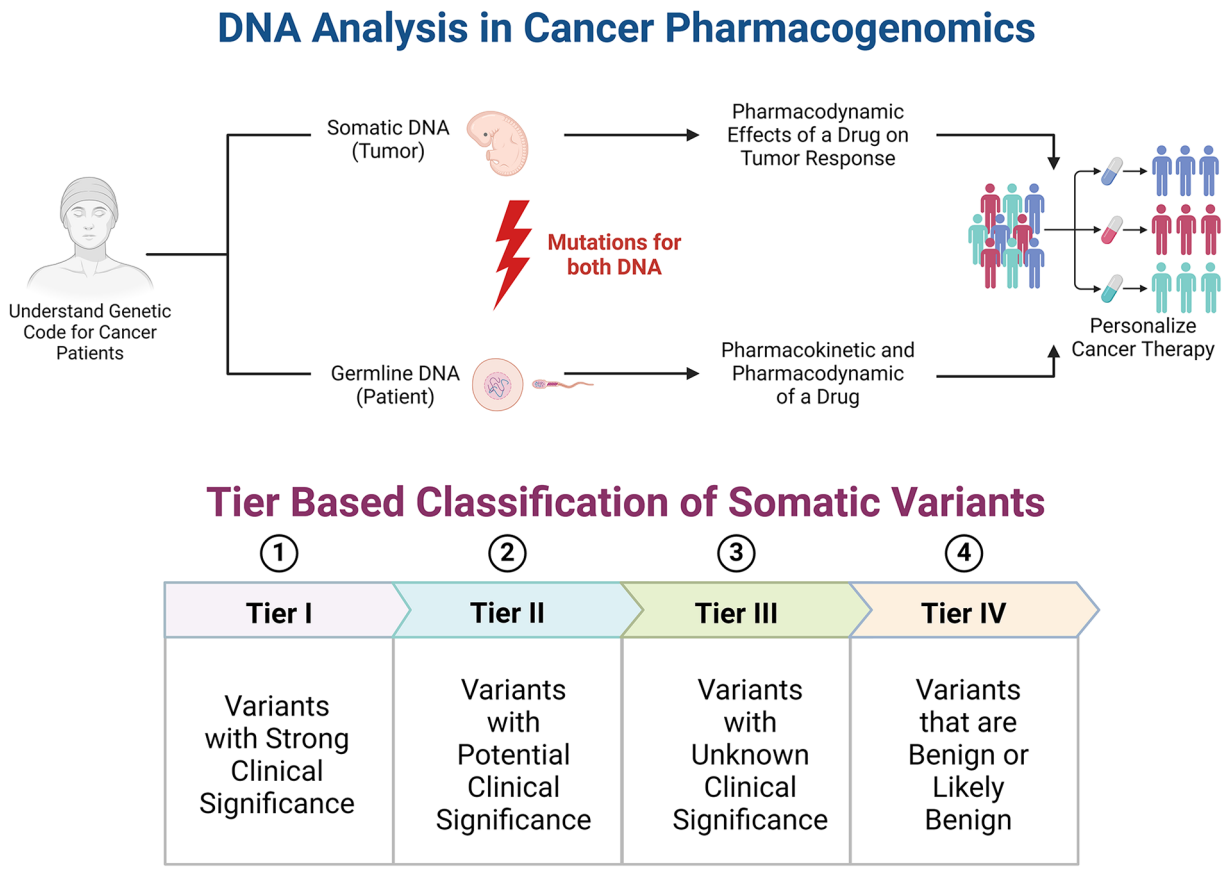

Figure 2. Biomarker classification based on genomics and clinical utility. Somatic DNA, found in tumors, is useful for assessing the pharmacodynamic effects of a drug on the tumor response. Germline or inherited DNA variations predict the pharmacokinetic effect of a drug and its response. Multiple frameworks exist for categorizing the pathogenicity of somatic variants. One classification system is categorized as follows: Tier I for variants with strong clinical significance, tier II for variants with potential clinical significance, tier III for variants with unknown clinical significance, and tier IV for variants that are benign or likely benign.

Personalized medicine for lung cancer involves screening all advanced-stage patients for key mutations, such as those in epidermal growth factor receptor (EGFR), anaplastic lymphoma kinase (ALK), and ROS1, to tailor treatment plans.[8,18] The EGFR is overexpressed in 10% to 50% of patients with non–small cell lung cancer (NSCLC), making it a great molecular target. The presence of EGFR exon 19 deletions or EGFR exon 21 L858R mutations is predictive of treatment benefit from EGFR-TKI therapy, such as osimertinib. The 2 predominant mutations observed in the EGFR gene are deletions in exons 19 and 21. On the contrary, approximately 5% of patients with NSCLC exhibit rearrangements in the ALK gene, and ALK inhibitors, such as alectinib, brigatinib, ceritinib, crizotinib, and lorlatinib, all of which have received Food and Drug Administration (FDA) approval, can be used in the metastatic setting.[8,18] However, drug resistance remains a challenge in lung cancer treatment.[18-20] Common resistance mechanisms include mutations such as T790M in EGFR and amplification of MET or HER2. Combining drugs targeting different mechanisms is a potential strategy to combat this resistance.[18]

Breast cancer. Breast cancer is the most frequently diagnosed cancer worldwide, with approximately 2.3 million new cases each year.[6] This disease is highly heterogeneous, involving various genetic and environmental factors, making its treatment complex.[8] Genetic factors such as mutations in the BRCA1 and BRCA2 genes significantly increase breast cancer risk. The prognosis and response to treatment vary greatly depending on tumor size, type, histological score, metastasis status, and receptor status, necessitating individualized treatment approaches.[21]

In breast cancer, targeted therapies have become increasingly important, particularly for estrogen receptor (ER)-positive cancers, which constitute approximately 75% of all breast cancer cases.[21] Tamoxifen, an FDA-approved endocrine therapy, is widely used for these cancers.[22] Fulvestrant, another ER antagonist, has shown efficacy comparable to that of anastrozole in clinical trials.[23] For human epidermal growth factor receptor 2 (HER2)-positive breast cancer, trastuzumab, a mAb, has been shown to be effective at improving survival rates.[21] Pertuzumab, another antibody targeting HER2:HER3 dimerization, has shown significant results in metastatic breast cancer. Lapatinib, a tyrosine kinase inhibitor (TKI) targeting HER2 and EGFR, is effective when used in combination with trastuzumab.[24] On the contrary, triple-negative breast cancer (TNBC) cells, particularly those with BRCA1/2 dysfunction, respond well to poly-ADP ribose polymerase inhibitors (PARPi), such as olaparib and talazoparib.[22,25]

Table 1. Selected treatment-driven cancer biomarkers in the settings of advanced solid cancer diseases.

CANCER TYPE	BIOMARKERS	FDA-APPROVED THERAPIES	TARGETED THERAPY CLASSIFICATION
Lung cancer	EGFR exon 19 and 21	Afatinib, erlotinib, dacomitinib, gefitinib, osimertinib	Small molecules
	EGFR Exon 20 Insertion Mutation	Amivantamab-vmjw	Monoclonal antibody (bispecific)
	ALK Rearrangement	Alectinib, brigatinib, ceritinib, crizotinib, lorlatinib	Small molecules
	ROS1 Rearrangement	Ceritinib, crizotinib, entrectinib, repotrectinib	Small molecules
	BRAF V600E Mutation	Dabrafenib/trametinib, Encorafenib/ binimetinib, Dabrafenib, Vemurafenib	Small molecules
	NTRK1/2/3 Gene Fusion	Larotrectinib, entrectinib	Small molecules
	MET Skipping Mutation	Capmatinib, crizotinib, tepotinib	Small molecules
	RET Rearrangement	Selpercatinib, pralsetinib, cabozantinib	Small molecules
Breast cancer	Germline or somatic BRCA1/2 mutation	PARPi (olaparib, talazoparib)	Small molecules
	HER2-positive	Trastuzumab, pertuzumab	Monoclonal antibody combination
		Neratinib	Small molecules
	HER2-Negative and ER/ PR-positive	CDK 4/6 inhibitors (palbociclib, abemaciclib, ribociclib)	Small molecules
	ESR1 mutation	Elacestrant	Small molecule
	PIK3CA mutation	Alpelisib + fulvestrant	Small molecules
	AKT1/PTEN-activating mutation	Capivasertib + fulvestrant	Small molecules
Colorectal cancer	(KRAS/NRAS/BRAF WT and left-sided tumors only)	EGFR monoclonal antibodies (panitumumab, or cetuximab)	Monoclonal antibodies
	VEGF	Bevacizumab, aflibercept and ramucirumab	Monoclonal antibodies
		regorafenib and fruquintinib.	Small molecules
	KRAS G12C mutation	Sotorasib, adagrasib	Small molecules
	HER2-positive and RAS and BRAF wildtype	Trastuzumab/lapatinib, trastuzumab/ tucatinib	Monoclonal antibody/ small molecule combinations
		Trastuzumab/pertuzumab	Monoclonal antibody combination
		fam-trastuzumab deruxtecan-nxki (T-DXd)	Monoclonal antibody (ADC)
	BRAF V600E mutation	Encorafenib/panitumumab, encorafenib/cetuximab	Small molecule/monoclonal antibody combination
		dabrafenib/trametinib	Small molecules

Sacituzumab govitecan is an ADC that targets the Trop-2 surface antigen expressed in breast cancer and was initially approved for relapsed/refractory TNBC. In the recent Tropics-02 trial, sacituzumab govitecan demonstrated longer overall survival (OS) in treatment-resistant HR-positive breast cancer, indicating a greater role for ADC in addressing treatment resistance in breast cancer.[26] Furthermore, low-HER2 breast cancer classification has gained increased attention since the approval of trastuzumab deruxtecan (T-DXd) for patients with advanced breast cancer with low HER2 expression. In the DESTINY-Breast04 trial, T-DXd was associated with favorable progression-free survival (PFS) and OS compared with standard chemotherapy.[27]

Emerging targeted therapies for breast cancer include the inhibition of intracellular molecular pathways. For example, mTOR pathway inhibitors have shown improved outcomes in

resistant endocrine breast cancers.[28] CDK 4/6 inhibitors, such as palbociclib, abemaciclib, and ribociclib, in combination with aromatase inhibitors, have been shown to be effective in treating hormone receptor–positive breast cancer, significantly improving disease-free survival (DFS) rates.[29] These advances have led to the FDA approval of several new drugs, such as elacestrant for ESR1 mutations, PI3K inhibitors, and AKT inhibitors, in a short period of time.

Despite these advances, drug resistance remains a significant challenge in breast cancer treatment. Resistance mechanisms include increased drug efflux, enhanced metabolic enzyme production, and alterations in drug targets.[30] To address resistance to single agents, combination therapy has been widely applied to treat breast cancer.

The use of personalized medicine for the treatment of breast cancer, driven by molecular stratification and multigene microarray analysis, is evolving rapidly. This approach enables tailored treatment choices and specific target selection, reducing breast cancer–related mortality and changing the standard of care.[21] The use of molecular assays and multigene microarrays, such as Oncotype DX and MammaPrint, allows for more individualized treatment decisions among patients with breast cancer. With ongoing advancements in targeted therapy, informed by gene expression analysis and high-throughput screening, the field is moving toward more effective, personalized treatments.

Colorectal cancer. Colorectal cancer ranks as the third most common and second deadliest cancer worldwide.[6] Notably, 25% of patients with CRC are diagnosed at a late stage, rendering surgery ineffective.[31] This highlights an urgent need for new therapeutic strategies to improve survival rates and mitigate the severity of CRC. Advancements in chemotherapy and targeted therapies have markedly improved outcomes for patients with metastatic CRC (mCRC), extending the average survival to nearly 40 months.[8]

The introduction of mAbs targeting EGFR, such as cetuximab and panitumumab, has been pivotal.[32] These treatments have shown significant promise in improving PFS and OS, especially when combined with chemotherapy regimens such as FOLFOX.[31,33] However, the efficacy of these anti-EGFR drugs as second-line treatments remains limited. In addition, antiangiogenic agents targeting vascular endothelial growth factor (VEGF), such as bevacizumab, aflibercept, regorafenib, and ramucirumab, have been approved for mCRC treatment following positive clinical trial results. However, these agents do not require testing for VEGF in patients with cancer since VEGF proteins are upregulated in CRC tissue and are one of the hallmarks of cancer.[14,31] Recently, the FDA granted approval to fruquintinib, a novel oral kinase inhibitor that acts on VEGFR 1, 2, and 3.[34] Its effectiveness and safety were assessed in 2 randomized, double-blind, phase 3 clinical trials named FRESCO and FRESCO-2.[35,36]

Other recent targeted therapies for mCRC include 2 KRAS G12C inhibitors, sotorasib and adagrasib.[31] KRAS G12C inhibitors are recommended for the treatment of previously treated patients with mCRC harboring this mutation. Sotorasib or adagrasib should be given in combination with cetuximab or panitumumab or may be considered as a single agent. Other targeted therapies used for mCRC include BRAF V600E mutation, for which treatment combinations such as cetuximab or panitumumab combined with encorafenib are being used. In patients with mCRC with HER2 amplification, 4 different treatment regimens can be used: fam-trastuzumab deruxtecan-nxki (T-DXd) as a single agent or trastuzumab combined with pertuzumab, lapatinib, or tucatinib.[31]

Despite advances in molecular medicine and targeted drug development, drug resistance in mCRC remains a significant challenge. Resistance to anti-EGFR therapy, linked to mutations in genes such as BRAF, RAS, and PIK3CA, limits the effectiveness of these treatments to approximately 40% of patients with mCRC.[37] Addressing resistance mechanisms and developing new biomarkers and therapeutic pathways are crucial for enhancing treatment efficacy. Personalized medicine has gained importance in CRC treatment, with multiple targeted therapies showing promise. The molecular diversity of tumors necessitates individualized treatment plans, guided by biomarkers such as KRAS mutations, to tailor therapies such as cetuximab and panitumumab to each patient's specific needs.[37] However, there is a growing need for new indicators to predict responses to both existing and experimental treatments.

Selected targeted cancer therapies in hematologic cancers

The swift advancement of targeted therapies for blood cancers is transforming how we approach treatment, focusing on key aspects of cancer development. This section explores how cancer biomarkers play a crucial role in the most common global blood cancers. By pinpointing treatment biomarkers, treatment can be customized for better effectiveness and fewer side effects. In Table 2, we present a summary of significant treatment-driven biomarkers and the corresponding targeted therapies for cancer. This individualized method offers great potential for improving patient results, reducing negative impacts, and changing the scope of hematologic malignancy treatment.

Acute myeloid leukemia. Acute myeloid leukemia (AML) accounts for 80% of all acute leukemia in adults worldwide.[39] Despite the availability of multiple prognostic factors for AML, the mortality rate is still high.[40] FMS-like tyrosine kinase 3 (FLT3) is considered one of the crucial biomarkers tested in AML patients and can classify patients as high versus low risk.[41] The role of FLT3 in hematopoietic cells includes controlling cell prefoliation, differentiation, and survival.[42] Patients with AML who tested positive for FLT3 were

Table 2. Selected treatment-driven cancer biomarkers for hematologic malignancies.

CANCER TYPE	BIOMARKERS	FDA-APPROVED THERAPIES	TARGETED THERAPY CLASSIFICATION
AML	FLT3	Midostaurin, Gilteritinib, Quizartinib	Small molecules
	BCL-2	Venetoclax	Small molecule
	IDH1/IDH2	Ivosidenib, Olutasidenib, Enasidenib	Small molecules
CML	BCR-ABL	Imatinib, bosutinib, dasatinib, nilotinib, and ponatinib	Small molecules
Lymphoma	CD30	Brentuximab vedotin	Monoclonal antibody (ADC)
	ALK	Alectinib, Brigatinib, Ceritinib, Lorlatinib	Small molecules

Recent trends in cancer biomarkers underscore the continuous evolution of diagnostic and therapeutic strategies aimed at improving patient outcomes. Multiple trials are ongoing exploring the benefit of using targeted therapies and whether personalized medicine is more beneficial than standard-of-care treatment. The TAPUR Study, which stands for the Targeted Agent and Profiling Utilization Registry, is a clinical trial initiative in oncology.[38] It is designed to explore the effectiveness of targeted therapies outside of their approved indications. The TAPUR Study aims to investigate whether targeted therapies approved for one type of cancer may also be effective against other types of cancer with specific genetic mutations or biomarkers.

considered at high risk of relapse/recurrence compared with those missing this mutation.[42] FLT3 mutations are classified as either internal tandem duplications, which are usually located within the juxta membrane, or tyrosine kinase domain, which are considered missense mutations.[41] Luckily, multiple targeted agents, such as midostaurin, gilteritinib and quizartinib, have been approved for targeting FLT3.[43]

B-cell lymphoma 2 inhibition (BCL-2) is another essential biomarker usually considered an adverse prognostic factor in AML.[44] The role of BCL-2 in hematopoietic cells is to control antiapoptotic proteins, which ultimately promote the progression of malignant cells. Venetoclax is an approved drug that targets BCL-2 in patients with AML.[45] Other prognostic biomarkers in AML include isocitrate dehydrogenase (IDH1 and IDH2), which are responsible for the conversion of alpha-ketoglutarate to 2-hydroxyglutarate, which disrupts epigenetic regulation and eventually blocks the differentiation of hematopoietic cells.[46] The prognostic potential of IDH in AML is not yet clear, with variations in prognosis based on IDH mutational isoforms.[47] There are 2 approved agents targeting IDH isoforms, namely, ivosidenib and olutasidenib for IDH1 mutation and enasidenib for IDH2 mutation.[47,48] The identification and targeting of crucial biomarkers such as FLT3, BCL-2, and IDH have significantly improved the management of AML, offering hope for better outcomes in patients facing this challenging disease.

Chronic myeloid leukemia. The discovery of breakpoint cluster region and Abelson murine leukemia viral oncogene homolog (BCR-ABL) gene has played a tremendous role in understanding cancer development in patients with chronic myeloid leukemia (CML).[49] It was first described by Nowell et al[50] in 1960 and was then named after the city (Philadelphia chromosome) where it was first discovered. The fusion of BCR-ABL gene is responsible for the translocation of chromosomes 9 and 22, which enhances cancerous cell growth and proliferation.[49] Luckily, the BCR-ABL gene pathway is dependent on tyrosine kinase activity, making it an optimal target for treating patients with CML. The first approved TKI-targeted agent in CML was imatinib, which was introduced to the market in early 2001 after its FDA approval, making it a transformational treatment for CML.[51] However, despite the initial success of imatinib, resistance, and intolerance issues necessitated the exploration of alternative treatment strategies. This has prompted extensive research efforts aimed at developing novel agents capable of overcoming these challenges, such as developing second-generation TKIs targeting BCR-ABL, including dasatinib, bosutinib, nilotinib, and ponatinib.[51] Despite initial successes, ongoing efforts to address resistance and intolerance issues have spurred the development of second-generation TKIs, revolutionizing the treatment landscape for patients with CML and offering renewed hope for improved outcomes.

Lymphoma. Malignant lymphoma is composed of a variety of types and is classified based on cell origin. This section summarizes some biomarkers that help in guiding disease management. One of the biomarkers commonly examined in lymphoma is CD30.[52] CD30 is a membrane-bound ligand that is expressed in multiple forms of lymphoma, including diffuse large B-cell lymphoma (DLBCL).[52] The signaling cascade of CD30 promotes cancer cell survival and proliferation and renders cancer cells resistant to self-destruction.[53] The US FDA approved the first ADC targeting CD30 in patients suffering from refractory Hodgkin lymphoma (HL) or anaplastic large cell lymphoma.[54,55] Another biomarker rarely used in lymphomas is ALK.[56] The ALK fusion is usually observed in NSCLC, and it has been a target of interest in this population.[57] The ALK fusion has been reported to be expressed in DLBCL, T-cell lymphomas, and other types of lymphoma.[38] The presence of this gene alteration is attributed to worse prognosis in patients with lymphoma and is usually observed in patients who fail standard of care treatments.[38] Multiple ALK-targeted agents, such as alectinib, brigatinib, crizotinib, ceritinib, and lorlatinib, have been approved. The majority of those approved

agents were in the setting of NSCLC.[58] According to the NCCN guidelines, alectinib, brigatinib, ceritinib, and lorlatinib can be used for patients with lymphoma with ALK-expressing lymphoma if the first-line treatment fails.[59-63] The identification of such biomarkers has significantly advanced the management of malignant lymphomas, offering targeted treatment options for patients with refractory disease.

Overcoming resistance to targeted therapy

Resistance to treatment is a problem that is often encountered with targeted cancer therapy, making it important to explore treatment strategies to overcome potential therapy failure. Resistance to targeted therapy may be adaptive, as cancer cells are able to overcome the signal blockade caused by TKIs through the use of different downstream cellular pathways.[64] Adaptive resistance is often observed in $BRAF^{V600}$-mutated melanoma if BRAF-directed therapy is used alone, reactivation of downstream signaling through the RAS-MAPK pathway occurs, resulting in treatment resistance. This highlights the importance of using combination therapy, such as the combination of dabrafenib and trametinib, to block multiple targets in the MAPK pathway to prevent the development of adaptive resistance.[65] On the contrary, acquired resistance occurs in patients who were previously responsive to treatment for a period of time; it can occur as a result of new mutations or gene amplification, leading to eventual disease progression.[64] Achieving a deep initial response is a strategy that aims to lower the chances of resistance development; this strategy is employed with hematological cancers such as CML.[64] The efficacy of chronic-phase CML treatment is assessed through molecular and cytogenic milestones that correlate with a deep response, which is linked to decreased disease progression and improved survival.[66] Next-generation sequencing (NGS) serial tests are another strategy that has been successfully used to identify changes in tumor mutation expression once disease progression occurs, which can aid in tailoring new personalized treatment plans on the basis of molecular resistance patterns.[67,68] As a result of this growing application, ESMO recently published a statement recommending performing NGS testing in various advanced cancer types, including cancers of unknown origin.[69]

Predictive Biomarkers in Immunotherapy

The introduction of immune checkpoint inhibitors (ICPi) has dramatically changed the cancer treatment landscape.[70,71] In 2011, ipilimumab, the first ICPi approved by the FDA, was used for the treatment of advanced-stage melanoma.[72] Shortly thereafter, programmed death 1 (PD-1) inhibitors, including pembrolizumab and nivolumab, were introduced to the market, followed by the PD-1 ligand (PD-L1) inhibitors atezolizumab, durvalumab, and avelumab.[73-78] Currently, PD-1/PD-L1 inhibitors are approved for the treatment of a wide range of solid tumors, including but not limited to melanoma, head and neck, gastrointestinal, lung, breast, renal, and genitourinary cancers.[79] With the approval of pembrolizumab for the treatment of relapsed/refractory classical HL, indications have also expanded to include hematological malignancies after showing longer PFS in comparison with the standard of care.[80] Several biomarkers have been used to predict the response to ICPis; this section discusses the most recent advancements and challenges in this field.

Programmed death ligand 1

The PD-1/PD-L1 axis was first discovered in the early 1990s, and extensive research revealed its central role in immune tolerance.[81] The PD-1 is a transmembrane protein expressed on activated immune white blood cells, including B and T lymphocytes, whereas PD-L1 is expressed on lymphocytes as well as various other body tissues and organs.[82-85] The interaction between PD-1 and PD-L1 inactivates the immune response. Malignant cells overexpressing PD-L1 escape immune system surveillance, allowing them to continue to grow and proliferate.[86] Pembrolizumab was the first PD-1 inhibitor to gain accelerated FDA approval in 2014 for the treatment of unresectable melanoma.[87]

The PD-L1 expression detection through immunohistochemistry (IHC) is the most commonly used biomarker detection method to predict response to immunotherapy.[88] The PD-L1 biomarker detection has now received approval for various types of cancers.[89] Despite its wide use, PD-L1 IHC detection has been shown to be less sensitive than other PD-L1 detection methods.[90] In addition, the absence of PD-L1 expression does not rule out a response to immunotherapy, as noted in both CheckMate238 and KEYNOTE-054, where a recurrence-free survival benefit was observed in all patients regardless of PD-L1 expression status.[91,92] Moreover, IMPOWER-133 demonstrated an OS benefit in extensive-stage small-cell lung cancer patients with the addition of atezolizumab to etoposide and carboplatin chemotherapy backbone across all patients, including those with PD-L1 expression $\leqslant$1%.[93] These observations show variability in the thresholds for PD-L1 positivity as well as a great deal of heterogeneity in PD-L1 expression cutoffs between different trials and disease states, raising the need for additional research on alternative biomarkers to better predict immunotherapy responses.

Tumor mutational burden

Tumor mutational burden (TMB) refers to the extent of genetic derangements found in cancer cells.[94,95] Genetic abnormalities may lead to the activation of oncogenes, deactivation of tumor suppressor genes, production of abnormal proteins, and expression of neoantigens on the cell surface.[94] The TMB is detected clinically using NGS technology through testing cancer tissues for the number of somatic mutations per

megabase (mut/Mb).[96] The US FDA approved 2 NGS panels for TMB testing in clinic: F1CDx and MSK-IMPACT.[96] The TMB was approved based on the results of the KEYNOTE-158 trial, where a subgroup of patients with TMB high (TMB-H) (defined as ⩾10 mut/Mb) demonstrated an overall response and a complete response benefit.[97] Furthermore, a post hoc analysis of the TMB data from 12 trials using whole exome sequencing further confirmed a cutoff of 10 mut/Mb as an indicator of the response to ICPis.[98]

The use of the TMB as a predictor of response to ICPi therapy is challenging in some tumors that exhibit high microsatellite instability (MSI-H) as MSI creates a greater mutational burden compared with that of MSI-stable tumors, making it difficult to set a pan-cancer threshold.[99,100] Furthermore, TMB status failed to predict response in certain tumors, including but not limited to breast, prostate, and adrenocortical cancer.[101] The aforementioned observations represent challenges with the utility of TMB as a treatment response biomarker.

Recent in vitro research demonstrated that mutations occurring in a single-copy gene region or mutations with multiple copies were less likely to be eliminated from the cancer genome and are therefore denoted as persistent TMB (pTMB).[102] Persistent mutations are associated with persistent mutation-associated neoantigen expression, which allows for durable recognition of the tumor by the immune system during immunotherapy. The utility of pTMB as a predictor of response to immunotherapy has been observed in a number of cancers, including melanoma, NSCLC, and head and neck cancers, thus indicating that the pTMB is promising for predicting response to immunotherapy.[102]

Microsatellite instability

Gene microsatellites are short sequences of noncoding DNA that are typically composed of 1 to 6 base pairs that form during the DNA replication process.[103,104] The cellular mismatch repair (MMR) system works to correct such errors that occur during replication and failure to correct replication errors results in the accumulation of short tandem repeats, which leads to MSI and ultimately tumor development.[105,106] The MSI-high tumors are common in gastrointestinal (including colorectal) and endometrial cancers, making MSI a valuable biomarker for predicting the response to ICPi therapy.[106] Several methods are currently used to assess MSI/MMR status, including NGS, PCR, and IHC.[107] Interestingly, a new approach using machine learning (ML) models for magnetic resonance imaging (MRI) has been successfully used to predict MSI status in patients with rectal cancer, although further studies are needed; this approach represents a promising non-invasive diagnostic tool for patients with rectal cancer.[108] Moreover, PD-1 blockade with dostarlimab in patients with MMR-deficient locally advanced rectal cancer achieved a 100% complete response rate in patients who completed 1 year of dostarlimab treatment in a phase 1 study.[109] Currently, a phase 2 ongoing multicenter global trial is investigating the efficacy of dostarlimab on a larger scale in patients with MSI/MMR-deficient locally advanced rectal cancer and is expected to release preliminary results by 2026.[110]

AI Models in Response Prediction

In the field of clinical oncology and cancer research, there are at least 4 main types of biomarkers. First, susceptibility or risk biomarkers highlight an individual's likelihood of developing cancer. Second, diagnostic markers are used to determine whether cancer is present or absent. Third, prognostic biomarkers offer insights into the potential course of the disease, predicting its progression or recurrence. Finally, stratification markers help categorize cancer diagnoses into distinct molecular groups, facilitating tailored treatment plans and providing a clearer picture of possible disease trajectories.[111] Traditional histopathological methods, including IHC of solid tissues, remain the preferred approach for cancer diagnosis. However, the emerging field of liquid biopsy biomarkers holds significant potential for enhanced detection of early-stage, recurrent, or undetected cancers.[111] The rapid advancement of in-depth sequencing techniques and the analysis of genomes and transcriptomes from clinical samples form the foundation of precision medicine, a vision not yet fully achieved.[15] Due to technological progress in DNA and RNA analysis, nucleic acid–derived biomarkers have taken the forefront. Biomarkers can manifest in various forms—molecular, histological, radiographic, or physiological. While many biomarkers are based on observable clinical symptoms, some are derived from physiological measurements or laboratory tests.[15,111] Biomarkers that can be quantified depend heavily on established reference ranges to guide clinical decisions. Interestingly, most of the biomarkers used in current oncology are not quantifiable in a continuous manner. Genomic biomarkers, for instance, which are frequently used to forecast treatment outcomes or disease prognosis, typically present binary data. In addition, interpretations of histological, radiological, and MRI imaging biomarkers often involve subjective assessments by medical professionals.[112]

In the realm of oncology, emerging technologies such as AI and ML are being developed[113] Their strength lies in analyzing intricate nonlinear patterns in vast multidimensional datasets, a critical capability for contemporary clinical practices that require holistic analysis of real-world and multiomics data.[114] The ML excels at fusing information about both the patient and the tumor, enhancing the precision of predictive biomarkers. This leads to more tailored treatments and helps identify patients who could most benefit from immuno-oncology.[115] A number of ML models have been generated to classify NSCLC into its well-established subtypes and/or identify crucial NSCLC biomarkers that are differentially expressed across subtypes.[116,117] If adequate information is provided, deep

learning models have proven to be superior to traditional ML algorithms, but the users of these models are still unable to recognize how different features contribute to the task at hand. The explainable AI (XAI) concept was recently introduced in an effort to fill the explainability gap in deep models.[118] The XAI is a set of tools or techniques that aid developers in understanding the internal functions of a machine/deep learning model.[118] The XAI identified a small number of clinically significant NSCLC biomarkers for possible use in targeted therapy. Fifty-two biomarkers (NSCLC-Biomarkers-Set) were identified using a deep learning framework that was created using the XAI algorithms GradientSHAP, IntegratedGradients, and DeepLIFT. Forty-five of the 52 biomarkers discovered using the suggested framework have already been identified in previous studies. The 7 genes identified by XAI include AP2M1, C9orf69, FLJ44635, ID2B, CEL, LOC442308, and LOC728758.[118] These 7 genes have not yet been documented for subtyping NSCLC and could be the focus of additional studies by clinicians with the aim of developing targeted therapy for patients with NSCLC.[118] The proposed framework's XAI-based feature selection method outperformed other feature selection methods in terms of classification accuracy. Moreover, 28 biomarkers with P values $\leqslant .05$ were found to be helpful for predicting survival outcomes, and 14 of the newly discovered biomarkers may be druggable.[118]

AI in digital pathology

The AI has been used in digital pathology to improve cancer diagnosis and prognostication. In one case study, a multimodal AI architecture was developed to analyze digital histopathology images and clinicopathologic data from patients with prostate cancer. This AI model was trained on data from multiple clinical trials and successfully predicted clinical outcomes such as biochemical recurrence and OS, showcasing its potential in precision oncology.[119,120]

AI and DNA methylation analysis

Another example involves the use of AI in conjunction with DNA methylation analysis for lung cancer detection. Researchers applied AI algorithms, including support vector machines and deep learning, to analyze methylation changes in circulating cell-free tumor DNA. This approach identified potential biomarkers for lung cancer with high diagnostic accuracy, demonstrating AI's capability in enhancing early detection and understanding cancer pathogenesis.[121]

AI in breast cancer diagnosis

Machine learning and deep learning techniques have been extensively reviewed for their application in breast cancer diagnosis and classification through medical imaging. These AI methodologies have improved the accuracy and efficiency of detecting and classifying breast cancer, providing valuable insights into disease progression and treatment planning.[122]

Identification of novel biomarkers in precision oncology

A specific example of a biomarker identified through AI methodologies in precision oncology is the sphingomyelin (d18:0/22:0), which has been identified as a potential screening biomarker for lung cancer. This biomarker was discovered through a metabolomics study that analyzed metabolic perturbations related to lung cancer.[123] The study involved a nested case-control analysis within the Cancer Prevention Study cohorts, demonstrating the association of sphingomyelin (d18:0/22:0) with lung cancer risk. Another example is the identification of the biomarker VIPR1 in hepatocellular carcinoma (HCC) using ML algorithms. This biomarker was identified through the analysis of gene expression data and was found to have significant diagnostic value for HCC, showing potential as an independent prognostic factor.[124] These examples illustrate how AI and ML can be used to identify novel biomarkers that have significant implications for cancer diagnosis and treatment.

AI in multi-omics integration

The AI has been pivotal in integrating multiomics data, which include genomics, transcriptomics, proteomics, and metabolomics, to enhance cancer diagnosis and treatment. For instance, AI models have been used to analyze multimodal datasets, leading to improved cancer subtyping, risk stratification, and prognostication. A study demonstrated the use of AI to integrate multiomics data, which resulted in better diagnostic and therapeutic outcomes by identifying distinct cancer subtypes and predicting patient responses to treatments.[125]

Multiomics and AI in Cancer

The aim of multiomics methods is to better understand the molecular and clinical characteristics of cancers by integrating numerous omics datasets collected from the same patients into unique frameworks. Currently, there are novel opportunities to further classify cancers into subtypes, enhance the prognosis and therapeutic outcome of these subtypes, and comprehend important pathophysiological processes through various molecular layers due to a wide range of emerging omics and multiview clustering algorithms. A multiomics analysis is a data-driven scientific study that aims to uncover the complexity of cells and their surroundings by analyzing a variety of high-dimensional datasets at several levels and sizes. The advent of high-throughput technologies in genomics and transcriptomics, coupled with increased efforts in large-scale research collaboration and computational algorithm innovation, has led to a paradigm change in cancer research toward multiomics approaches.[126-128] In cancer, AI has proven to be

capable of analyzing complementary multimodal datasets. The advancement of cancer precision medicine has accelerated with the simultaneous development of AI algorithms and multiomics technology.[129] Artificial intelligence techniques are frequently used at different stages of clinical cancer treatment, as they have shown success in addressing the heterogeneity and complexity of multiomics data. Currently, AI algorithms are able to combine data from various platforms, such as radiomics, genomics, transcriptomics, proteomics, metabolomics, and pathomics, to enable more accurate identification of cancer subtypes and to suggest reliable tools for predicting cancer prognosis and response to treatment.[130,131] This introduced the role of AI-based multiomics analysis to aid in cancer precision medicine, including cancer detection and screening, diagnosis, classification, and grading.[129]

Cancer Biomarker Trends in Middle Eastern Populations

Validated biomarkers of genetic alterations are becoming key tools for disease prevention, disease prognosis, and therapy selection in oncology settings. These mutations are classified as either germline static or somatic dynamic mutations. Germline mutations are found in germ cells (detected in both normal and tumor cells) and have a role in identifying genetic predisposition and guiding screening and treatment. Somatic mutations are found only in nonreproductive cells and have a role in identifying predictive/prognostic mutations for disease prognosis and therapy selection.[132,133] There are 53 FDA-recognized genes for predicting response to 87 cancer drugs and an additional 24 genes considered a standard of care and recognized in professional guidelines that show a predicted response to 45 FDA-approved drugs. The majority of these therapeutic biomarkers are somatic mutations, such as ALK rearrangement, BRAF, EGFR, RET rearrangements, and ROS-1[134] (Table 1).

The evidence investigating the prevalence of cancer biomarkers in the MENA region is limited.[135] In Saudi Arabia, a report showed the testing rate for the most common biomarkers assessed by cancer type[136] (Figure 3). In addition, Alharbi and colleagues revealed the prevalence of KRAS mutations among 248 Saudi patients diagnosed with CRC (49.6%), followed by NRAS mutations (2%) and BRAF mutations (0.4%). The survival rate is worse among carriers of KRAS mutations than among carriers of wild-type KRAS tumors.[137] This finding was consistent with more recent data from local and MENA region studies. Nasser and colleagues discovered several novel KRAS mutations in Saudi patients diagnosed with CRC.[138-140] On the contrary, Rasool and colleagues reported novel mutations in the BRAF gene at c.1758delA, c.1826insT, c.1860insA, and c.1860insA/C in Saudi patients with CRC.[141] Such mutation uniqueness could be attributed to environmental factors, among other factors, such as ethnic/racial variation, that reflect different gene methylation patterns and dissimilar molecular pathogenesis.[140,142-144]

Investigational efforts explored the spectrum and frequency of germline variants through NGS-based multigene testing (180 genes associated with cancer predisposition) in Bahraini women with breast cancer. Their work detected 2 BRCA1 variants in 2 patients, namely, the missense variant c.287A > G (p.Asp96Gly) and the truncating variant c.1066 C > T (p.Gln356Ter). Moreover, they yielded additional genomic information on low-penetrance genes, where 4 patients carried pathogenic/likely pathogenic or potential pathogenic variants together with distinct other variants of unknown significance.[145] Such efforts and findings can serve as supplementary knowledge to traditional genetic counseling.

Zooming into BRCA1 and BRCA 2 gene mutations, a double-strand DNA repair homologous mutation that showed a positive association in patients treated with PARP inhibitors.[145-147] In addition, it has value in predicting response to platinum therapy.[148] An analysis of a large cohort from the Middle Eastern population revealed 2 novel founder mutations that account for 46.4% of all BRCA mutant cases and 1.6% of all breast cancer cases. Understanding the mutation distribution in the Middle Eastern population is exceptionally important for developing cost-effective genetic testing strategies in clinical practice.[149,150] Regarding the clinical impact on patient outcome, in a small cohort of 61 Saudi female patients who were diagnosed with primary ovarian, fallopian tube, or peritoneal carcinoma, the results were consistent with those of previous studies showing a better response to chemotherapy owing to the deficiency of DNA repair mechanisms and increased DFS and OS associated with BRCA gene mutations, resulting in an 8-month increase in DFS in the BRCA mutant group, whose patients received either first- or second-line treatment.[151]

Embedding Cancer Biomarkers and Precision Oncology Within Health Systems

Integrating precision oncology into the standard of care seems to be at the top of the health care collective agenda. It has emerged as a priority not only because of its pivotal role in advancing patient care but also because of its potential to preserve health care resources while allocating and using cutting edge resources. Biomarker assays, often called companion diagnostics, are good examples of emerging clinical tests that are essential for identifying individuals who are expected to benefit from therapy. Currently, biomarker assays are needed to meet the needs of targeted therapy production and use in practice.[152]

The Early Detection Research Network (EDRN) marked the threshold for the qualification of biomarkers during the development process to be inexpensive, robust, and translatable to guide risk assessment, detection, diagnosis, prognosis, and response to therapy. Approvals by regulatory agencies in conjunction with the drugs they are paired with are essential for the transition from research to practice.[153] Thus, a shift in the

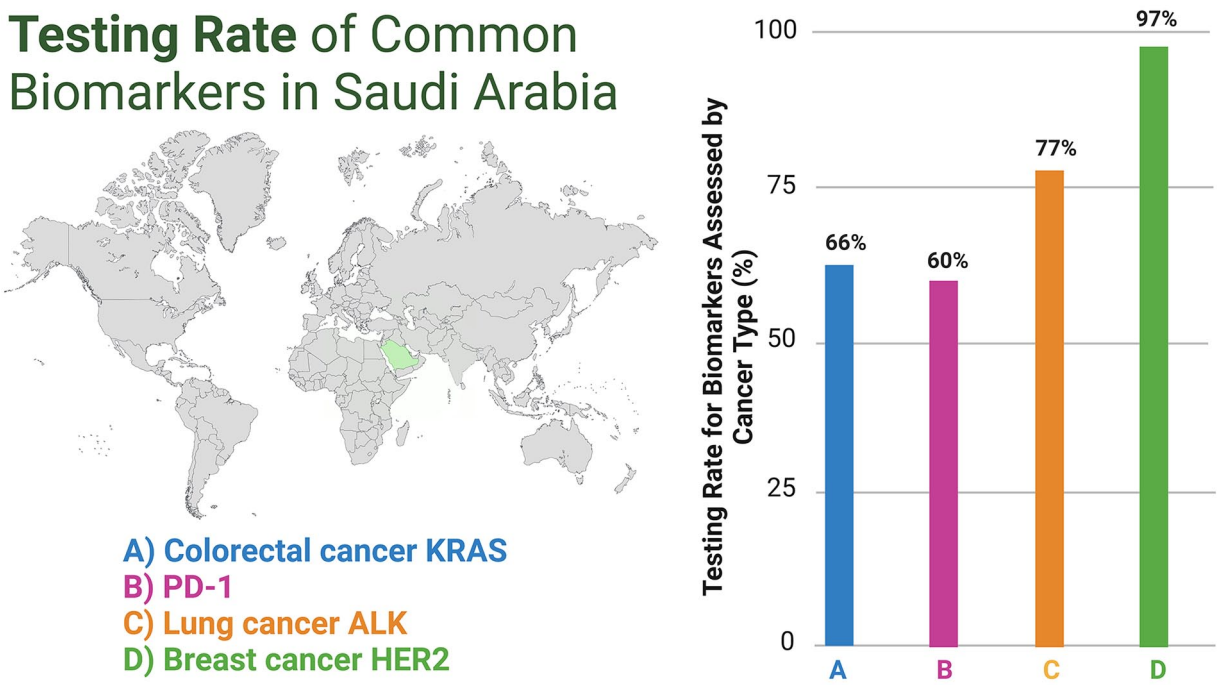

Figure 3. Common cancer biomarkers detected among Saudi patients. Testing rate for the most common biomarkers assessed by cancer type; breast cancer HER2 (97%), NSCLC ALK (77%), and PD1 (60%), and in colon cancer KRAS (~66%).

cognitive framework toward precision oncology in medicine and research demands redefining cancers on the basis of their molecular characteristics in addition to their organ of origin. Some enablers for this shift are the industrial development model, the development of sustainable reimbursement models that cover equal access high-throughput genomic sequencing of tumor genomes, and the engagement of stakeholders and regulatory agencies responsible for drug approvals to reinforce the adoption of genetic data from the early stages of drug approval all the way to the bedside.[153,154] One of the success stories is the accelerated development of widely used targeted therapy due to the substantial results in early clinical trial phases. For instance, crizotinib, a TKI targeting ALK, was approved by the FDA in 2011 for the treatment of ALK-positive relapsed or refractory systemic anaplastic large-cell lymphoma in pediatric patients aged 1 year and older.[8]

An example of an initiative that paved the way for embedding cancer biomarker testing in practice was launching the Program for the Assessment of Clinical Cancer Tests (PACCT) by the National Cancer Institute (NCI) in 2000, which aimed to ensure the translation of new knowledge about cancer and new technologies into clinical practice and to develop more informative laboratory tools to help maximize the impact of cancer treatments.[155] Another program released in 2012 by the NCI was the Clinical Assay Development Program, which targeted the development of assays for therapy response prediction, mainly for use in clinical trials.[156]

Such advances in molecular profiling have improved not only the genomic classification of a patient's tumor but also the development, approval, and availability of precision therapies.[157] However, there are still unleashed possibilities for analyzing all cancer-associated genetic alterations in a single assay and germline and somatic mutations, such as with NGS.[157]

On the contrary, there could be some challenges hindering the routine adoption of cancer biomarkers in practice. For instance, it is difficult to determine the associations among biological data, disease, and clinical translation to make meaningful medical decisions. The threshold for the lowest level of evidence acceptable for a variant allele to become a viable biomarker. Another major challenge is the translation of biomarkers from laboratory identification/isolation to clinical use and interpretation.[8,158]

Challenges in Biomarker Development

Although the number of ongoing research efforts to establish clinically relevant biomarkers has increased significantly over the years, very few biomarkers have been used clinically. This can be attributed to several pitfalls during the identification and validation process. Studies with flaws in design and execution may fail to detect significant results. For example, collecting few samples or failing to match age and sex between healthy volunteers and patients could result in failure of biomarker identification.[159] Tumor heterogeneity represents a challenge in the area of biomarker discovery; cancer cells harbor genetic mutations as they replicate, making distinguishing driver mutations from passenger mutations difficult.[4,160] The intertumor variability of biomarker cutoff values, such as TMB in ICPi therapy, makes standardizing cutoffs among various cancer

types difficult. Analyzing other biomarkers in the tumor microenvironment may aid in reaching a more accurate prediction of treatment response; however, this remains a growing area of research.[159] In addition, laboratory assays that fail to achieve adequate sensitivity and specificity will hinder the process of biomarker validation.[159] Problems encountered during sample collection and transportation could affect the quality of samples. Rigorous quality control measures must be followed during all stages from sample collection, testing, storage, and analysis. Guidelines and standards set by EDRN and PACCT help in streamlining the research and validation processes.[153]

Future Directions

The rapidly developing field of cancer biomarkers holds a promising future, as many novel concepts have been introduced for the purpose of improving cancer detection and treatment. A novel development in the cancer treatment pipeline is the use of chimeric receptor antigen T-cell therapy (CAR-T) in solid tumors. The CAR-T cells were first approved in 2017 for hematological malignancies. Currently, multiple phase 1 and 2 CAR-T cell therapies targeting biomarkers including HER-2 and EGFR in solid tumors are in progress.[161]

The area of ADCs has experienced many advancements since the introduction of the first ADC, gemtuzumab ozogamicin in 2000. Several clinical trials are currently evaluating ADCs that target C-mesenchymal epithelial transition factor (c-Met). The c-Met is a tyrosine kinase receptor found on the surface of various cancer cells, making it a potential target for ADC agents.[162] Like ADCs, immunotoxins (IT) are antibody conjugates that selectively deliver toxins to cancer cells.[163] Tagraxofusp is an IT used for blastic plasmacytoid dendritic cell neoplasm and is the only available IT product available on the market. Tagraxofusp has shown positive outcomes in clinical trials. A new recombinant bispecific IT that targets CCR4-IL2 for the treatment of cutaneous T-cell lymphoma is being tested in animal models, and it has demonstrated efficacy and an acceptable safety profile in rats and minipigs.[164]

Conclusion

This comprehensive review covers the pivotal role of cancer biomarkers in revolutionizing oncology, particularly through the lens of precision medicine and targeted therapies. This review highlights the importance of categorizing biomarkers into prognostic and predictive biomarkers and their significant impact on managing solid and hematologic cancers. Innovations in biomarker research have led to the development of personalized treatment regimens, enhancing efficacy and reducing the adverse effects of cancer therapies. Moreover, the integration of AI and multiomics approaches can refine the prediction of treatment responses and advance the implementation of precision oncology.

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Author Contributions

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Mohammed AlZahrani: writing sections (2.3, 2.3.1, 2.3.2, 2.3.3) and formulation of Table 2.
Tariq AlQahtani: writing sections 4 and 5.
Sahar AlGhamdi: writing introduction and drawing of Figures 1, 2, and 3.
Hisham Badreldin: writing article conclusion, proof reading, and revision.
Hana Al AlShaykh: writing sections 6 and 7.

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